An Integrated Research, Education/Training and Industry Practice Framework to Accelerate the Innovation in Biopharmaceuticals Manufacturing and Eliminate Drug Shortage

Wei Xie, Jared Auclair, Jinxiang Pei

Abstract: The biomanufacturing industry is growing rapidly and becoming one of the key drivers of medicine and life science. Since biopharma manufacturing is based on living organisms, there exists inherent uncertainty in raw material supply, production process, storage and delivery, which leads to highly volatile outcomes. Even though rich data are collected during drug development and production processes, industrial practitioners tend to lack knowledge on big data analytics, risk analysis, real-time control and risk management for complex biopharmaceutical manufacturing system. This not only impacts public health safety, but also leads to high risk of failures, drug shortage and financial loss. To improve the industry practice, our interdisciplinary team composed of researchers and educators in Operations Research (OR) and biochemistry at Northeastern University, Biopharmaceutical Analysis Training Lab (BATL), and public health regulators collaborates to develop an integrated research, education/training and industry practice framework to promote biopharmaceutical manufacturing knowledge and skills for various levels of students and trainees. Basically, the research development in biomanufacturing is driven by challenges and critical needs in the industry. Then, interdisciplinary educational and training programs, including hands-on training and experiential learning, are introduced to seamlessly transform new knowledge to skilled workforce and industry practice. Therefore, the proposed framework can effectively facilitate the innovation of biomanufacturing industry.

Key Words: Academic, regulatory and industry collaboration; experiential learning; biomanufacturing innovation; continuous and flexible manufacturing; risk management and control

Section 1 Introduction

In the past decades, pharmaceutical companies invest billions of dollars in the research and development of new bio-medicines for the treatment of many sever illnesses, including cancer cells and adult blindness. The biomanufacturing industry is growing rapidly and becoming one of key drivers of personalized medicine and life science. It continuously grows in double digits annually in both sales and profits. The revenue will exceed $300 billion in 2019 over the entire industry, which grows by 10% vs previous year. The portion of biopharmaceuticals in total pharmaceutical revenue continues to expand, with more than 40 percent of overall pharmaceutical industry research and development (R&D) and products in the development pipeline being biopharmaceuticals and this percentage is expected to continuously increase in the future. The number of biomolecules increases threefold in the last decade, and they account for 40 percent of new launched pharma products in 2013 [4].

However, drug shortages in U.S. occurred at unprecedented rates over the past decade, which directly limits patient access to critical medicines and undermines health care. A majority of drug shortage is due to the lengthy lead time and manufacturing quality issues [3]. In this paper, we consider the traditional bio-drugs (i.e., biologic/biosimilar/vaccines) and the advanced emerging

therapies (i.e., gene therapy, cell therapy, and tissue engineering). Figure 1 illustrates the flow chart of biopharmaceutical supply chain from drug development to products being sold to patients. New drug development is composed a sequence of steps, including discovery, pre-clinical animal trials, FDA application, product and process development, three phases of clinical trials, FDA review and approval, and launch [3]. The clinical trials constitute an expensive part in the new bio-drug development, which takes 5-7 years to test the safety, efficacy and side effects. Then, the new drug application is submitted to the regulatory agency FDA for review. If approved, the drug becomes commercialized. In the biomanufacturing process, the drug substance or the Active Pharmaceutical Ingredient (API) production is based on living organism (i.e., bacteria, virus, animal or patient cell), which introduces several manufacturing challenges, such as batch-to-batch variability in terms of quality, production yield and cycle time. Biopharma manufacturing requires 9-12 months from raw materials sourcing to finished API [4]. Then, pharmaceutical necessities and excipients (e.g., binders, fillers, flavoring and bulking agents, preservative and antioxidants) are mixed with active drug substances to produce the formulated drug [14]. The formulation can take about 1-2 months. After that, another challenge of the biopharma supply chain is the cold-chain storage and transportation, which are complex and must be closely monitored to track temperatures along the route. For global pharma supply chains, the distribution network takes about 2 weeks to deliver finished goods to consumers. The pharmaceutical industry is highly regulated and the regulatory agencies (e.g., Food and Drug Administration (FDA)), involve in the whole biopharmaceutical supply chain to ensure the right drug is delivered to the right patient at the right time.

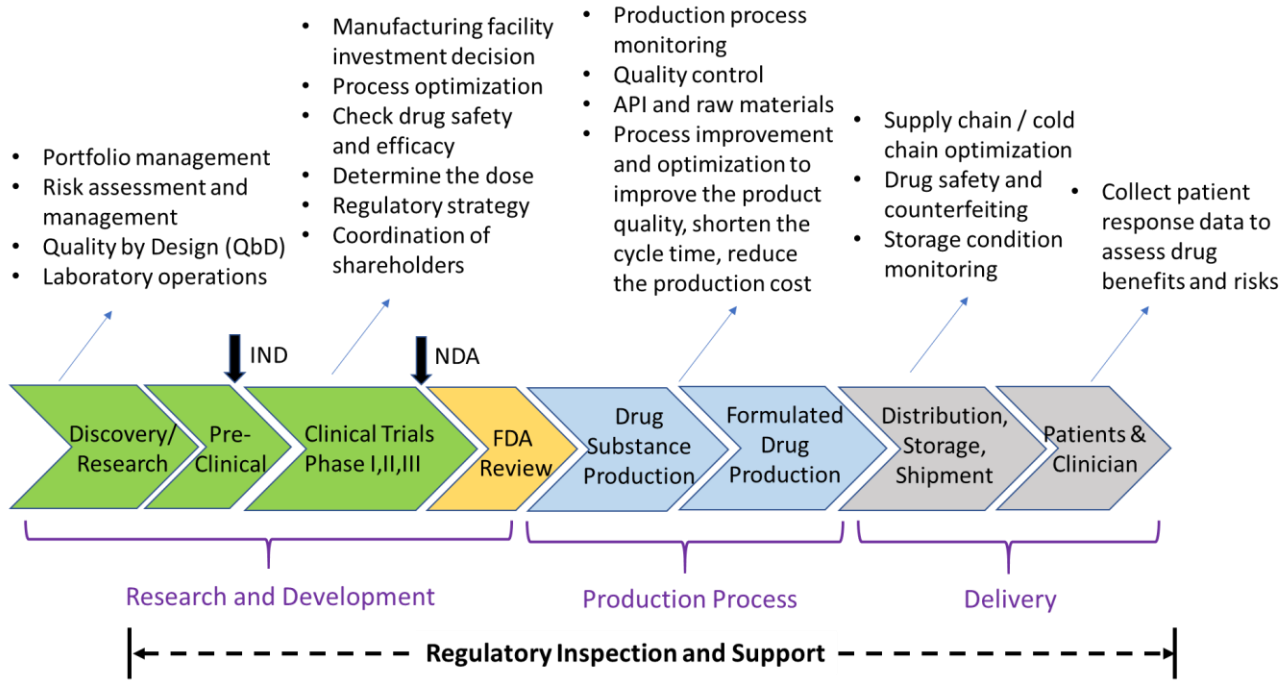

Figure 1 Flow chart of biopharmaceutical supply chain from drug development to patients (IND: Investigational New Drug; NDA: New Drug Application)

In the biopharma supply chain, stakeholders can be mainly categorized as follows.

1. Small and Medium-Sized enterprises (SMEs) for drug development: To hedge against the challenges and risks of drug development, many large manufacturers subcontract various phases of bio-drug research and development to SMEs, which could be startups from research labs with some unique expertise.
2. Primary Suppliers: They basically provide needed ingredients for Primary /Active Pharmaceutical Ingredient (API) Manufacturing below.
3. Primary Manufacturing/ Active Pharmaceutical Ingredient (API) Manufacturing: This involves cell culture and separation stages (i.e., fermentation and purification) with long manufacturing lead times. At the same time high inventory between stages in batch setting to buffer against supply variability and downstream demand volatility.
4. Secondary Suppliers: Since same drug substance can be converted into different final product forms such as injectables, capsules, tablets, syrups, and so on, secondary suppliers provide packaging materials for Dosage Formulation (DF) Manufacturing.
5. Secondary Manufacturing /Dosage Formulation (DF) Manufacturing: This takes quality-API from upstream players, then adds excipient materials followed by further filling and packaging processes to produce final products. Secondary manufacturing is usually separated from primary manufacturing to optimize total cost. Critically, the secondary and primary manufacturing are not well orchestrated in practice as they face different demand and supply variabilities.
6. Wholesalers/ distributors and retailers: they are middle layers in the supply chain networks who are responsible for effectively and efficiently transporting final products to end-users.
7. Clinician and patients: they are end users of pharmaceutical products and services.
8. Regulators: As pharmaceutical industry is a highly-regulated one where FDA and other regulators play critical roles that we normal don't see in other industry sectors. They get involved in every stage of the pharmaceutical supply chain and also the entire life cycle of pharmaceutical products.

Among the major challenges, product- and process-related complexity in biopharma is frequently observed. The complexity can arise from different sources, such as complicated SKU portfolio in global markets, production material and versions, both noticeable supply, production & demand uncertainty, regulatory restrictions and the coordination of many stakeholders [4,13]. In this paper, we focus on the biopharmaceutical development and production processes. The complexity has resulted in slow, inefficient biomanufacturing processes and led to longer development and production cycle times than necessary. In addition, since biomanufacturing is based on living organisms, it introduces large batch-to-batch variation in terms of quality, production yield, processing time.

Therefore, driven by the challenges and critical needs in biomanufacturing industry, in this paper, we introduce an integrated research, education/training and industry practice framework to move forward the industry practice through academic/regulatory/industry collaboration, facilitate the innovation in biopharmaceutical manufacturing and eliminate the drug shortage.

Section 2 Integrated Research, Education/Training and Industry Practice Framework

To improve the stability of bio-drug quality, increase the efficiency of the biomanufacturing process, shorten the time to market, and eventually eliminate the drug shortage, in this paper, we propose an integrated research, education/training and industry practice framework to facilitate the knowledge innovation and seamlessly transform it into the skilled workforce, ultimately becoming standard regulations and industry practice. This framework includes an iterative process as shown in Figure 2. Basically, the research development for biomanufacturing process management is driven by real challenges. The new developed methodologies and technologies should meet the critical needs of patients and the industry expectations. Then, the research innovations are transformed and incorporated into education and training to advance the industry and regulatory workforce. At the same time, both research and education/training development should account for the adoptability of industry practice and workforce background. That means we should explore the underlying biotechnology domain knowledge to make the decision making for complex biopharmaceutical supply chain reliable and interpretable.

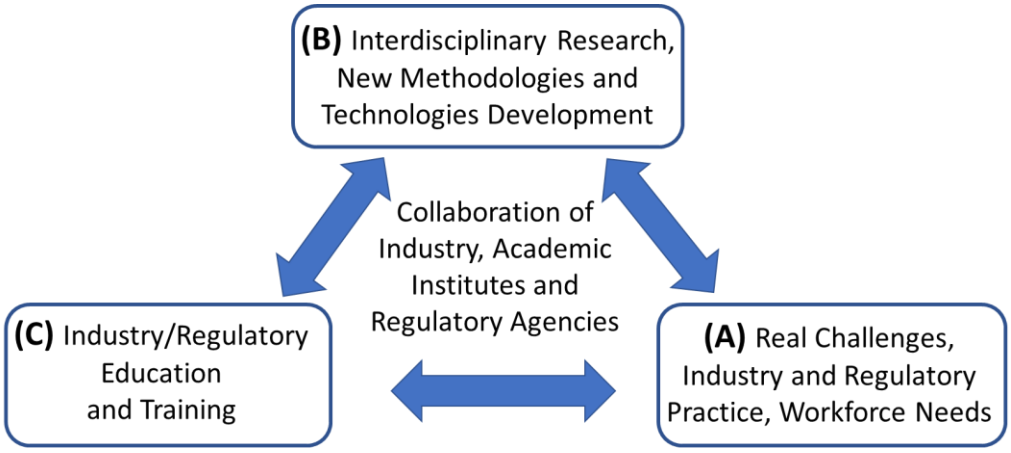

Figure 2 The illustration of integrated research, education/training and industry practice framework

Specifically, the iterative process of integrated research, education/training and industry practice framework in Figure 2 includes the main components as follows.

From Industry Challenges (A) to New Research Development (B): The new methodology development is driven by the industry challenges in order to meet patients' needs. Unlike the traditional small-molecule chemical drugs, bio-drug production is based on large-molecule biologics comprised of complex structural elements and undergoes post-translation modifications (PTMs). There exist various key challenges in the biopharmaceutical manufacturing as discussed in Section 2.1, such as complex development and production processes including many sources of uncertainty. The current industry workforce lacks advanced understanding of biologics production process and risk/science-based knowledge/skills to manage and operate complex integrated biomanufacturing process, which leads to a high risk of failure, regulatory delays, financial loss and drug shortages. In our team, interdisciplinary researchers in Operations

Research and biochemistry collaborate to develop innovative methodologies and technologies to solve these critical challenges.

From Research Progress (B) to Industry and Regulatory Feedback (A): The development of new methodologies and technologies should consider their performance in the real operating conditions and also the adoptability by the industry workforce. Thus, after the introduction of new methodology and technology, we will facilitate collecting the feedback from regulators and industry participants, which will inform the next round of research to update them. Then, through the collaboration with industry partners, we will test the performance of proposed approaches in the real operating environments and validate it by using the real problems.

From Research Progress (B) to Education/Training (C): Innovation in research guides us in upgrading training and education. We actively transform new developed research methodologies to education and training. First, research progress will be used to redesign the education and training programs. Second, we will disseminate our results to a wide audience, through publications, conference presentations, outreach education, and a project website. Third, we will develop the education software and online education video to facilitate both online and on-ground experiential learning.

From Education/Training (C) to Research Progress (B): The feedback from education and training experiences provides further improvement on our methodologies and education program/software design so that it can be better adopted by students and workforce. In addition, since the participants can use the real data and problems from their companies during the training, the education/training could potentially evaluate the performance of new proposed methodologies/technologies. It could accelerate the collaboration between academic and industry, which can further drive the next round new research development.

From Education/Training (C) to Industry Workforce (A): Insights and knowledge of science- and risk-based biomanufacturing management methodologies and technologies are used to educate industrial and regulatory practitioners through training programs (e.g., BATL and ICH training program), which can quickly transform the research progress to facilitate the innovation of workforce in the biopharmaceutical manufacturing industry.

From Real Problems and Workforce (A) to Education/Training Development (C): Real industry problems and real-world data are used in the education and training process, which can also validate the performance of new technologies with broad datasets and problems. Furthermore, the workforce background should be fully considered in the education process preparation. Different levels of courses and hands-on training are developed for trainees with diverse backgrounds and needs.

Since research development should be driven by industry-wide problems, we first describe the challenges and needs from biomanufacturing industry in Section 2.1. Then, we present the critical needs and expectations for new methodologies and technologies from biomanufacturing industry and regulatory agencies in Section 2.2. Accounting for the uniqueness of biomanufacturing, we discuss the promising research studies which could lead to the technology innovation overcoming these challenges and address the industry needs in Section 2.3.

2.1 Challenges of Current Biopharma Industry Practice

While the biomedical technology is on the cutting edge of innovation, the development and production of living organisms using such technologies are faced with various unique challenges.

- Complexity: Firstly, the biomanufacturing becomes more and more globalization. Roughly 80% of active pharmaceutical ingredients (API) and 40% of finished drug products are imported into the U.S. from overseas. Manufacturers in China and India are the key source. There is increased use of multiple regional/national clinical trials. Secondly, new drugs (e.g., advanced therapies, or cell and gene therapies) require more advanced manufacturing considerations and they tend to become more and more "personalized." For example, the first CAR T-Cell therapy, KymriahTM(Novartis), approved in 2018 by the US FDA [4], requires that each therapy to be manufactured in each individual patient's own cells, on demand. Thirdly, there could exist many commercial and clinical drug products with totally different demand patterns sharing the same testing, production, cold-chain storage and raw materials. Fourthly, to hedge against risks, most large pharmaceutical companies subcontract various phases of biomanufacturing research and development to small and medium-size enterprises. The coordination with many stakeholders becomes more challenging.
- Long lead time and large inventory: The average lead time of a new biopharmaceutical drug development is about 10 years. Each phase of clinical trials takes about 1-2 years. Biopharma manufacturing requires 9 to 12 months from raw materials sourcing to the finished API and requires another 2 to 3 months for quality testing and release [4]. The biopharma companies hold on average 290 days of inventory [4].
- Highly variability: Both bio-drugs produced in living organisms and raw material supply have significant variation. The production process and storage conditions also impact the drug properties or critical quality attributes. Thus, there exists large batch-to-batch variability, which could be induced by hundreds of factors. In addition, many sources of uncertainty in drug development and production (e.g., clinical demand and contamination) are hard to predict.
- Rapid changes in technologies, processes and regulatory environment: Biomanufacturing is a high-tech industry. Even though the lead time is super long, the expected product life cycle is short (i.e., 1.5-3 years) and bio-drugs tend to have high marginal value (the average cost per batch exceeds $1 million [4]). Thus, even though there is large batch-to-batch variation and hundreds of factors could impact on drug quality, the amount of data, say the number of batches, is often very limited.

Facing with these new and increasingly complex challenges, the current workforce in biomanufacturing industry lacks advanced knowledge and skills for analyzing and managing complex dynamic biomanufacturing process with high uncertainty, which leads to a high risk of failure, regulatory delays or lack of standard regulations, financial loss and drug shortages.

2.2 Industry and Regulatory Needs and Expectations for Technology Innovation

To overcome the challenges described in Section 2.1, here we discuss industry and regulatory expectations on technology innovations [1,2,6,8,9-12,15,16], which can support the next generation of biomanufacturing process and ensure the consistent supply of high-quality bio-

drugs. Specifically, we describe main technology needs for biomanufacturing system management, which are closely connected with each other.

- Quality by Design (QbD) and Integrated Process: QbD is defined by the International Council for Harmonisation as "a systematic approach to pharmaceutical development and manufacturing with defined objectives, emphasizing product and process understanding and process control based on sound science and quality risk management" (ICH-Q8R2) [7]. QbD is driven by the needs of the patient and the specific quality attribute requirements of this product linking to safety and efficacy. During the design and development of bio-drug, we build quality into the process, and consider product in a systematic, science- and risk-based manner. It means that the drug development accounts for the complexity and challenges of production process, storage, delivery and patient's usage. Thus, we need to consider the impact of various sources of uncertainty (i.e., selection of raw materials and specification of process parameters) on the product quality and critical quality attributes. Thus, a key component of the quality-by-design is the implementation of process analytical technology.
- Process Analytical Technology (PAT): PAT has been defined by FDA as a mechanism to design, analyze, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP) which affect Critical Quality Attributes (CQA) [8]. The process is the product. The variability introduced by raw materials interacting with the inherent variability in process impacts the product quality. Process analytical techniques are important to provide a complete understanding of underlying complex interactions and find the critical sources of variability. Then, we can identify the critical raw material attributes and process control parameters and also specify their ranges. Thus, the objective of PAT is to understand the processes by defining their CPPs and then accordingly (online) monitor and control them so that we can reduce over-processing, enhance consistency, minimize failures and ensure on-time drug delivery.
- Continuous and flexible manufacturing: Built on a thorough production process understanding from PAT, continuous manufacturing efficiently integrates upstream cell culture and downstream purification, and incorporates a surge vessel (for perfusion) and flow/time balancing [9-11]. It eliminates non-value-added unit operations (e.g., shutdown, cleaning, quality assessment/clarification testing, intermediate hold steps, startups and turnaround between batches). Compared to the classical batch-based production, continuous manufacturing removes manual handling of products, facilitates the real-time monitoring and testing, and allows better dynamic control in production process. By implementing the coherent and optimal decision making for the entire bioprocessing, we can improve the consistent quality, shorten the production cycle time, increase the process throughput/yield and flexibility, and reduce cost and inventory.

2.3 Research and Education Driven by Industry and Regulatory Needs

The continuous and flexible biomanufacturing requires highly skilled workforce. The academic development for systematic biopharmaceutical manufacturing risk management is still in its infant stage. Driven by the industry and regulatory needs described in Section 2.2, we list the

critical advanced knowledge and professional skills for new generation of workforce, which can facilitate the innovation in biopharmaceutical manufacturing.

Big data analytics and risk analysis: Since there are a lot of sensor data monitoring and controlling the production process, to support Process Analytical Technology development, new big data analytics and risk analysis are needed to improve the understanding of underlying complex process and interactions (e.g., the underlying physical mechanics causing the interdependence of raw material attributes, production process parameters, and bio-drug properties or critical quality attributes related to safety and efficacy). These methodologies explore the underlying interdependence between operating conditions and critical quality attributes (CQAs) of raw materials/Active Pharmaceutical Ingredients (API)/excipients/in-process materials/drug product, identify main sources of variation, and quantify their impact on product quality. Thus, big data analytics and risk analysis can shed a clear light on where there is a potential to reduce risk and suggest the efficient mitigation action.

Design of Experiments (DoE): Hundreds of factors, such as raw materials attributes and operating conditions occurring in the production process (including both critical process parameters and uncontrollable variables, e.g., contamination), could impact the product critical quality attributes and the production cycle time. Since there is the high-dimensional design space and each experiment is expensive, guided by the updated knowledge of production process (i.e., PAT) learned through big data analytics and risk analysis, new design of experiments needs to be developed in order to efficiently and quickly locate the requirement for critical quality attributes and find the optimal specification for critical process parameters to control the impact of risk, guarantee the consistent drug quality and improve the production efficiency.

Artificial Intelligence (AI) and End-to-end Biomanufacturing Risk Management for Real-Time Production Process Control: To facilitate the development of continuous and flexible manufacturing, new AI and end-to-end biomanufacturing risk management need to be developed. These methodologies can support the optimal real-time monitoring and systematically controlling the complex biomanufacturing process so that we can response quickly to any operation error and uncertainty occurring in raw material attributes and production process, speed up the time to market/patients, improve the quality consistency, and reduce the cost. For the gene and cell therapies, the production process design and control strategy depend on the attributes of cell from patient. Typically, patients need these therapies are very ill. Any long lead time (or delay) and drug quality deviation could put some patients at great peril. Thus, advanced AI and end-to-end biomanufacturing risk management methodologies could provide real-time precise control on complex production process that simultaneously manufactures many personalized bio-drugs.

Once introduced, we will validate proposed solution methodologies experimentally and then test their performance in real operating environments. After that, the validated new methodologies will be transformed into the education and training to prepare the skilled workforce for new generation of biopharmaceutical manufacturing.

Section 3 An Implementation Platform to Facilitate Biomanufacturing Innovations

Based on the integrated research, education/training and industry practice framework presented in Section 2, in this section, we first describe the corresponding platform as shown in Figure 3 to facilitate the academic, regulatory and industry collaboration so that we can achieve our goal and also the NIIMBL's mission: "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." Here, NIIMBL stands for the National Institute for Innovation in Manufacturing Biopharmaceuticals. Then, we describe our on-going works related to moving forward methodology/technology innovations and providing progressive experiential training/education for workforce upgrading.

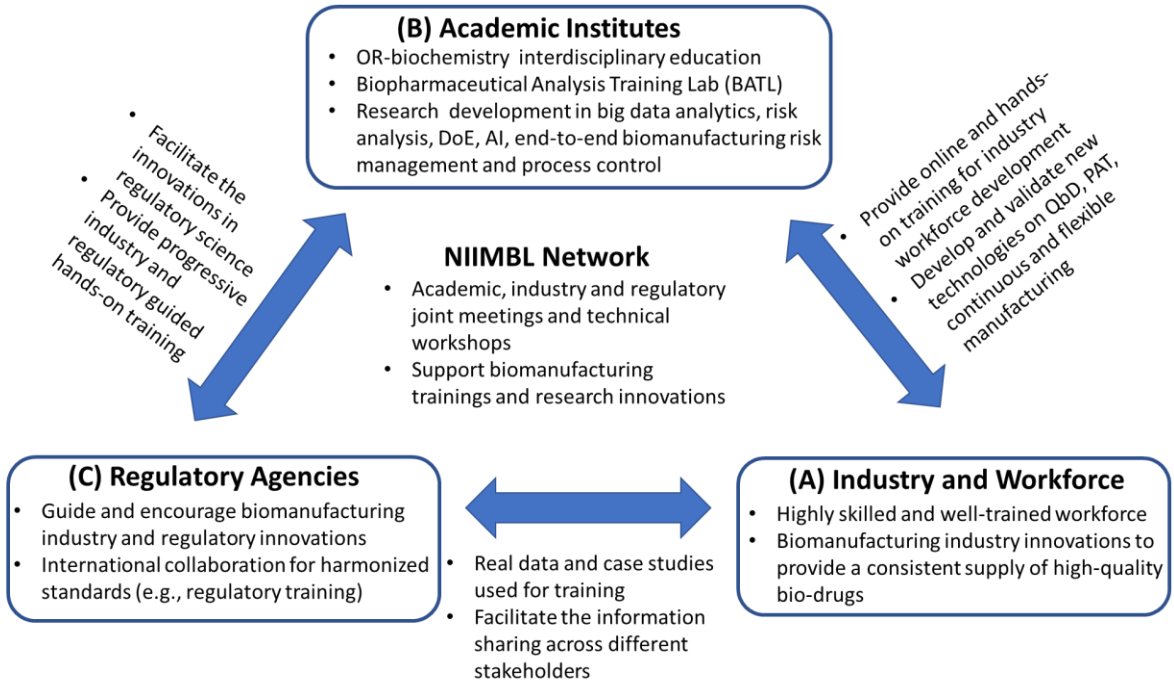

Figure 3 An integrated platform for academic, regulatory and industry collaboration (NIIMBL: National Institute for Innovation in Manufacturing Biopharmaceuticals; BATL: Biopharmaceutical Analysis Training Laboratory)

3.1 An Academic, Industry and Regulatory Collaboration Platform

Figure 3 illustrates the implementation platform to facilitate the academic, regulatory and industry collaboration. It is centered around NIIMBL composed of 113 members from academic institutes, regulatory agencies, biomanufacturing industry and workforce representatives. The NIIMBL community focuses on the technologies and training programs to accelerate the biopharmaceutical manufacturing innovation, which can strengthen our economy and improve health outcomes for all patients. We have regular meetings and technical workshops to highlight industry-wide industry needs for technology innovation. It promotes the academic, industry and regulatory teaming and collaborations. Thus, the NIIMBL community serves as an important network to discuss the industry critical needs and share the research/training experiences and

results. In addition, NIIMBL also provides the project funding support for developing the urgent and critical technologies. It also facilitates the deployment of solution methodologies for industrially relevant manufacturing challenges.

Based on the information of industry needs (see Section 2.2) from NIIMBL and our industry partners, we develop new methodologies on big data analytics, risk analysis, DoE, AI and end-to-end biomanufacturing risk management and process real-time control; see Section 2.3. These methodologies will be validated by real data and real-world problems. They are further improved based on the feedbacks from our regulatory and industry collaborators. Then, the methodology improvement can facilitate the technology innovations on QbD, PAT, continuous and flexible manufacturing.

According to the FDA, 80% of deviations in manufacturing is caused by human error and lack of process knowledge. We estimate that appropriate training in theory and practice, and continuous (re)training, can reduce this error by 50% or more. It is critically important to nucleate the talent/knowledge, skills, education and training to meet increasingly complex biomanufacturing and regulatory demands. Thus, in the platform, new developed methodologies and technologies (e.g., production process risk analysis, dynamic control on integrated biomanufacturing process) will be transformed to provide progressive interdisciplinary OR-biochemistry education and Biopharmaceutical Analysis Training; see Section 3.2. We provide many types and multiple-levels of courses and hands-on training for industry and regulatory trainees with different background, including those who are entering the workforce and those in need of additional skills or advance in the workforce.

3.2 Relevant Research, Training/Education and Industry Collaboration Activities

Here, we present our on-going works relevant to the proposed platform in Figure 3.

3.2.1 Biopharmaceutical Manufacturing Industry Innovation - NIIMBL Community

NIIMBL is composed of stakeholders from all areas of the biopharmaceutical. In the past two years, it has funded 44 technology and workforce projects with a total value of nearly $45 million dollars to support biopharma industry and workforce innovation. In the year 2018, NIIMBL industry partners graciously hosted four technology workshops focused on pertinent topics in biomanufacturing: Process Innovations for biologics; Analytical Technology, Modeling, and Control; Cell Therapy Manufacturing Innovation; and Adventitious Agent Detection Methods and Controls.

NIIMBL has 49 Technical Activity Committee (TAC) voting members (with 11 from industry and 3 from nonprofit organizations). The remaining TAC members come from 34 academic institutions (3 from IE related fields and 31 from chemical engineering and pharmaceutical science). The responsibility of the TAC includes ensuring that the relevant and high-quality projects are being pursued to achieve the NIIMBL mission. Thus, the main focus areas for the TAC include: (1) applied research and technology, (2) identifying and reducing barriers to commercialization; (3) proposing actions to enable rapid innovation and commercialization; (4) initiating Project Calls and evaluating the proposals.

The authors, Dr. Jared Auclair (from biochemistry) and Dr. Wei Xie (from Operations Research), serve as Northeastern representative Technical Activity Committee (TAC) for NIIMBL. We collaborate to develop new biomanufacturing technologies and training programs to accelerate the biopharmaceutical manufacturing innovation. We are also actively involved in the NIIMBL activities. Jared and Wei will host the 2019 NIIMBL Technology Workshop I – Process Intensification in April at Northeastern University. In this workshop, we focus on Process Intensification, including continuous/integrated processing technology development, PAT, high-throughput technologies and process validation. The workshop serves as a platform to highlight industry needs for technology innovation. It also offers opportunities to promote teaming across the NIIMBL ecosystem to accelerate the development and deployment of real-world solutions for relevant manufacturing challenges.

3.2.2 Inter-disciplinary Research Development for Methodology and Technology Innovations

Driven by the challenges and industry needs, we are developing new methodologies (i.e., big data analytics, risk analysis, DoE and AI) for end-to-end biomanufacturing risk management and real-time production process control, which can facilitate QbD, PAT, continuous and flexible manufacturing. Operations research (OR) typically focuses on finding the optimal design, planning and operational decisions for complex stochastic systems, such as integrated biopharmaceutical manufacturing system. The OR methodology development for biopharmaceutical supply chain is still in its infancy [7].

State-of-the-art OR analytical models and methodologies for biopharmaceutical operations and supply chain management have several key limitations; see the detailed description in [7]. First, the existing OR approaches introduced for biomanufacturing still focus on developing general methodologies, and they do not fully explore the pharmaceutical biotechnology domain knowledge (e.g., the underlying physical mechanics causing the interdependence of raw material quality, production process, and bio-drug properties in safety and efficacy). This limits OR methodology performance as well as its adoption in real applications. Second, as far as we know, existing approaches tend to focus on a certain (limited) part of the biomanufacturing system and there is no appropriate and reliable end-to-end system management framework guiding coherent bio-drug development and manufacturing. Third, there exists a large gap between industry practice and academic research on biomanufacturing risk management.

Considering the key challenges described in Section 2.1, authors in [7] point out simulation-based risk analysis and simulation optimization for finding the optimal risk mitigation action have great promise for addressing the problems in the biopharmaceutical industry. Built on previous works on simulation, data analytics and stochastic optimization, we explore biotechnology domain knowledge and develop big data analytics, risk analysis, DoE and AI methodologies, which can support QbD, continuous and flexible manufacturing. They can overcome these limitations of existing OR approaches.

3.2.3 Academic/Industry/Regulatory Collaboration for New Methodology and Technology Validation and Upgrading

For new proposed methodologies on big data analytics, risk analysis, DoE and AI for end-to-end biomanufacturing risk management and real-time production process control, we first evaluate

their performance in the simulation and lab environments (i.e., BATL end-to-end biomanufacturing process in Figure 5). Then, we select and convene focus groups comprised of industry practitioners and regulators to explain new proposed methodologies. In this focus group we will facilitate feedback from the participants, which will inform the next round of research to update the methodologies. The participants retrospective experience, and available data from their companies, will be used to validate or refine the proposed methodologies. This iterative process connects inter-disciplinary operations research and biochemistry stakeholders (academia, regulators, and industry).

At the same time, this approach will acquaint trainees to the concepts of highly customized OR and begin to apply the proposed state-of-the-art biomanufacturing methods to the biotech industry. It will help us learn from regulators and industry what gaps may exist in our approaches and how efficiently they can be adopted in the industry practice, which informs updates to our methodologies. This iterative process provides a robust opportunity to enhance our methodologies in a practical way. It also helps create a user-friendly tool to both regulatory and industry workforce.

3.2.4 Interdisciplinary OR-biochemistry Education

Dr. Wei Xie has started to redesign operations research (OR) core courses, including graduate and undergraduate levels Discrete-Event Simulation and Analysis, to better prepare students with the interdisciplinary knowledges needed by highly skilled biomanufacturing workforce. In Spring 2019 semester, we integrate research outcomes (i.e., systematic uncertainty quantification, sensitivity analysis, DoE, simulation-model-based biomanufacturing risk analysis) into courses.

First, we increase the interdisciplinary OR-biochemistry knowledge in the course materials. We cover the methodologies, including risk analysis, uncertainty quantification, sensitivity analysis, and design of experiments for complex stochastic system. We also discuss complex high-tech manufacturing risk management. Most challenges listed in Section 2.1 are shared by biopharmaceutical and semiconductor manufacturing management, which are two course project topics assigned to students.

Second, real case studies are used in the class to build the students' skills on data analytics, risk analysis, DoE, and simulation optimization for integrated biomanufacturing process decision making. For example, in the class, we study an end-to-end biopharmaceutical manufacturing system producing various antibody bio-drugs. The stochastic system has the flowchart shown in Figure 4. The production process includes steps, including (1) pre-culture and expansion, (2) fermentation and harvest, (3) centrifugation, (4) chromatography/purification, (5) filtration, (6) quality control, and (7) fill and finish. We consider various sources of uncertainty, including raw materials, process operation parameters and other uncontrol variables, which could impact on the critical quality attributes, such as protein and impurity levels. We also guide students to incorporate the bio-technology knowledge into simulation modeling for biomanufacturing process, such as how the raw material attributes and the critical process parameters (i.e., temperature and operating time) impact on the critical quality attributes of intermediate and final products.

Third, hands-on experiences (i.e., course project) can improve students' experiential learning on using stochastic simulation for risk analysis and developing DoE to quickly find the optimal upstream and downstream critical process parameter values. This learning experience can improve students' understanding on the production process, identify sources of uncertainty and quantify their impacts on product quality. Both undergraduate and graduate simulation course projects are motivated by real biopharmaceutical manufacturing case studies. Undergraduate students are required to use the simulation and data analytics software (i.e., Arena and @Risk) to study how the interactions of CPPs and CQAs impact on the system performance, including batch-to-batch variation in production cycle time, protein and impurity levels. For graduate students, they need to develop Python code to conduct simulation experiments and DoE. We also assign students open-ended tasks, such as risk analysis and system control for integrated production process to find where there is a potential to reduce risk and what is the mitigation action. This creates a real problem-solving environment.

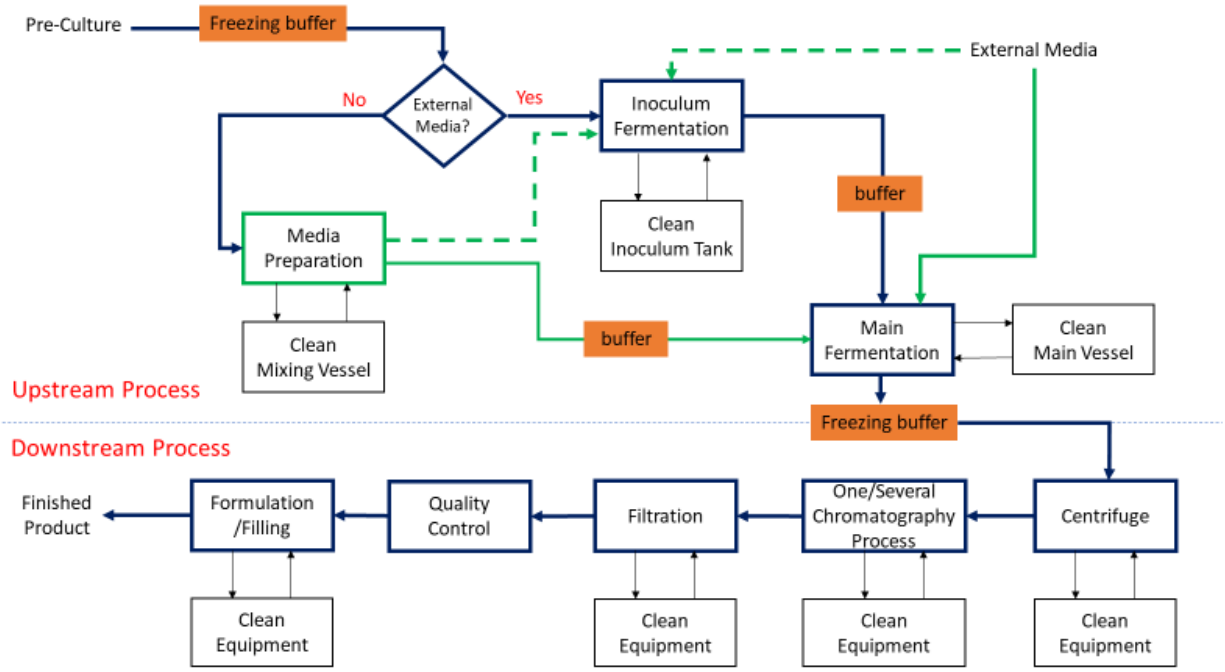

Figure 4 The flowchart of a simulation model for an end-to-end Biomanufacturing system producing multiple antibody bio-drugs that may or may not require external media

3.2.5 Biomanufacturing Experiential Learning for Workforce Development – BATL

As a critical training node in biopharmaceutical manufacturing community, Northeastern Biopharmaceutical Analysis Training Laboratory (BATL) directed by Dr. Jared Auclair provides training throughout an individual's career from high school through advanced training; which starts right from the beginning with theory and practice training. It offers many types of programs including: an APEC approved course in biotherapeutics and Biosimilars; an ICH trusted-training program in Drug Stability; Intact Mass Analysis, Glycoproteins, & Quality by Design; and a hands-

on graduate course in Protein Mass Spectrometry, to name a few. Since March 1, 2017, when BATL was recognized as an APEC Center of Excellence in Biotherapeutics, approximately 625 students have been trained through BATL programming. The training is comprised of online training, didactic lectures, chalk talks, case studies, design tree exercises to encourage critical thinking, and hands on experimental lab/manufacture work. Learners have spanned Northeastern undergraduate and graduate students, industry workers, and national and international regulatory professionals.

The objectives of BATL training include: (i) creating a holistic resource for training and education in the burgeoning field of biomanufacturing, with a novel focus on curricula that integrates manufacturing training with real-time analytics training; (ii) meeting clear demands in the local biopharmaceutical industry for trained quality control and regulatory experts; (iii) offering workforce development opportunities for biotech and biopharma workers as well as local high school, college and graduate students; (iv) addressing a global need for convergence and training in regulatory practices related to quality and biologics; and (v) generating opportunities for improvements and innovations in training and procedural efficiencies in biotherapeutics manufacturing, especially related to advanced (cell) therapies and real-time analytics during the manufacture process.

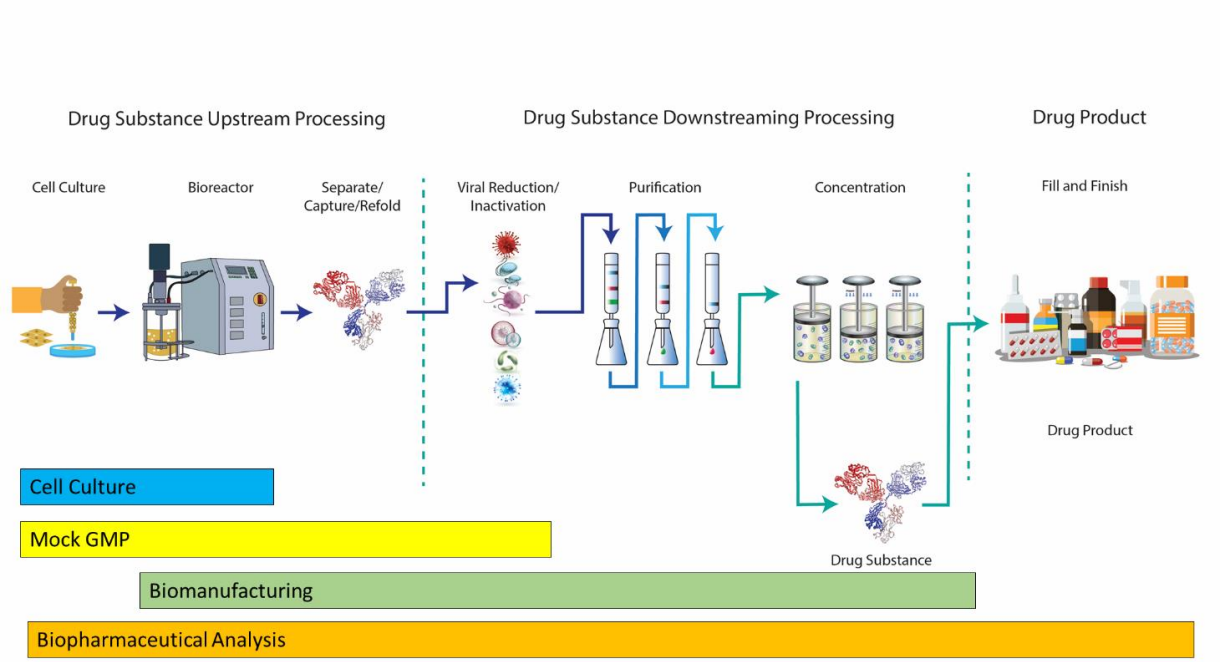

Figure 5 BATL end-to-end Biomanufacturing process training workflow

Built on the previous success, BATL is building the end-to-end Biomanufacturing process training workflow as shown in Figure 5. The new curricula will include traditional biologic/biosimilar/vaccines production and the production of advanced emerging therapies (i.e., gene therapy, cell therapy, and tissue engineering). The cell culture lab (blue bar) will allow for training in sterile technique as well as seeding of small cultures that will be used for scale-up to bioreactors. The mock GMP lab (yellow bar) will allow for training in the sterile environment (clean room) in which biologics/biosimilars are produced. The biomanufacturing lab (green bar)

will allow for hands-on training with manufacture scale single-use bioreactors, purification, and concentration apparatus used in the production of biologics (antibody shown in this example). The biopharmaceutical analysis lab (orange bar) will allow for training in the characterization of biologics. It will allow for the development and training in real-time analytics of biologics, including advanced (cell) therapies. This equipment can also be used to provide the data for continuous manufacturing research development and our proposed technology validation.

Our training can help address the significant shortage of highly skilled biomanufacturing workforce in cell and gene-based therapy manufacturing in the United States. Table 1 lists two progressive industry and regulatory guided hands-on trainings provided by BATL: (1) Suspension-based lentiviral vector production; and (2) quality advanced therapies production. Northeastern's unique approach to training employs both theory and practice. We link theory with practical case studies and hands-on training to provide learners with the most current science, technology, and application, while keeping patients in mind.

Table 1 Training sample courses for creating a skilled workforce with patients in mind: (1) Suspension-based lentiviral vector production; and (2) quality advanced therapies production

PARTNERS	**Case 1:** Training for Suspension-based production processes of Lentiviral Vectors	**Case 2:** Progressive industry and regulatory guided, hands-on training courses, in advanced therapies for workforce development
NEEDS 	Viral vector production technology has not kept pace with demand, owing to difficulties producing high quality product at large scales. Transient transfection also results in contaminations of the final product due to excess plasmids and residual transfection reagent. High numbers of infectious units of vector per patient are needed. Thus, because of the low stability of LV, we opted for the development of a production process in perfusion mode.	According to the Government Accountability Agency (GOA) (Congress): 40% of finished drugs are made overseas, 80% of Active Pharmaceutical Ingredients are made overseas. GOA classifies this as a "high risk issue" for U.S. patients. The U.S. FDA has approved approximately 10 Advanced Therapy Medicinal Products. There are over 500 ATMPs in development, requiring intricate biomanufacturing processes.
APPROACHES	• Use online dynamic digital copies/twins of actual equipment and control systems.	• Focus on Flow Cytometry, freeze/thaw, and ancillary materials qualification. • Develop an internationally recognized curriculum based

	• Use the model-based DoE to improve the production efficiency of viral vectors. • Provide in person, hands-on, experiment training in viral vector manufacturing.	on our theory and practice approach to training. • Draw on expert faculty across the colleges (engineering, computer science).
BENEFITS 	To accelerate the adoption of Viral Vector Manufacturing we can educate the workforce and highlight the critical aspects which need particular attention from a QbD perspective in order to reduce failed batches and improve product quality.	A trained and certified workforce will be able to effectively manufacture quality products that ensure patient safety, all while being innovative and meeting regulatory standards.

Section 4 Conclusions

In this paper, we introduce an integrated research, education/training and industry practice framework to accelerate the innovation in biopharmaceutical manufacturing so that we can eliminate drug shortage. We present the corresponding implementation platform centering around NIIMBL. The biomanufacturing industry practice can be moved forward through academic, regulatory and industry collaboration. Specifically, the industry needs drive the development of new methodologies and technologies. The proposed approaches can be incorporated into the training and education, which can progressively prepare the highly skilled workforce required by next generation of biomanufacturing.

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We appreciate the helpful discussion with Peter E Baker. He has over ten years' working experiences at Food and Drug Administration (FDA), was as named FDA Investigator of the Year in 2013, performed more than 100 facility inspection in China/India, developed a new inspection technique to detect and report breaches in integrity (laboratory and production), contributed to the drafting of data integrity guidance for industry (PDA, WHO) and trained governments in China, India, Mexico, Brazil.

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