






ARTICLE

End-to-end collaboration to transform biopharmaceutical development and manufacturing

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Abstract

An ambitious 10-year collaborative program is described to invent, design, demonstrate, and support commercialization of integrated biopharmaceutical manufacturing technology intended to transform the industry. Our goal is to enable improved control, robustness, and security of supply, dramatically reduced capital and operating cost, flexibility to supply an extremely diverse and changing portfolio of products in the face of uncertainty and changing demand, and faster product

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development and supply chain velocity, with sustainable raw materials, components, and energy use. The program is organized into workstreams focused on end-to-end control strategy, equipment flexibility, next generation technology, sustainability, and a physical test bed to evaluate and demonstrate the technologies that are developed. The elements of the program are synergistic. For example, process intensification results in cost reduction as well as increased sustainability. Improved robustness leads to less inventory, which improves costs and supply chain velocity. Flexibility allows more products to be consolidated into fewer factories, reduces the need for new facilities, simplifies the acquisition of additional capacity if needed, and reduces changeover time, which improves cost and velocity. The program incorporates both drug substance and drug product manufacturing, but this paper will focus on the drug substance elements of the program.

KEYWORDS

biopharmaceutical, manufacturing, innovation, technology, factory of the future, continuous bioprocess, process intensification

1 | INTRODUCTION

At the beginning of a new decade, it is fitting to reflect on where the industry has come from and where it is going. Individual biopharmaceutical companies made great progress in the last 40 years largely working alone. However, the industry has matured to the point where there is a greater desire to collaborate and a recognition that problems of the future are more likely to be solved by working together. The National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) is leading this cultural change in the US by developing a shared vision of the future and forming a partnership of people from industry, academia, and government to do things we could never do on our own.

NIIMBL is a public-private partnership funded in part by the National Institute of Standards and Technology (NIST) with substantial additional contributions from industry, non-profits including academic organizations, as well as state and local governments. NIIMBL's 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. The consortium is currently comprised of more than 150 member organizations including many of the largest biopharmaceutical manufacturers and technology suppliers. By working together, the industry has an opportunity to share best practices as well as to conceptualize, develop, and test manufacturing innovations with the goal of adoption and implementation of technologies in areas of common interest. The ability to work within a consortium helps de-risk these activities.

Industry leaders from 14 major biopharmaceutical manufacturers and suppliers, FDA and NIST met for 3 days in February

2020 to discuss a bold vision for the future of protein therapeutic biomanufacturing and to chart a course to achieve that vision by the end of the decade. There was remarkable agreement on the problems to solve and the path forward. We enthusiastically agreed that we have a significant opportunity to impactfully transform CMC development and manufacturing through end-to-end integration and technology advancement. We also concurred that collaboration in a consortium will significantly accelerate the transformation and develop shared principles of practice. Success will be enabled by the expertise, leadership, and capability of industry leaders committed to this vision. The development of new technology is not enough. It must be adopted by technology suppliers and biopharmaceutical manufacturers. We will have succeeded when we can walk into biopharmaceutical factories in the future, point to technological advances that we have developed and adopted, and hear how those advancements have benefitted patients, workers, and companies.

By 2029, we propose to invent, design, demonstrate, and support commercialization of drug substance (DS) and drug product (DP) manufacturing capability enabling the following:

1. improved control, robustness, and security of supply;
2. dramatically reduced capital and operating cost so it is much less of a barrier to the availability of capacity, innovation, or change, and supports global access to biologics medicines;
3. flexibility of facilities and equipment to supply an extremely diverse and changing portfolio of products in the face of uncertainty and changing volume demand;
4. faster product development and supply chain velocity;
5. sustainable raw materials, components, and energy use.

The elements of the vision are synergistic. For example, process intensification can result in capital cost reduction as well as

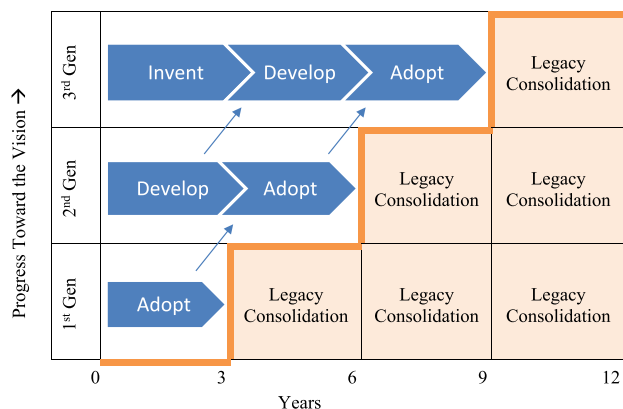


FIGURE 1 High-level technology strategy. First generation processes have already been developed but still need to be adopted into commercial manufacturing. Second generation processes will provide intermediate benefits. Third generation processes will deliver the 10-year vision, but the underlying technology needs to be invented before they can be developed

increased sustainability if the same amount of product can be produced with smaller plant, equipment, and single-use components, with less energy, water, and raw material. If plant and equipment can be made small and inexpensive enough, they might be standardized, which should decrease time to build new facilities, as described below, by decreasing the long equipment lead time currently required. Standardization of physical, electronic, and information connections between pieces of equipment should enable greater interchangeability of equipment, which would make facilities more flexible. Flexibility allows more products to be consolidated into fewer factories, reduces the need for new facilities, simplifies the acquisition of additional capacity if needed, and reduces changeover time, which improves cost and velocity. Improved robustness leads to less inventory, which improves costs and supply chain velocity. The program includes both DS and DP, but this paper will focus on the DS elements of the program.

Intermediate targets will provide incremental value while the technology to enable the long-term targets is developed. There also needs to be a way to transition legacy products and facilities. Figure 1 shows how this might be done using three parallel tracks. The first track highlights that over the next 3 years, we need to accelerate adoption of technologies that have already been developed but are not yet widely commercialized to achieve the first step change in productivity. After that, a period of consolidating and/or transitioning of legacy processes that are difficult to change may be needed. The upgrade strategy for legacy processes, equipment, and facilities is integral to our technology strategy. For example, changing a commercial process can be a very expensive and lengthy endeavor in some markets. Therefore, we expect that manufacturers will keep some legacy capacity for these markets. In markets where change is easier, the benefits need to outweigh the costs of the change, so each step change needs to be significant. The next step change, highlighted by the second track, could occur in the following three years, with the development and adoption of second generation processes.

We need to start developing these processes now. The second generation technology will be designed with third generation technology in mind, where possible, to ease the transition. The last step change happens in 9 years, with the third generation processes that deliver the vision. The underlying technology for third generation processes likely does not exist now and needs to be invented in the next three years, so the following 3 years can be spent on development and the final 3 years on adoption.

A commonly confronted barrier to innovation is the perception of regulatory hurdles in one or more markets that either delay deployment and launch or hinder global manufacturing solutions. Divergence of regulatory expectation and practice across different geographies is an additional issue. There is a rich history of mitigating these concerns through the development of consensus principles of practices through ICH or industry groups and a continued focus on risk-based, patient-centered, data-driven control of both product and processing (Broverman, 2017; FDA, 2018, 2020a, 2020b). The evolution of the Emerging Technologies Program in CDER and the Advanced Technologies Programs in CBER within the US FDA are a recognition by regulators of this issue and demonstrate a willingness to partner in enabling advanced technologies (Hahn & Shah, 2020). Peer-reviewed publications and consensus technical documents, frequently with authors from several different companies and institutions, further enable these discussions and form the foundation of the growing portfolio of widely accepted voluntary consensus standards. The development of enabling archetypes such as NIIMBL's N-Mab case study allows discussions between sponsoring companies, suppliers, and regulators that in turn develop shared understanding of expectations using relevant examples external to specific submissions. We believe the single greatest mitigator of regulatory concern is data-driven understanding and crisp, clear articulation of process, and product variability and its relevance, or lack thereof, to clinical outcomes.

A big barrier to innovation is the capital cost and long lead time for building capacity. This is a significant problem because it forces companies to make investment decisions before they know how much they need, and when forecasts increase after launch, they do not have time to build more capacity to react to the market. The high capital cost is a significant portion of the COGS (Kelley, 2009), which forces plant managers to try to operate at as close to 100% capacity as possible, increasing risk of stockout should there be any disruptions in operations. Operation close to capacity is another barrier to innovation because the plant time needed to validate and generate qualification batches of new processes reduces time available to meet current demand. The high capital cost also requires high-level corporate approvals, which makes the process take even longer. If either lead time or cost could be reduced, this would not be as much of a problem. If capital costs were high, for example, but capacity could be built in a matter of weeks, companies would only build what they knew they needed and add capacity only when there was a strong demand signal from the market. If building capacity had long lead times, but the cost was trivial, companies would overbuild just to make sure they had enough capacity. Since it is unlikely that we

TABLE 1 Estimated capital costs for biopharmaceutical and small molecule API facilities

	Biopharmaceutical		Small molecule API ^a	
	6-pack	2k SUB	Batch	Continuous
Capital (\$)	500 MM	125 MM	73 MM	31 MM
Capacity (kg/year)	4000	4000	200,000	200,000
Normalized Capital \$/ (kg/year)	125,000	31,000	370	160

^aAPI capital figures include working capital, while biopharmaceutical figures only include the cost of the facility.

will be able to make lead time or cost trivial, we need to reduce both. Commercial forecasts often work on 6-month cycles, so a 6-month approval/build/validate cycle for additional capacity would fit well. While these issues are important under normal circumstances, the recent COVID-19 pandemic has shown that surge capacity is critical in responding to a crisis like this.

A capital cost goal will help us to set the right amount of ambition in our vision. Biopharmaceuticals are often criticized because they cost a lot more than small-molecule drugs (Wilson & Neumann, 2012). If biopharmaceutical facilities could be built as inexpensively as small molecule API facilities making the same mass of product, that would help remove a barrier for biopharmaceuticals. A traditional “six-pack” biopharmaceutical drug substance facility is estimated to cost about \$500MM and could produce 4000 kg/year, with a titer of 2 g/L in 14 days (Kelley, 2009). Dividing the capital cost by the capacity results in a normalized capital cost of \$125,000/(kg/year). Kelley estimates the capital cost of a comparable facility based on single-use technology would be one-quarter of that for the traditional facility, which would bring the normalized capital cost to about \$31,000/(kg/year). In contrast, capital cost for a small molecule batch API facility producing 200,000 kg/year is estimated to be \$73MM, while a comparable continuous facility is estimated to be less than half of that, \$31MM (Schaber et al., 2011). This results in a normalized capital cost of about \$370/(kg/year) for batch and \$160/(kg/yr) for continuous, which is two orders of magnitude lower than the normalized cost for today's flexible biopharmaceutical facilities. The figures for API include working capital, which is not included in the biopharmaceutical figures, making the difference in facility cost even larger. These capital estimates are summarized in Table 1.

This reduction in biopharmaceutical facility cost would need to come from intensifying both cell culture and downstream unit operations so more product can be made in smaller equipment, and by eliminating the costs associated with large-scale equipment like custom equipment engineering, fabrication, installation, and validation and the additional facility cost for reinforcing floors for heavy equipment. If the equipment were small and inexpensive, we could use a catalog of standard sizes or even multiple pieces of standardized equipment instead of custom designing each piece of equipment to fit a particular process. Standardizing equipment would bring down the cost even more. This approach would require

collaboration across the industry between pharma manufacturers and equipment manufacturers. Once capital cost has been reduced, it will not matter so much to have a facility, that is, completely utilized, and depreciation will no longer be as significant a part of COGS. This will enable companies to build expansion space, increase the security of supply, distribute production geographically, and give room in the plant schedule to make further process improvements.

Inexpensive, standardized, smaller scale process equipment could be kept in inventory by suppliers, thus dramatically reducing lead-time. For example, a custom centrifuge has an 18-month lead-time and bioreactors and other large equipment have lead-times of a year. If new equipment could be purchased “off the shelf,” delivered in 2 weeks, assembled in a relatively small, unclassified room, and validated in another couple of weeks, the lead-time for increasing capacity could be shortened by years.

Further opportunities to reduce costs will come from the advanced strategies for the overarching control of integrated processes. The vision of autonomous control of self-correcting processes within a set design space, that incorporate real-time control and release should improve robustness and efficiency. This should reduce the burden for offline sample analysis and offline quality deviation investigations. The saved resources for operations, QA, and QC can be redeployed to support other projects within flexible facilities with expanding portfolios of multiple products. Ultimately the dramatic change in costs we propose needs a combined impact from capital, raw materials, consumables, and labor. This impact to lowering the total cost of ownership has been shown feasible by applying intensified and integrated processing (Pollard et al., 2016).

The amount of capital tied up in inventory for biopharmaceutical products is high because of the high unit COGS, long manufacturing cycle times, the need to buffer against process upsets, and in some cases the large amounts produced for validation. This is a problem, because as biopharmaceutical portfolios grow relative to small molecules, so does inventory, but the pharmaceutical industry is trying to reduce inventory to release cash for reinvestment. Manufacturing strategies relying upon single-use systems and scale-out can help minimize the amount of product manufactured during validation, which can reduce inventories required for new products. Further reductions in inventory can be accomplished by shortening the cycle time and improving reliability enough to give a high degree of confidence that all orders will be filled, which should permit a reduction of safety stock. Assuming manufacturing cycle times are on the order of 12 months and safety stock is about 6 months (Ma, 2011), a factory needs to be starting a batch 18 months before finished medicine reaches the distributor. This makes it difficult to respond to changes in market demand. A substantial improvement in reliability could enable a reduction in safety stock to 3 months. Reduction in manufacturing cycle time from 12 to 3 months would speed up supply chain velocity to a cycle time of 6 months (3 months to make and 3 months safety stock), which is much more responsive. This would allow multiproduct plants to adjust production to the pull of the market.

TABLE 2 Summary of workstreams and how they meet the program goals

Workstreams	Program goals				
	Improved control, robustness, and security of supply	Reduced capital and operating cost	Flexibility in volume and type of product	Faster product development and supply chain velocity	Sustainability
End-to-end control strategy	X			X	
Equipment/facility flexibility			X	X	
Next generation technology		X			X
Sustainability					X
Test bed	X	X	X		X

The vision will be achieved through industry leadership and integration of DS and DP expertise into five workstreams. The workstreams are end-to-end control strategy, equipment flexibility, next generation technology, sustainability, and a physical test bed to evaluate and demonstrate the technologies that are developed. Each workstream is responsible for creating and maintaining the strategy for their area and also scoping and starting up specific projects to implement the strategy. The overall vision and strategy are coordinated by a steering team of senior industry leaders. Table 2 lists the workstreams and program goals, showing which goals each workstream supports.

2 | NEXT GENERATION TECHNOLOGY

Enabling a true paradigm shift in the cost and speed of manufacturing biopharmaceuticals requires advances in technology and processing that may be considered still in their infancy today. Development and commercialization of truly disruptive technologies by equipment suppliers is slow as there is no guarantee of industry-wide acceptance and adoption across manufacturing organizations and thus, no guarantee of a return of revenue on their R&D investments. As a result, technology suppliers struggle to identify and meet the diverse demands of their consumers. By developing an industry consensus on specific technology needs and standards throughout the process, our consortium approach will increase the likelihood that what is developed will be used, which reduces risk for the suppliers.

The business drivers for the introduction of new processing methodologies and novel technologies vary widely across the industry. Many companies have leveraged various modeling approaches to identify current bottlenecks and cost sinks in their processes, as well as ways to improve their plant productivity, but these approaches are as diverse as their pipelines, and the models require specialized knowledge about cost estimation and detailed knowledge of the specific facility being modeled. This makes it difficult for technology developers to use these models and understand how to develop the technology for the best benefit.

The next generation workstream is tasked with identification of the technologies and methodologies necessary for the industry to reach the intermediate improvement objectives within the next 3–5 years (second generation) as well as the breakthrough approaches (third generation) to achieve the ambitious 2029 vision. The workstream is taking a multistage approach to the identification of the technologies for both the second and third generation processes through

1. Conceptual design of what second and third generation factories would have to look like, and how innovations would have to work together to achieve the vision
2. Process and economic modeling of potential new technologies to set the appropriate ambition and show how the vision can be achieved.
3. Technology scouting and prioritization based on results of the modeling and conceptual design.

4. Encouraging new research to increase the technical readiness level (Engel et al., 2012) of nascent process science or to develop technologies not yet invented.

Process and economic modeling will form the base for future technology selection as the program progresses. Considerable progress in developing a consistent basis for the comparison of productivity between traditional batch and first generation continuous unit operations such as the production bioreactor has been accomplished to date (Bausch et al., 2019; Yang et al., 2020), but extending this type of analysis to the full process using an agreed-upon methodology remains to be done. For second generation processes, for example, a robust modeling framework will be expected to provide insights into the introduction of a new technology or processing method through comparison to the benchmark process (first generation process discussed in Section 6) to enable strategic decisions on implementation and commercialization. Such decisions can be leveraged by the technology supplier companies to ensure they are prioritizing their own resources on those technologies with the highest likelihood of broad adoption. In contrast, the third generation models are expected to work backward from the desired final output targets (e.g., capital cost, COGS, footprint, throughput, sustainability, etc.) to develop technology requirements that can be easily understood and estimated by the people developing new technologies. We will develop a high-level conceptual design of a facility that would meet the requirements of our vision for throughput and ability to expand capacity rapidly. Since the unit operations in the facility would most likely be the products of disruptive innovations, we will have to treat them as black boxes. Example attributes of those black boxes are the productivity of a new host or the residence time and product concentration in a novel separation process. These requirements will be used to recommend research areas for further work. The expectation is that these novel technologies will need to be developed to a state where they can be fully commercialized and implemented at scale by 2029.

3 | CONTROL STRATEGY

The manufacturing control strategy for the production of a biopharmaceutical is crucial to ensuring consistent and robust process performance and product quality (International Conference on Harmonization Q11, 2012). In traditional batch processes, unit operations are usually considered discretely, each receiving its own set of control elements and acceptable ranges (A-mAb: A case study in bioprocess development, 2009). These unit-operation-level control strategies are then assembled to provide an overall control strategy for the entire process.

Integrated and continuous biomanufacturing processes offer exciting new opportunities for control strategies while simultaneously posing new challenges (Croughan et al., 2015; Farid, 2019; Warikoo et al., 2012). The control strategy workstream was created to explore and address these opportunities and challenges, with the

goal of proposing new control strategies optimized for biological processes of the future. In particular, the workstream will consider the following areas and their potential implications.

1. Real-time: Integrated continuous systems present more entry points for real-time or near-real-time process and product monitoring throughout the process flow (cell culture, purification, and formulation). As appropriately capable sensors are developed and tested, and accompanying control loops are designed, process control based on real-time monitoring can be implemented (Patel et al., 2018). Ultimately, this study will culminate in strategies for reduced post-hoc testing for specific attributes and potentially real-time release of drug substance and drug product.
2. Robustness: Control strategies for next-generation continuous processes should possess improved risk profiles relative to current control strategies. While the increased interdependencies between unit operations in a continuous process may bring more complexity, they also offer new opportunities for holistic approaches to control, which in turn could lead to increased reliability.
3. Automation and digitalization: A fully connected biologics manufacturing process in theory should require reduced manual intervention, but to realize this, increased adoption and greater sophistication of automation and digitalization will be required. This workstream aims to prioritize and then investigate automation strategies that will have the greatest impact on end-to-end control strategies (Feidl et al., 2020).
4. Integration into process development: Updated control strategies must be accompanied by updated process development methods to ensure that current process development timelines and resource requirements are equivalent or even better for integrated and continuous processes. Because such processes may require longer times between cleaning than their batch counterparts, this will require new and innovative development approaches to bioburden control.

4 | FLEXIBLE EQUIPMENT

Flexible facilities and equipment address several problems facing the industry. First, demand for pharmaceuticals is notoriously difficult to forecast and changes dramatically over the product lifecycle (Cha et al., 2013). As a result, the optimum production scale is usually either smaller or larger than what was designed for a given biopharmaceutical medicine. Second, traditional manufacturing plants are expensive and often under-utilized. It is not currently feasible to consolidate products operating at different scales into the same facilities to increase utilization, which would decrease both capital and operating cost. Finally, personalized and targeted medicines are moving the product mix to many small volume products. If facilities cannot quickly changeover from product to product, the changeover time can consume valuable plant time. Flexibility will also obviate the need to build or modify facilities to make new products in existing

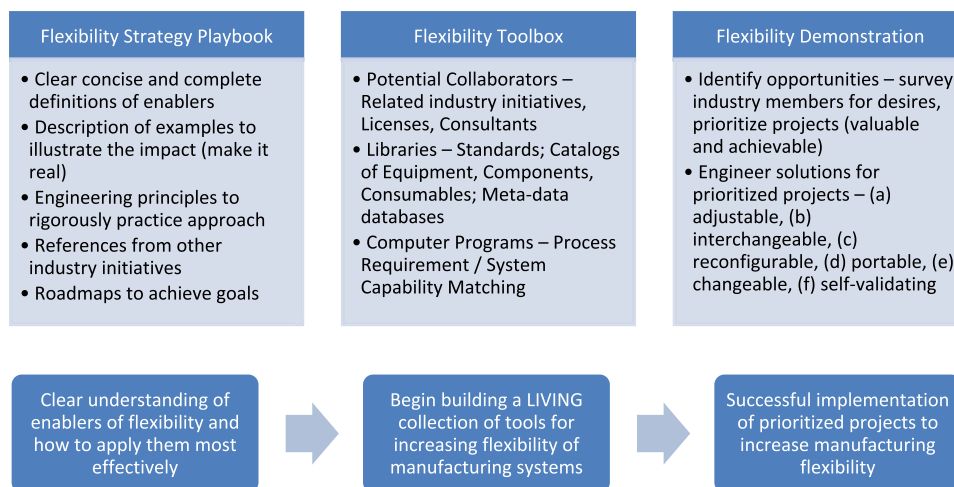


FIGURE 2 Three-pronged strategy of flexibility workstream: playbook, toolbox, demonstration

facilities, saving significant time as well as capital and operating cost (Shukla & Gottschalk, 2013).

To realize the vision of the NIIMBL process intensification program and meet the needs for flexible manufacturing described above, the flexibility workstream has committed to design, build, optimize, and support commercialization of manufacturing systems and components incorporating the following elements.

1. Adjustable production rate: Manufacturing systems and individual components are intentionally and holistically engineered with large production rate turndown ratios to enable a wide production capacity. Manufacturing plants are designed to allow ease of scale-up/down and scale-out/in within a given facility.
2. Component interchangeability: System is designed with appropriate connectivity standards (physical, data, power, etc.) such that components can be swapped with equivalent alternatives without need for customization or relying on specific vendors. Components are designed to be Internet of Things smart devices that are self-recognizable, allowing for true plug-and-play connectivity.
3. System reconfiguration: System is designed to allow individual modules (unit operations, components, etc.) to be added, removed, or connected in a different sequence without requiring customization.
4. System portability: System is designed to operate in a different environment or in a different location than it was initially created/validated in without requiring rework or customization. For example, a “pod” based suite is built and validated in one location, then transported to another location for manufacturing.
5. Rapid process change-over: Facility is designed to minimize the time between production campaigns and switching from production of one product to another in a multiproduct facility.
6. System self-validation: System is designed to autonomously and automatically perform component diagnostic and connectivity tests to ensure the system is configured to operate in a cGMP validated state. For example, the system will “check” to confirm that all components are compatible with the intended process as

the operator connects them and will confirm that all validation requirements are met before the start of a campaign.

Taken together, these elements would constitute a major step forward in improving the flexibility of biologics manufacturing. We envision a future where multiple small production lines are running simultaneously in a ballroom production suite, with each line comprised entirely of smart (Lu et al., 2016), off-the-shelf components to enable self-validation. These multiple production lines can be rapidly reconfigured between products to respond to changing demand. Finally, this manufacturing facility can be replicated in multiple locations, allowing for decentralized production responsive to the pull of the customer. The flexibility workstream has identified a three-pronged strategy to realize these ambitious goals, as outlined below and in Figure 2.

1. Establishing a unified Strategy Playbook that provides a clear understanding of enablers of flexibility and how to apply them most effectively. The playbook will include clear and concise definitions of the goals of the workstream and project roadmaps to achieve them. Creating a detailed roadmap in the playbook with options for different starting and end points will allow companies to easily create an action plan suited to their unique requirements.
2. Building a Flexibility toolbox to act as a “living document” of available tools to achieve flexibility goals. This toolbox will include a list of prior/ongoing relevant industry initiatives that can avoid redundancies (e.g., BPOG plug-and-play, ISPE Pharma 4.0, etc.), libraries of tools (standards, equipment, components, etc.), and software programs, among others.
3. Demonstrating the flexibility solution through a series of interconnected proof of concept projects designed to achieve the final vision. These demonstrations are envisioned to be performed in both member institutions and the NIIMBL test bed.

This strategic approach will be applied to a list of mutually exclusive and collectively exhaustive focus areas that define a

manufacturing system: hardware, single-use consumables, software, and data. By focusing on these key areas, with a clear set of goals in mind, and working collaboratively, we believe that we can dramatically improve the flexibility of biologics manufacturing and make a meaningful change in how we bring biopharmaceutical medicines to our patients.

5 | SUSTAINABILITY

The biopharmaceutical industry is making some progress through process intensification, to improve the productivity of integrated upstream and downstream processes (Bisschops & Brower, 2013; Brower et al., 2015; Jungbauer & Walch, 2015), shrink the manufacturing footprint, and reduce energy and water use (Pollard & Pralong, 2017). The complexity of achieving carbon-neutral bioprocessing has been highlighted by initial assessments (Budzinski et al., 2019; Pietrzykowski et al., 2013). For example, the first process mass intensity analysis showed bioprocesses to be heavily water intensive, where 90% of the mass was from water (Budzinski et al., 2019; Madabhushi et al., 2018) and 1 g of biological drug requires up to 65 L of water (Jungbauer & Walch, 2015). Lifecycle assessment (LCA) studies have demonstrated that single-use (SU) technologies provide additional environmental impact advantages over the traditional stainless-steel manufacturing, such as eliminating clean-in-place water usage, reducing HVAC energy usage through the use of closed systems and provide smaller footprint processing (Pietrzykowski et al., 2013). The LCA also showed that the SU

material contributed only a small part (<5%) of the total environmental impact, while the most influential impact was energy utilization with respect to the power generation source, geographical location, and facility size. One major drawback of SU technologies is their manufacture using resins from fossil fuel sources that are not readily recyclable. However, plastics strategies to reduce, recycle, and reuse are gaining momentum, with efforts to develop a circular plastic economy (European Plastic Pact, 2020). Examples include employing pyrolysis catalysts to process used plastics back to plastic monomer building blocks (Qureshi et al., 2020). Additionally, technology providers continue to drive innovative approaches to reduce packaging while maintaining shipping and storage protection of plastics, especially for cell culture bag films (Meherishi et al., 2019).

Nevertheless, despite these initial pioneering efforts, there remains a significant industry challenge to answer fundamental questions, such as the following.

1. How can we achieve carbon-neutral manufacturing?
2. How can we establish "Design for Sustainability" across all areas of bioprocess manufacturing—from raw material sourcing, technology R&D, process development, facility design, and manufacturing operations?
3. How do we develop circular economies for raw materials and consumables, such as plastics and packaging?

The sustainability workstream aims to tackle these challenges as an end-to-end perspective from raw material sourcing to manufacturing technology, process, and facility design, use, and waste recycling.

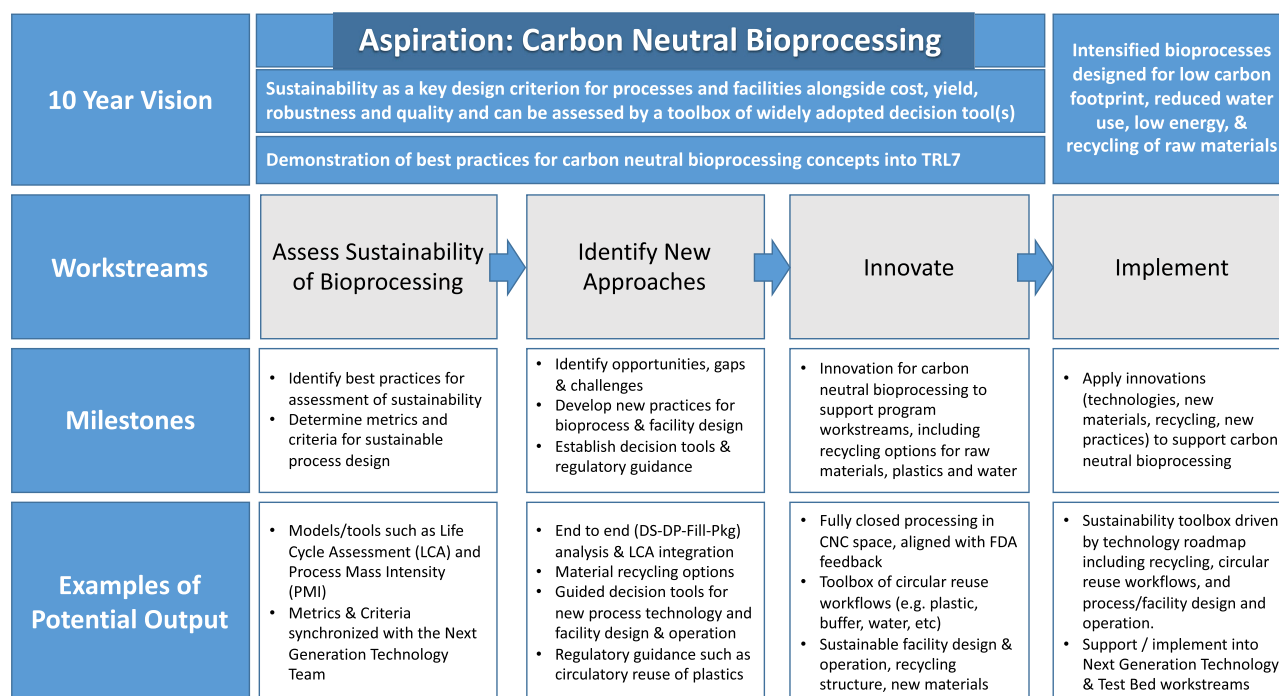


FIGURE 3 The sustainability workstream 10-year vision for carbon neutral bioprocessing, including milestones and potential output examples

Simplest Industry Platform

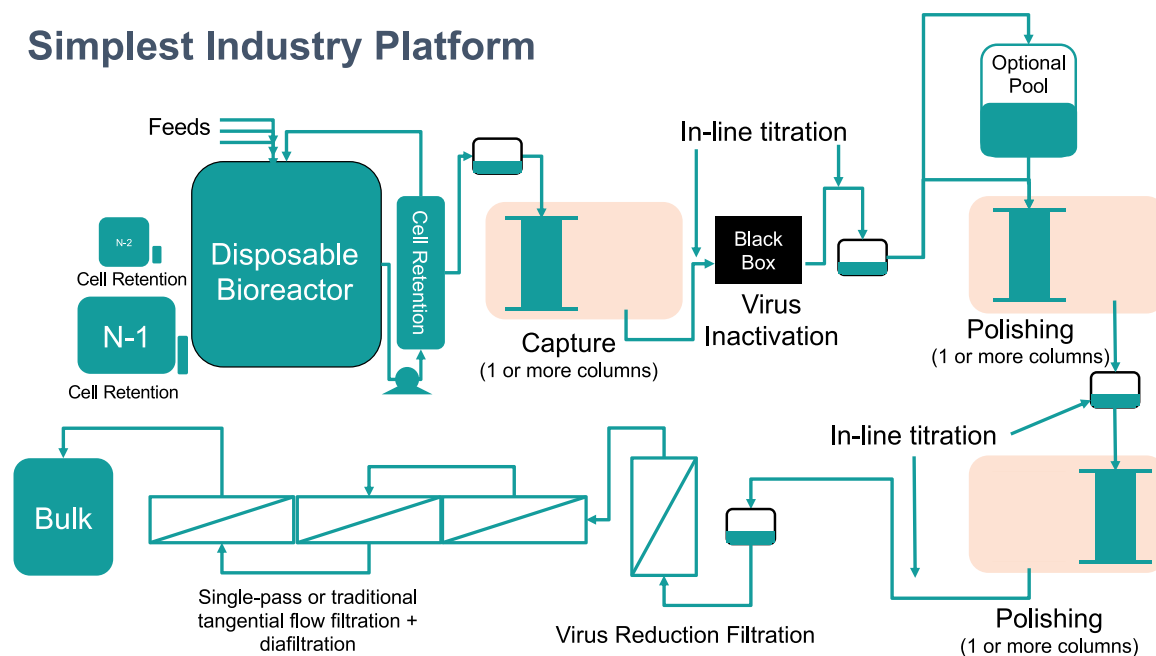


FIGURE 4 Consensus continuous platform process for test bed

Wherever feasible, the team aims to leverage existing tools (Pietrzykowski et al., 2013) and best practices such as from BPOG and BPSA (Barbaroux et al., 2020). The 10-year vision is outlined in Figure 3 and plans to establish carbon-neutral bioprocessing by the combination of new innovations of technologies, new materials, recycling, and new practices. Other key outputs include new decision tools and technologies to enable process developers to consider sustainability as a key design criterion for bioprocessing alongside cost, yield, robustness, and quality so that appropriate trade-offs can be made. New practices will establish an understanding and implementation of sustainability principles into the selection of raw materials, technologies, design of the process, facility, and operations. A toolbox of options will be implemented for recycling of waste materials that support a circular economy approach, including plastics. It is recognized this is a significant industry challenge that will require collaborators from academia, government, and industry to resolve the significant gaps. Examples include reducing reliance on petroleum-based raw materials, transitioning to biosourced products, establishing a single recycling stream for mixed plastic waste, and developing user-friendly tools for rapid sustainability assessment.

6 | TEST BED

To achieve the overall goals of the program, a new testing environment will be established to demonstrate novel technologies developed by the sister workstreams. Upon completion, the end-to-end manufacturing test bed will be utilized experimentally to evaluate integrated/continuous bioprocess platforms at the laboratory/pilot scale, targeting a throughput of up to 100 g monoclonal antibody per day. The capabilities of this test bed will need to reflect those desired not only for first generation intensification projects (i.e., those

intensified processes currently being commercialized), but also for second and third generation processes that represent the future state of manufacturing.

The workstream produced a process flow diagram for the lowest common denominator first generation processes (Figure 4) which is being used as a design basis for the test bed. Details on a number of first generation advanced processes have recently been publicly presented (Pinto & Brower, 2020; Xu et al., 2020). The NIIMBL platform process is representative of common features of many of these first generation processes. However, the test bed is envisaged to be a dynamic environment used to accelerate maturation and adoption of novel technologies developed with the NIIMBL consortium by providing early access to a fully integrated bioprocess and/or providing standard feedstocks for experiments to be performed at other locations. As such, the test bed will maintain a flexible foundation and automation architecture that will allow for updating over time with novel unit operations and control strategies as they emerge. To that end, the flexibility will be built into the test bed infrastructure to facilitate swapping in plug-and-play sensors and equipment as they become available (NAMUR, 2020).

In addition to housing the process space itself, the test bed will also provide for all typical process analytics, incorporate process analytical technologies (where appropriate), and facility infrastructure such as on-site buffer and media prep.

7 | SUMMARY

This paper lays out our vision for the industry and a framework for achieving it. Our next step is to work with our NIIMBL partners from academia, small companies, and government to develop and mature

the specific technologies and capabilities that will deliver the vision over the next decade.

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AUTHOR CONTRIBUTIONS

John Erickson leads the program and is the overall author. Shawn Barrett, Mark Brower, Lisa Connell-Crowley, Michael Coolbaugh, Eric Garr, Christopher Gillespie, Roger Hart, David Pollard, Irina Ramos, Gene Schaefer, and Jason Walther lead workstreams and/or wrote the sections describing their workstreams. John Erickson, Jeffrey Baker, Ciaran Brady, Ruben Carbonell, Tim Charlebois, Jon Coffman, Eric Fallon, Allison Haug, Roger Hart, Gregg Nyberg, Michael Phillips, David Pollard, Maen Qadan, Kelley Rogers, and Kelvin Lee contributed to the conception, design, and leadership of the program.

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REFERENCES

- A-mAb: A case study in bioprocess development. (2009). Retrieved from https://cdn.ymaws.com/www.casss.org/resource/resmgr/cmc_no_amer/cmc_amab_case_study/A-Mab_Case_Study_Version_2-1.pdf
- Barbaroux, M., Horowski, B., Mokuolu, S., Petrich, M., & Whitford, W. (2020). The green imperative: Part one life cycle assessment and sustainability for single use technologies in the biopharmaceutical industry. *Bioprocess International*, 18(6), 12–19. <https://bioprocessintl.com/manufacturing/single-use/the-green-imperative-part-one-life-cycle-assessment-postuse-processing-and-sustainability-for-single-use-technologies-in-the-biopharmaceutical-industry/>
- Bausch, M., Schultheiss, C., & Sieck, J. B. (2019). Recommendations for comparison of productivity between fed-batch and perfusion processes. *Biotechnology Journal*, 14(2):1700721. <https://doi.org/10.1002/biot.201700721>
- Bisschops, M., & Brower, M. (2013). The impact of continuous multicolumn chromatography on biomanufacturing efficiency. *Pharma Bioprocessing*, 1(4), 361–372.
- Broverman, I. (2017). FDA standard recognition process. Retrieved from https://www.nist.gov/system/files/documents/2017/02/06/17a_nist_slide_deck-fda-broverman.pdf
- Brower, M., Hou, Y., & Pollard, D. (2015). Monoclonal antibody continuous processing enabled by single use, *Continuous processing in pharmaceutical manufacturing* (pp. 255–296). Wiley. <https://doi.org/10.1002/9783527673681.ch11>
- Budzinski, K., Blewis, M., Dahlin, P., D'Aquila, D., Esparza, J., Gavin, J., Ho, S. V., Hutchens, C., Kahn, D., Koenig, S. G., Kottmeier, R., Millard, J., Snyder, M., Stanard, B., & Sun, L. (2019). Introduction of a process mass intensity metric for biologics. *New Biotechnology*, 49, 37–42. <https://doi.org/10.1016/j.nbt.2018.07.005>
- Cha, M., Rifai, B., & Sarraf, P. (2013). Pharmaceutical forecasting: Throwing darts? *Nature Reviews Drug Discovery*, 12(10), 737–738. <https://doi.org/10.1038/nrd4127>
- Croughan, M., Konstantinov, K., & Cooney, C. (2015). The future of industrial bioprocessing: Batch or continuous? *Biotechnology and Bioengineering*, 112(4), 648–651. <https://doi.org/10.1002/bit.25529>
- Engel, D. W., Dalton, A. C., Anderson, K. K., Sivaramakrishnan, C., & Lansing, C. (2012). Development of technology readiness level (TRL) metrics and risk measures. European Plastic Pact. Retrieved from <https://europeanplasticspact.org/>
- Farid, S. S. (2019). Integrated continuous biomanufacturing: Industrialization on the horizon. *Biotechnology Journal*, 14(2):1800722. <https://doi.org/10.1002/biot.201800722>
- FDA. (2018). Appropriate use of voluntary consensus standards in premarket submissions for medical devices: Guidance for industry and Food and Drug Administration staff. Retrieved from <https://www.fda.gov/media/71983/download>
- FDA. (2020a). Recognized consensus standards. Retrieved from <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm>
- FDA. (2020b). Standards and conformity assessment program. Retrieved from <https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/standards-and-conformity-assessment-program>
- Feidl, F., Vogg, S., Wolf, M., Podobnik, M., Ruggeri, C., Ulmer, N., Wälchli, R., Souquet, J., Broly, H., Butté, A., & Morbidelli, M. (2020). Process-wide control and automation of an integrated continuous manufacturing platform for antibodies. *Biotechnology and Bioengineering*, 117(5), 1367–1380. <https://doi.org/10.1002/bit.27296>
- Hahn, S., & Shah, A. (2020). Investing in advanced manufacturing to support public health preparedness. Retrieved from <https://www.fda.gov/news-events/fda-voices/investing-advanced-manufacturing-support-public-health-preparedness>
- International Conference on Harmonization Q11. (2012). Retrieved from <https://database.ich.org/sites/default/files/Q11%20Guideline.pdf>
- Jungbauer, A., & Walch, N. (2015). Buffer recycling in downstream processing of biologics. *Current Opinion in Chemical Engineering*, 10, 1–7. <https://doi.org/10.1016/j.coche.2015.06.001>
- Kelley, B. (2009). Industrialization of mAb production technology: The bioprocessing industry at a crossroads. *mAbs*, 1(15), 443–452. <https://doi.org/10.4161/mabs.1.5.9448>
- Lu, Y., Morris, K. C., & Frechette, S. (2016). *Current standards landscape for smart manufacturing systems*, National Institute of Standards and Technology. <https://doi.org/10.6028/NIST.IR.8107>
- Ma, Y. (2011). *Risk management in biopharmaceutical supply chains* (thesis). University of California, Berkeley, CA. Available from ProQuest Dissertations & Theses A&I data base. Retrieved from <https://escholarship.org/uc/item/70d7s6xw>
- Madabhushi, S. R., Gavin, J., Xu, S., Cutler, C., Chmielowski, R., Rayfield, W., Tugcu, N., & Chen, H. (2018). Quantitative assessment of environmental impact of biologics manufacturing using process mass intensity analysis. *Biotechnology Progress*, 34(6), 1566–1573. <https://doi.org/10.1002/btpr.2702>
- Meherishi, L., Narayana, S., & Ranjani, K. (2019). Sustainable packaging for supply chain management in the circular economy: A review. *Journal of Cleaner Production*, 237, 117582. <https://doi.org/10.1016/j.jclepro.2019.07.057>
- NAMUR. (2020). NAMUR open architecture. Retrieved from <https://www.namur.net/en/focus-topics/namur-open-architecture/>
- Patel, B. A., Gospodarek, A., Larkin, M., Kenrick, S. A., Haverick, M. A., Tugcu, N., & Richardson, D. D. (2018). Multi-angle light scattering as a process analytical technology measuring real-time molecular weight for downstream process control. *mAbs*, 10(7), 945–950. <https://doi.org/10.1080/19420862.2018.1505178>
- Pietrzykowski, M., Flanagan, W., Pizzi, V., Brown, A., Sinclair, A., & Monge, M. (2013). An environmental life cycle assessment comparison of

- single-use and conventional process technology for the production of monoclonal antibodies. *Journal of Cleaner Production*, 41, 150–162. <https://doi.org/10.1016/j.jclepro.2012.09.048>
- Pinto, N. D. S., & Brower, M. (2020). Wide-surface pore microfiltration membrane drastically improves sieving decay in TFF-based perfusion cell culture and streamline chromatography integration for continuous bioprocessing. *Biotechnology and Bioengineering*, 117, 3336–3344. <https://doi.org/10.1002/bit.27504>
- Pollard, D., Brower, M., Abe, Y., Lopes, A., & Sinclair, A. (2016). Standardized economic cost modeling for next-generation MAb production. *BioProcess International*, 14(8), 14–23.
- Pollard, D., & Pralong, A. (2017). Single use technology implementation to commercial manufacturing. In L. G. Jagschies, K. Lacki, & P. Galliher (Eds.), *Biopharmaceutical processing: Development, design and implementation of manufacturing processes* (p. 721). Elsevier.
- Qureshi M. S., Oasmaa A., Pihkola H., Deviatkin I., Tenhunen A., Mannila J., & Laine-Ylijoki J. (2020). Pyrolysis of plastic waste: Opportunities and challenges. *Journal of Analytical and Applied Pyrolysis*, 152, 104804. <https://doi.org/10.1016/j.jaap.2020.104804>
- Schaber, S. D., Gerogiorgis, D. I., Ramachandran, R., Evans, J. M. B., Barton, P. I., & Trout, B. L. (2011). Economic analysis of integrated continuous and batch pharmaceutical manufacturing: A case study. *Industrial & Engineering Chemistry Research*, 50(17), 10083–10092. <https://doi.org/10.1021/ie2006752>
- Shukla, A. A., & Gottschalk, U. (2013). Single-use disposable technologies for biopharmaceutical manufacturing. *Trends in Biotechnology*, 31(3), 147–154. <https://doi.org/10.1016/j.tibtech.2012.10.004>
- Warikoo, V., Godawat, R., Brower, K., Jain, S., Cummings, D., Simons, E., Johnson, T., Walther, J., Yu, M., Wright, B., McLarty, J., Karey, K. P., Hwang, C., Zhou, W., Riske, F., & Konstantinov, K. (2012). Integrated continuous production of recombinant therapeutic proteins. *Biotechnology and Bioengineering*, 109(12), 3018–3029. <https://doi.org/10.1002/bit.24584>
- Wilson, A. W., & Neumann, P. J. (2012). The cost-effectiveness of biopharmaceuticals: A look at the evidence. *mAbs*, 4(2), 281–288. <https://doi.org/10.4161/mabs.4.2.18812>
- Xu, J., Xu, X., Huang, C., Angelo, J., Oliveira, C. L., Xu, M., Xu, X., Temel, D., Ding, J., Ghose, S., Borys, M. C., & Li, Z. J. (2020). Biomanufacturing evolution from conventional to intensified processes for productivity improvement: A case study. *mAbs*, 12(1):1770669. <https://doi.org/10.1080/19420862.2020.1770669>
- Yang, O., Qadan, M., & Ierapetritou, M. (2020). Economic analysis of batch and continuous biopharmaceutical antibody production: A review. *Journal of Pharmaceutical Innovation*, 15(1), 182–200. <https://doi.org/10.1007/s12247-018-09370-4>

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