Doi:10.32481/djph.2023.11.003

Harmonizing Progress:

Bridging BioPharma, Technology, Academia, and Healthcare for Advanced Drug Manufacturing

Patrick Callahan, JD

Director, LabWare; Advisory Board Member, BioCurrie and Acellus Health. Head, Science and Technology Committee, Prosperity Initiative, State of Delaware

Abstract

This paper proposes a quadrilateral approach to advance biopharmaceutical manufacturing by fostering collaboration among biopharma, lab informatics, healthcare systems, and academia. Through a retrospection based on Gary Pisano's analysis and real-world examples like insitro and Spark Therapeutics, we highlight the imperative of continuous process innovation and regulatory collaboration. We emphasize leveraging technological advancements, particularly in machine learning and artificial intelligence (AI), to catalyze a paradigm shift in drug manufacturing and delivery. The discussion extends to fostering academic and business partnerships, akin to Silicon Valley's ecosystem, and engaging healthcare systems in a more integrated role, exemplified by the advent of point-of-care manufacturing. The paper underscores the unique potential of the State of Delaware to propel forward the biopharma manufacturing space, advocating for a coordinated effort to translate scientific advancements into real healthcare benefits.

Introduction

The landscape of biopharmaceutical manufacturing and delivery is at a pivotal juncture, poised for transformative advancements. At the heart of this transformation lies a collaborative synergy among biopharma, lab informatics, healthcare systems, and academia. Each sector brings to the table a wealth of knowledge, innovative solutions, and unique capabilities, the harmonization of which could usher in a new era of drug manufacturing and delivery, marked by efficiency, precision, and patient-centricity.

A retrospective glance into the business dynamics of the biopharma sector, as analyzed by Gary Pisano in his books "The Science-Based Enterprise"[1] and "The Development Factor,"[2] sheds light on both the challenges and the opportunities. Pisano's scrutiny over a span of three decades revealed that despite a cascade of scientific discoveries, the expected profitability remained elusive for the biopharma industry. He underscored the imperative of continuous process innovation as a linchpin for competitive advantage, nudging firms towards an integrated strategy encompassing both product and process innovation.

Fast-forward to the present, the narrative is evolving. A remarkable wave of scientific advancements in biopharma, coupled with leaps in technology and artificial intelligence (AI), has been breaking ground. These advancements herald not only new cures for intractable diseases but also underscore the potential for a paradigm shift in manufacturing and delivery of these new discoveries. The new capabilities in machine learning, for instance, are now unlocking new horizons in drug discovery, as seen by pioneers like Daphne Koller, CEO and founder of insitro,[3] a machine learning-driven drug discovery company or the protein folding capabilities of Google

Doi:10.32481/djph.2023.11.003

DeepMind's AlphaFold project. However, the potential of these advancements can only be fully harnessed if paralleled by transformative strides in the biopharma manufacturing domain.

This paper delves into the nexus of collaborative engagement among biopharma, lab informatics, healthcare systems, and academia, outlining a quadrilateral approach towards pioneering transformations in biopharma manufacturing. Through a multi-faceted lens, we advocate how leveraging technology, enhancing regulatory collaboration, fostering academic and business synergy, and harmonizing healthcare systems can be instrumental in bridging the gap between groundbreaking discoveries and their seamless delivery to patients. Through this discussion, we aim to chart a way forward, envisioning a cohesive ecosystem that is primed to advance the biopharma manufacturing space right in our backyard.

Pioneering Transformations in Biopharmaceutical Manufacturing: A Quadrilateral Approach

In the biopharmaceutical sector, innovation is key. Manufacturing is a crucial step in this process. Although there has been rapid progress in research and development, the success of these innovations largely depends on effective manufacturing and delivery systems. The interaction between technology, regulatory cooperation, academic efforts, and healthcare provider involvement creates a necessary framework to advance the sector and increase its effectiveness and impact.[4]

Leveraging Technology, Managing Data, and Integrating AI in Biopharmaceutical Manufacturing

"Biopharmaceuticals could become the core of the pharmaceutical industry, but achieving this status requires significant transformations in laboratories, strategies, technology, and operations."[5] In biopharma, the production of large molecule medications through sophisticated biological processes and technologies necessitates a deep reliance on intricate data sets and a profound understanding of disease mechanisms and patient-specific profiles due to the nuanced nature of biological products. These ideas are particularly self-evident in products like autologous cell therapies, where the medicine is manufactured using the patient's own cells.

Advancements in bio-manufacturing entail a slew of alterations across the process spectrum: moving from batch sampling to real-time sampling[6]; handling a diverse range of raw materials—unlike pharma which often deals with fewer than ten ingredients, biopharmaceuticals interact with over a hundred, including complex items like DNA, cell lines, and single-use components; improving environmental monitoring, by transitioning from facility monitoring in pharma to batch-specific monitoring in biopharma; and adapting to the distinct methods of drug creation, with pharma utilizing chemical processes, while biopharmaceuticals use living cells to produce drug substances.

In this context, reimagining data science, technology, and lab information management systems is crucial for crafting personalized treatments,[7] deciphering complex biological pathways, and adhering to regulatory standards. The continuous collection and thorough analysis of diverse data sets are key, as they help unravel complex biological interactions and improve manufacturing processes, underscoring the vital role of sophisticated data management systems in biopharmaceutical development.[8]

The introduction of fully autonomous labs, real-time mechanistic models, and enhanced connectivity between labs has the potential to greatly improve biopharmaceutical manufacturing capabilities. Real-time mechanistic models are crucial as they help predict how environmental variables affect cell creation, a core aspect of biopharmaceutical products. Furthermore, the seamless integration of labs and AI, channeling into unified manufacturing execution systems, have become necessary to the success of manufacturing.

Daphne Koller, through her company insitro, is heavily involved in leveraging machine learning (ML) and AI to enhance understanding of complex biological pathways and tailor treatments. The primary objective is to "de-convolute" the biology of human diseases, which is often misunderstood or oversimplified due to traditional coarse-grained symptomatic classifications. The company focuses on collecting high-content data, including imaging data like MRI and histopathology, and molecular measurements from patients to understand the underlying biological processes corresponding to diseases. Machine learning is utilized to identify subtle patterns that help distinguish distinct patient subsets, providing a clearer picture of disease biology.[9]

Enhancing FDA Collaboration to Expedite Biopharmaceutical Manufacturing through AI and Data Science

The regulatory landscape in biopharmaceutical is intricate and dynamic, with agencies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) laying down rigorous guidelines and requirements. The complexity arises from the diverse nature of biopharmaceutical products, each necessitating specialized evaluation frameworks. Compliance with these regulations is non-negotiable and necessitates extensive documentation, validation, and quality assurance processes throughout the product lifecycle. The continual evolution of regulatory norms mandates that biopharmaceutical entities remain abreast of the latest updates and modifications, ensuring that their practices align with the prevailing standards and are poised to adapt to forthcoming changes.

Tighter collaboration between regulatory bodies such as the FDA and innovators in the biopharmaceutical sector is essential for leveraging advancements in technology, AI, and biopharmaceutical and can be substantiated by recent initiatives and discussions facilitated by the FDA. This is already underway with several initiatives including the “Scientific Public Private Partnerships and Consortia”;[10] the FDA’s investment in Advanced Manufacturing, and the FDA’s interest in better AI and ML collaborations.[11] However, this requires an even greater involvement by thinking of whole new paradigms in industry regulation. One positive aspect derived from the COVID-19 pandemic, despite its devastating effects, is the collaborative approach exhibited by the federal regulatory and global governing bodies during the development of COVID-19 vaccines. Many publications have discussed this collaborative endeavor, but the question remains on whether the practices forged during this time have been assimilated for future development efforts.[12]

Considering the swift and substantial advancements in technology, artificial intelligence, and biopharma, it's not surprising that global regulatory bodies might struggle to keep up. However, just as the industry has utilized these advancements for progress, regulatory agencies could also leverage these technological strides, along with the recent experiences from the past pandemic. This situation underscores the need for increased collaboration between government entities and innovators. While maintaining oversight is crucial to avoid risking lives, halting progress for the

same reason is not a feasible alternative. Given the complexity of biopharma manufacturing (as described earlier), it stands to benefit significantly from AI and data science practices. These advantages are crucial for biopharma facilities to attain operational success comparable to traditional pharma. Achieving this delicate balance requires a collaborative approach to cultivate a favorable environment for the rapid manufacturing and delivery of new biopharmaceutical drugs, ensuring both safety and innovation are upheld.

Fostering Academic and Business Partnerships in Manufacturing and Delivery

In the State of Delaware, we are privileged to have a federal delegation and community leaders who ardently advocate for innovation in biopharmaceutical manufacturing. Their efforts culminated in the establishment of the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) in 2017, under the auspices of the National Institute for Standards and Technology.[13] Since its inception, substantial investments have been funneled at various levels to propel NIIMBL into a premier institution. Located within the STAR campus of the University of Delaware, the facility benefits from shared resources with faculty and researchers as well as leaders in the chemical industry.[14] Its strategic location has the potential to serve as a magnet for major biopharmaceutical enterprises to our region, fostering a collaborative setting for sharing advancements and promoting development.

Adjacent to Delaware, the Philadelphia region houses an array of distinguished organizations and research institutions. These entities have spearheaded significant advancements in cell and gene therapy discovery, earning the region the moniker "Cellicon Valley" as a testament to the burgeoning industry.[15]

A potent catalyst for enriching this ecosystem could be the influx of additional biopharmaceutical science businesses. By melding research and a fervor for education and innovation with the entrepreneurial spirit of both established companies and startups, a collaborative effect is on the cusp of being achieved. This blend of academic and business realms not only holds the promise of advancing biopharmaceutical manufacturing but also incubates a thriving nexus of commerce, education, and innovation.

The alliance between academia and business in driving advancements in biopharmaceutical manufacturing echoes the transformation witnessed in Silicon Valley. The iconic region demonstrates how the unintentional interactions between academic institutions like Stanford University and numerous tech enterprises transcends mere technological advancements. Silicon Valley's enduring leadership in business model innovation delivers deep and transformational insights, which have been pivotal to its success.[16] Similarly, the biopharma sector could harness business model innovation, spurred by academic research and industry collaboration, to foster an environment conducive for groundbreaking advancements and economic growth. Just as Stanford's academic research and technological innovations provided a fertile ground for entrepreneurial endeavors and established firms, the biopharma sector can leverage a symbiotic relationship between academia and business to fuel not only technological progress but also business model innovations that could significantly propel the sector forward. This illustrates a pathway for biopharma to achieve a blend of technological and business model innovation, mirroring the transformative ecosystem of Silicon Valley.

Doi:10.32481/djph.2023.11.003

Healthcare and BioPharma Manufacturing: A Necessary Partnership for a Promising Future.

The biopharmaceutical field often faces increased complexities, especially during the final stage of its lifecycle: delivering the product to the patient. With a shift towards personalized medicine, a manufacturing model is needed where living organisms, often using the patient's own cells, are cultured either externally or within the patient. Biopharmaceuticals have a short shelf life, requiring careful monitoring during drug administration. This highlights the crucial role of hospitals and healthcare providers in both the manufacturing and delivery aspects of biopharmaceuticals.

Point of care manufacturing in biopharma is a decentralized approach where certain advanced therapy medicinal products (ATMPs) are produced near or at the care location instead of in a centralized manufacturing facility. This approach aims to uphold strict product quality standards, improve patient access to vital treatments, and reduce therapy costs.[17] The advent of point-of-care manufacturing is a step towards a more decentralized, patient-centered healthcare approach, aiming to reduce logistical issues and improve therapeutic outcomes by maintaining the quality of cellular products.[18] However, there are operational, scalability, and regulatory challenges that need to be addressed to fully realize its potential, requiring continuous improvements in manufacturing processes. Alongside, advanced lab management solutions are emerging as important components, aiding better organization, efficiency, and compliance in biopharmaceutical research by providing improved data management, analytics, and collaboration solutions.[19]

Transitioning to a more integrated role in the biopharmaceutical lifecycle requires changes in how hospitals and healthcare providers operate and perceive their roles. First, adopting a lab-centric approach could change the traditional operational structure, allowing these entities to see themselves as active labs involved throughout the process, not just as endpoints. This view supports a smoother operational flow in line with the evolving nature of biopharmaceuticals. Second, promoting innovation is essential. Current strict frameworks in many healthcare IT departments can discourage startups. A more open and collaborative approach could energize the innovation scene, bringing in new and effective solutions to improve manufacturing and delivery processes. Lastly, engagement should extend beyond just discovery. By taking on a more active leadership role in the manufacturing sector, hospitals and healthcare providers can diversify their contributions and enhance the entire biopharmaceutical process, working more comprehensively towards delivering personalized medicine.

The active participation of hospital systems in the biopharmaceutical manufacturing and delivery realm is a key step towards unlocking the promise of personalized medicine and raising the quality of patient care. The emerging sector of cell- and gene-based therapy manufacturing in North Carolina, boosted by a vibrant life science ecosystem driving innovative therapies from idea to market, serves as an example of such a collaborative ecosystem. It highlights the benefits brought by strong research frameworks, biopharma manufacturing expertise, ample resources, top-tier talent, and a supportive business environment. By intertwining their operations with the biopharmaceutical sector, hospitals can notably reduce drug development timelines, ensuring a quick transition from lab discoveries to patient delivery. Moreover, the involvement of healthcare facilities provides a richer data pool, essential for refining drug formulations and delivery methods. This combined effort not only aligns with the goals of personalized medicine

but also lays the groundwork for a more nimble, efficient, and patient-centered biopharmaceutical ecosystem.[20]

The journey of Spark Therapeutics encapsulates another example of the transformative power of collaboration between academia, hospital systems, and the biopharmaceutical sector. Originating from the Children's Hospital of Philadelphia (CHOP), which had a longstanding commitment to gene therapy research, Spark Therapeutics was nurtured and propelled into a pioneering entity that led to the development and commercialization of LUXTURNA, the first FDA-approved gene therapy for a genetic disease.[21] This narrative accentuates the crucial role that hospital systems play within the broader biopharmaceutical realm. By cultivating a fertile environment for research and innovation, and by forging synergistic alliances with emerging biopharmaceutical entities, hospital systems like CHOP not only facilitate the inception of groundbreaking companies like Spark Therapeutics but also expedite the trajectory of innovative therapies from research labs to patient bedside. The Spark Therapeutics case exemplifies how these collaborative frameworks can significantly compress drug development timelines, ensuring that novel therapies swiftly reach the patients in need. Furthermore, it underscores the substantial contributions hospital systems can make to (and benefit from) the evolving field of personalized medicine and biopharmaceutical manufacturing and delivery, delineating a roadmap towards a more agile, efficient, and patient-focused healthcare ecosystem.

Charting the Way Forward: Fostering Growth and Innovation in Biopharmaceutical Manufacturing in a Region Primed for Advances.

In the State of Delaware, a confluence of advantageous circumstances, ranging from significant advancements in technology and AI to a strong foundational legacy in science, notably marked by the evolution of DuPont, uniquely positions us to propel forward the biopharmaceutical manufacturing space. At LabWare, we find ourselves as a strong contributor to not only the local community, but amidst the vibrant ecosystem engaging with biopharmaceutical entities globally in the realm of lab informatics in the biopharma space. Our burgeoning global partnerships with our clients have been and continue to nurture the evolution of our next-generation software, ingrained with AI and process automation, tailored to cater to the unfolding demands of future biopharmaceutical iterations.

The local presence of visionary institutes like NIIMBL coupled with the global connections to other international organizations such as NIBRT (National Institute for Bioprocessing Research and Training) amplify the potential for a harmonized endeavor with the FDA and international regulatory bodies. These institutions as well and their potential collaborative framework aims at upholding the paramountcy of quality and safety standards whilst fostering the advancement of science.

Further enriching our regional ecosystem are our advanced educational institutions that harbor a cadre of distinguished researchers and academics. Their expertise, in a myriad of pertinent fields, magnetizes innovative minds, thus serving as the bedrock of progressive innovation. A testament to the potential encapsulated in community healthcare's interface with biopharmaceutical manufacturing is the recent spin out of Christiana Care's startup in the gene editing space, CorriXR Therapeutics.[22] This transition, albeit pioneering, underscores the necessity of a more accelerated pace in similar transitions, bolstered by a conducive community engagement and an aligned mindset. The industry requires a surge of such transitions, aiming for a hundred of these advancements annually.

Doi:10.32481/djph.2023.11.003

Conclusion

Planning a way forward involves forming a dedicated group to facilitate ongoing communication and feedback among all relevant stakeholders. Such a group, possibly overseen by Delaware Bio, would help keep responses aligned with the changing needs and challenges. Looking into global collaborations and adopting international best practices in biopharmaceutical manufacturing can offer a more comprehensive and globally coordinated framework for innovation. A clearly defined roadmap, listing short-term and long-term goals along with measurable metrics, will help in assessing the progress and impact of the initiatives planned in your quadrilateral approach. Additionally, creating a state chair position for science and technology could play a crucial role, liaising with our governor and legislature and advocating for our state's interests both internally and externally.

The core opportunity is recognizing that the biopharmaceutical manufacturing industry is at a crucial point, ready for necessary growth. This growth is key to delivering new, personalized therapies, translating many scientific advancements into real healthcare benefits. Additionally, creating an environment that encourages random discoveries and a culture of innovation like Silicon Valley's is important. Such an environment could lead to unexpected breakthroughs, advancing the industry further and emphasizing the significant impact of biopharmaceutical manufacturing on global healthcare. We have all the necessary elements and pieces in place - what's needed now is a belief in our systems and the right mindset from the leaders of each sector to believe in the vision, participate, and execute in a coordinated manner.

Mr. Callahan may be contacted at Patrick.callahan@labware.com.

References

1. Pisano, G. P. (2006). Science Business. Boston: Harvard Business Review Press.
2. Pisano, G. P. (1997). The Development Factory. Boston: Harvard Business School Press.
3. Insitro. (n.d.). About. Retrieved from insitro.com: https://insitro.com/about
4. Castro, B. (2019, Dec). The next wave in biopharma manufacturing. Retrieved from https://ispe.org/pharmaceutical-engineering/november-december-2019/next-wave-biopharma-manufacturing
5. Otto, R., Santagostino, A., & Schrader, U. (2014, Dec 1). Rapid growth in biopharma: Challenges and opportunities. Retrieved from https://www.mckinsey.com/industries/life-sciences/our-insights/rapid-growth-in-biopharma
6. Clint Pepper, P. (2019, Jun 5). Making real-time process analytical technology in biomanufacturing a reality. Retrieved from https://www.pharmasalmanac.com/articles/making-real-time-process-analytical-technology-in-biomanufacturing-a-reality
7. Johnson, K. B., Wei, W.-Q., Weeraratne, D., Frisse, M. E., Misulis, K., Rhee, K., . . . Snowdon, J. L. (2021, January). Precision medicine, AI, and the future of personalized health care. *Clinical and Translational Science*, *14*(1), 86–93. https://doi.org/10.1111/cts.12884 PubMed

8. Panahiazar, M., Taslimitehrani, V., Jadhav, A., & Pathak, J. (2014, Oct). Empowering personalized medicine with big data and semantic web technology: promises, challenges, and use cases. Proc IEEE Int Conf Big Data, 790-795. Doi: https://doi.org/10.1109/BigData.2014.7004307
9. The, L. (2022, Nov 16). 'It will be a paradigm shift': Daphne Koller on machine learning in drug discovery. Retrieved from https://www.mckinsey.com/industries/life-sciences/our-insights/it-will-be-a-paradigm-shift-daphne-koller-on-machine-learning-in-drug-discovery#/
10. FDA. (2023, Sep 8). Scientific public private partnerships and consortia. Retrieved from https://www.fda.gov/drugs/science-and-research-drugs/scientific-public-private-partnerships-and-consortia
11. Patrizia Cavazzoni, M. (2023, May 10). FDA releases two discussion papers to spur conversation about artificial intelligence and machine learning in drug development and manufacturing. Retrieved from https://www.fda.gov/news-events/fda-voices/fda-releases-two-discussion-papers-spur-conversation-about-artificial-intelligence-and-machine
12. Druedahl, L. C., Minssen, T., & Price, W. N. (2021, October 8). Collaboration in times of crisis: A study on COVID-19 vaccine R&D partnerships. *Vaccine*, *39*(42), 6291–6295. PubMedhttps://doi.org/10.1016/j.vaccine.2021.08.101
13. NC State University. (n.d.). national institute for innovation in manufacturing biopharmaceuticals (NIIMBL). Retrieved from https://kenan.ncsu.edu/initiative/national-institute-for-innovation-in-manufacturing-biopharmaceuticals-niimbl/
14. Chemours. (n.d.). New innovation center through strategic partnership with the University of Delaware. Retrieved from https://www.chemours.com/en/chemistry-in-action/future-chemistry/university-of-delaware-partnership
15. Penn Medicine / CHOP. (2023, Jun 21). Cellicon valley '23: The Future of cell and gene therapies. Retrieved from UPenn: https://www.med.upenn.edu/cellicon23/
16. Martins, H., Dias, Y. B., & Khanna, S. (2016, Apr 26). What makes some silicon valley companies so successful. Harvard Business Review. Retrieved from https://hbr.org/2016/04/what-makes-some-silicon-valley-companies-so-successful
17. Delgado, J., Roddie, C., & Schmitt, M. (2022). Point-of-care production of CAR-T cells. In N. Kröger, J. Gribben, C. Chabannon, I. Yakoub-Agha, & H. Einsele, eds., The EBMT/EHA CAR-T Cell Handbook. Springer, Cham.
18. Nayak, S., Blumenfeld, N. R., Laksanasopin, T., & Sia, S. K. (2017, January 3). Point-of-care diagnostics: Recent developments in a connected age. *Analytical Chemistry*, *89*(1), 102–123. https://doi.org/10.1021/acs.analchem.6b04630 PubMed
19. GEN: Genetic Engineering & Biotechnology News. (2022, Mar 1). Point-of-care drug production would aid patients and industry. Retrieved from https://www.genengnews.com/insights/point-of-care-drug-production-would-aid-patients-and-industry/
20. Bayer, S., Sandy, S., Schrader, U., & Spiegl, M. (2021, May 27). Leveraging digital and analytics in biopharma operations: Six principles. Retrieved from

https://www.mckinsey.com/capabilities/operations/our-insights/leveraging-digital-and-analytics-in-biopharma-operations-six-principles

21. Children's Hospital of Philadelphia. (2017, Dec 19). Children's Hospital of Philadelphia celebrates FDA approval of gene therapy for inherited blindness. Retrieved from https://www.chop.edu/news/childrens-hospital-philadelphia-celebrates-fda-approval-gene-therapy-inherited-blindness
22. Christiana Care. (2022, Oct 11). ChristianaCare spins out CorriXR therapeutics, new gene editing start-up. Retrieved from https://news.christianacare.org/2022/10/christianacare-spins-out-first-commercial-gene-editing-biotechnology-start-up-company-corrixr-therapeutics/