White Paper BPLM

Why Biopharma Lifecycle Management?

IDBS Polar

The Biopharmaceutical industry has big ambitions to accelerate the move towards industry 4.0. In this white paper we explore some of the major bottlenecks in the development lifecycle and the current barriers to effective digital transformation. We conclude by exploring the role effective BioPharmaceutical Lifecycle Management BPLM platforms will play in accelerating time to market for vaccines and therapies.

The global events surrounding the 2020 SARS-CoV-2 pandemic have put a renewed focus on the time and cost of bringing new therapeutics and vaccines to patients. Recent research highlighted that the average cost to develop a new drug sits at $1.3 Billion.[1] With timelines ranging from 8 to 16 years and attrition rates that can be as high as 88%, it is clear that the current state of biopharma drug development is a barrier to the timely and cost-effective treatment of disease.

According to research by pharmamanufacturing.com, in excess of 60% of biopharma organizations are still managing many of their critical steps with paper and Microsoft Office.

Development of cutting-edge biological medicines is underpinned by complex processes, but despite innovations in process science (enhanced product titers, the application of single-use technologies, the shift to continuous and semi-continuous manufacturing) the biopharmaceutical industry has so far failed to reap the benefits of digital transformation. According to research by pharmamanufacturing.com, in excess of 60% of biopharma organizations are still managing many of their critical steps with paper and Microsoft Office, while struggling to integrate the expanding ecosystem of equipment and data. This working method is long established. But in the digital age wasting 30–40% of time on basic data administration and documentation. We are entering the age of industrialized biology. A new world in which those who embrace efficiency, agility and smart ways to unlock the potential of their data will emerge as industry leaders.

Biopharma 4.0 is a bold vision, with smart factories and process automation, driven by real time data to constantly ensure quality and efficiency. The journey towards the vision starts with improved process understanding and characterization (ICH Q10/ QbD). This is supported by technology advances like high throughput process development (HTPD) as well as advances in data sciences that enable in-silico process development. Increases in data from equipment, instruments and sensors at all process scales quickly highlight the fragility of a lifecycle managed with paper records and silos of data, especially when contextualized data is the rocket fuel needed to drive speed and innovation.

30–40%
of time is spent on data and document administration

10%
of rework is based on data being unavailable

Only 4%
of data is typically used[2]

The biopharmaceutical development sector has historically been poorly served by the software industry. There is a long history of early adopters having to re-purpose technology designed to solve adjacent problems in pharmaceutical research (ELN, SDMS), or small molecule manufacturing (PLM, MES). While there have been moderate successes in this approach, this often comes at the cost of solutions that offer a poor user experience and require heavy and expensive customization. The result is a long and expensive IT deployment project and a disjointed ecosystem that is difficult to maintain, leaving the challenge of gaining meaningful process insight unsolved.

Is this a solvable problem? This will depend on software vendors' willingness to approach the problem – but only from the perspective of biologic drugmakers, who are strongly motivated by a reduction in the time and cost of developing new therapeutics. In other words, digital tools are oriented to the development process and deliver meaningful insights more rapidly than current systems. A Bio-Pharmaceutical Lifecycle Management (BPLM) platform can be envisaged – realized by using an operational foundation for biopharmaceutical development process workflows, with integration components that streamline complete integration into the development ecosystem from early development to clinical supply. By removing paper and by bringing process and analytical data together at the point the process is executed, such a system permits a contextualized data backbone that supports the drug development lifecycle.

"Time is Lost" and the Cost of the Problem

In biopharmaceutical development, time is lost to paper, Excel, and ad hoc systems posing operational challenges – wasting time, impeding progress, and jeopardizing process understanding and quality. Any delay in development has meaningful real-world consequences. While unmet medical need remains unmet, and the opportunity to recoup development cost against IP exclusivity is lost.

This cost is compounded by the high-risk nature of biologics development. Why is the risk profile of biopharmaceutical processes so high? Biological production conditions are a major source of unpredictable behavior. Most steps of biologics preparation can become prone to microbial contamination, introduced or aggravated by supply and environmental conditions. Equipment itself introduces risk: its bioburden, technical failure, and the incompatibility of materials with product (especially in single-use bioreactors).[3] Numerous biophysical properties that can jeopardize safety or manufacturing, require assessment and synthesis, for instance, thermal stability, fragmentation, solubility, and glycosylation. In parallel, immunogenicity of biologic drugs must be rigorously assessed, part of a rigid regulatory program in the class driven by ICH workgroup standards.

Manifestations of the Problem

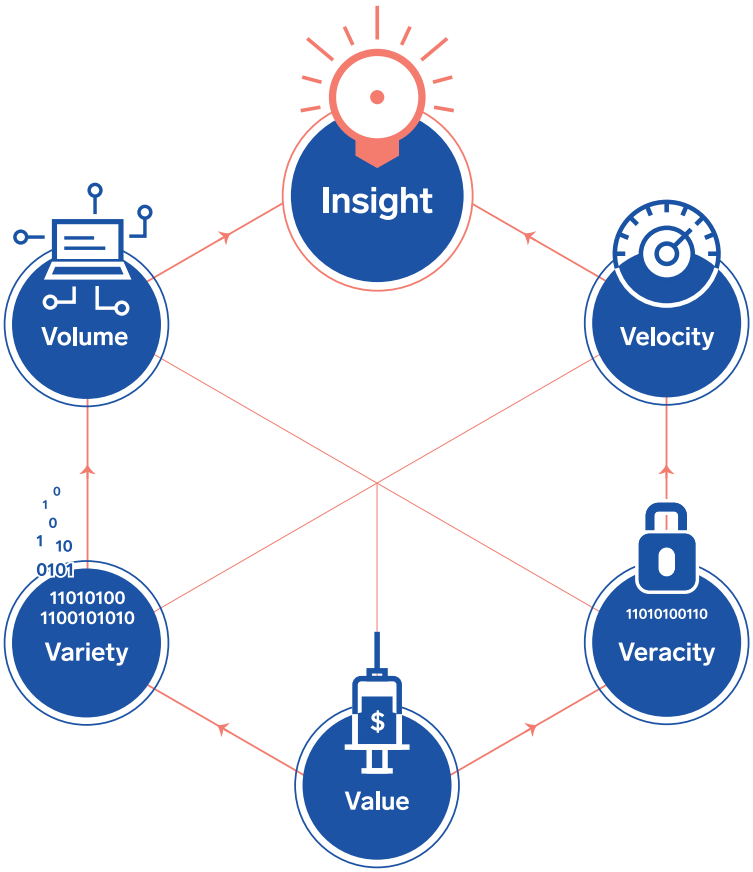
In the context of these risks, operational burdens manifest in two forms: an inability to understand root cause when undesired or unexpected outcomes occur and insufficient decision support – reducing the ability to make informed and timely decisions as a therapeutic candidate progresses. These handicaps threaten the progress of any single development campaign; applied across indications, sites, multiple indications, and pipeline volume, the competitive toll can be measured in several dimensions.

Having identified these risks and points of impact, where is the pain most commonly experienced? Along the axis of time: time to market, attrition rates in development,[5] time to trials, time to "go" or "no go", the impact of decision support. These impacts are on the order of 6–18 months. While time to market examines the full duration of the development and commercialization process, time to trials describes the period of IP exclusively over which the drugmaker has the greatest direct control – where operational interventions may have the greatest impact.

Dimensions impacting operational effectiveness in biopharma development[4]

Dimension	Evidence of Problem
Time to prepare Biologic License Application (BLA)	12 months to prepare Chapter 3
QA Effort	4-6 w./batch release for clinical supply (across all phases)
Tech Transfer	1–1.5 Years of work, opportunity to improve 25%
Rework	30% loss in time/$ spent
Time to File Biologic License Application	Delay to BLA filing (1–3 months)
Quicker to "No"	Widely reported

Source: Danaher Research



The burdens are not only operational. Biopharmaceutical drugmakers are eager to apply the power of in-silico data science in the form of modelling and simulation to the development process to shorten time to market[6]. As mentioned above, high rates of attrition in development are undesirable. Predicting the drug's mode of action, assessment of polypharmacology, formulation, selection of population for clinical trials, and drug repurposing have all been identified as areas where risk can be reduced with the application of artificial intelligence. However, data bound for use in advanced analytical methods must meet thresholds of data quality and relevance uncommonly found in biopharma data warehouses today. Academically called the "5 V's" – Volume, Variety, Velocity, Veracity, Value – these terms describe the conditions that must be satisfied by development and process data to deliver novel insight using modelling and simulation. In manufacturing scenarios, modelling applied to the creation of a "digital twin" can accelerate license approval and in manufacturing, permit process optimization, control and trouble shooting. When these techniques can be harnessed by biopharma, the impact will be broad and deep. But the effort must be supported by a data strategy to curate contextualized process and quality data.

Scientists and process engineers estimate they spend as much as half of their workday finding, reconciling, and assembling data maintained in disparate systems.

The cost impact of shortened time to market is not simply linear. Data presented in context, and consistency in execution reduce rework by an estimated 30%.[7] Scientists and process engineers estimate they spend as much as half of their workday finding, reconciling, and assembling data maintained in disparate systems. The absence of process understanding introduces the risk of low-yielding unit operations; when a typical biologic drug has a market value of greater than $10,000/gram, these costs accrete rapidly, particularly in the cascade of downstream development.

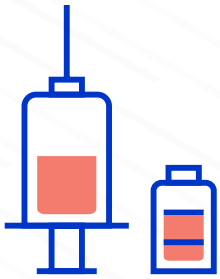
The Impact on Patients

The impact to patients of delays to market are both intangible and tangible. The social benefits to patients of the acceleration to market of the drugs rituximab (Rituxan) for non-Hodgkin's lymphoma and trastuzumab (Herceptin) for breast cancer have been studied. A development process that allowed rituximab to market one year sooner, in terms of patient "willingness to pay" would have increased the benefit to patients by $310 million and trastuzumab by $8 billion – several times their value to drugmakers.[8]

What does it mean to get to market first?

It is often assumed that being first-to-market confers a significant advantage to the prospects of the market entrant. This belief permeates countless markets including those of pharmaceuticals and healthcare. Myoung Cha and Flora Yu[9] at Mckinsey published an extensive survey in 2014 analyzing 492 drug launches in 131 categories marketed over a 27 year period. Drugs that achieved both revenues in excess of $100M per year and had more than one competitor, were assessed for their market share in the 10th anniversary year of the launch of the first drug in that class.

First-to-market products had a 6% market-share advantage over later entrants – although this was not a universal advantage: such market advantage was seen in less than 50% of the drug classes. The authors identified several characteristics that defined the more successful drugs. A first-mover drug was more successful if it was marketed in a specialty area – i.e. small numbers of prescribers and patients. Consistent with this, first-mover injectable drugs held stronger market share than orally administered products. Competition played a role and any advantage of early entry to the market was eroded as more products entered the market. Furthermore, the longer a product was alone in the market – its lead time – the greater the market-share advantage. Market reach and capability were significant factors too – large pharma with domain experience of the target indication were far more successful (gaining up to an additional 10% fair market share) than smaller organizations with limited domain knowledge. And finally, rapid expansion of indications had a dramatic, positive effect of around 13% above market share.

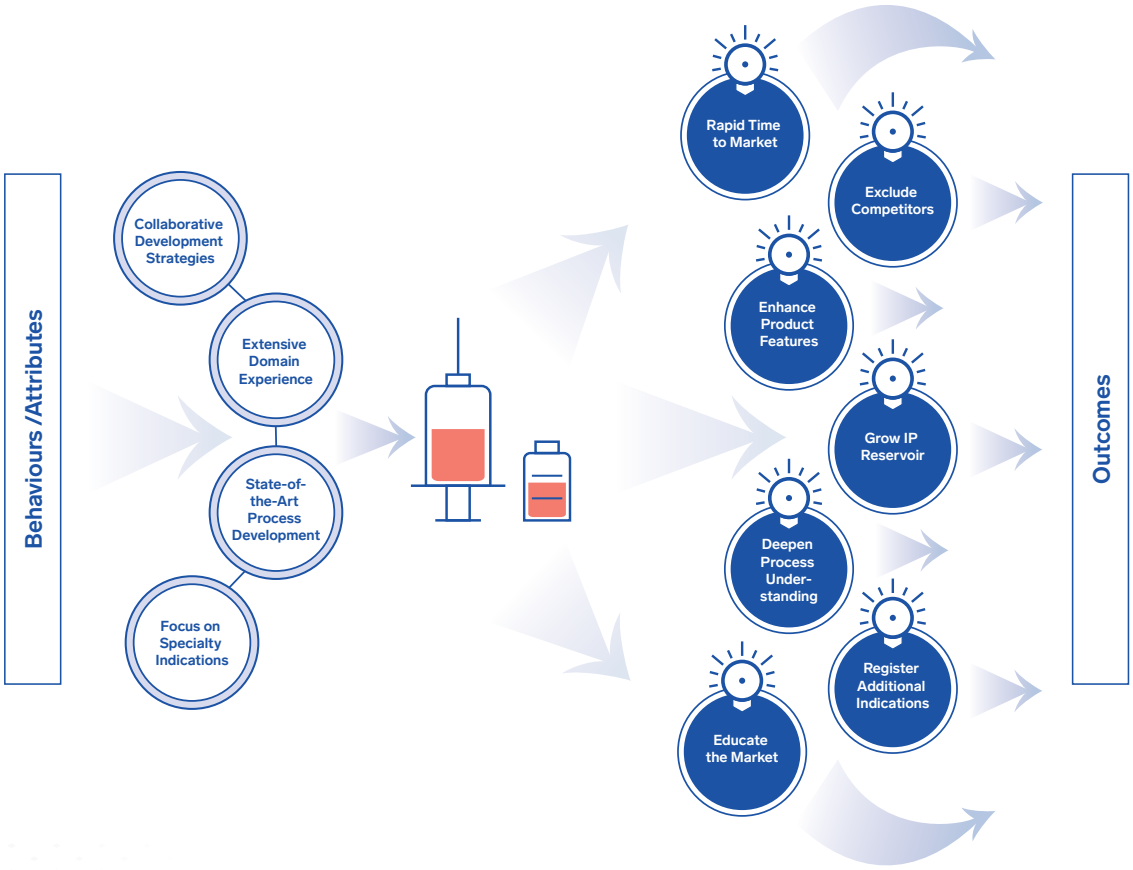


First-to-market advantages are seen in less than 50% of cases after 10 years. Post-launch innovation that consolidate the early advantages is what creates the long-term winners. This is why a full biopharmaceutical development lifecycle management perspective is needed.

Another consulting group, SMC represented by Siddhartha Jain in 2016[10] looked at factors that indicate the likelihood of a product succeeding, the point of entry to the market being but one of four influencing factors. The patient experience – ease of use, for example - was key in addition to having high safety and effectiveness alongside a competitive price.

Both SMC and Mckinsey make valid points about the time of entry to market. Time does not supplement innovation – it doesn't necessarily make for a superior product that wins in the market place – but the time afforded by establishing a foothold where others don't allows resources to be diverted into strengthening the product position - post-launch innovation takes place and it these activities that consolidate the early advantages gained from a first-past-the-post position.

First-to-market advantages are seen in less than 50% of cases after 10 years. Post-launch innovation that consolidate the early advantages is what creates the long-term winners. This is why a full biopharmaceutical development lifecycle management perspective is needed.



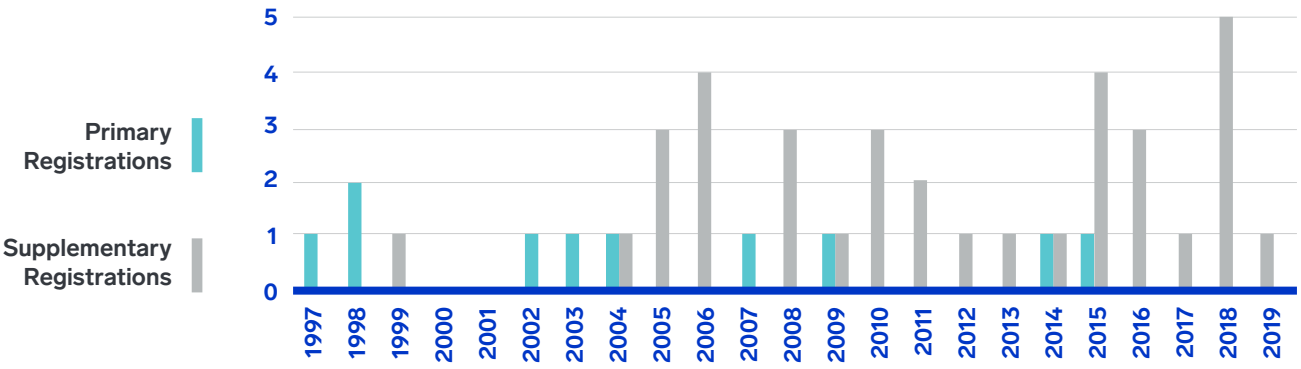
Expanding indications, extending IP

In 2018 revenues of the top ten best-selling mAbs was estimated at $73BN. Every one of these antibodies had been registered for more than one indication, and indeed supplementary registrations have been widely applied throughout the lifecycles of this family of products. The highest revenue achiever, Humira with sales of $19.9BN in 2018, had been registered for use in nine indications[11] and the importance of these expanded indications cannot be overlooked when it comes to understanding the success of this product, which was first marketed in 2002.

Supplementary registrations play an important role in managing revenues for biopharmaceuticals. Taken in the context of the analysis provided by Mckinsey, IP extensions serve a major role in securing a place as a market leader by excluding or staying ahead of the competition.

Intellectual property originating from modified formulations, the discovery of combination therapies, modified drug delivery mechanisms or dosage regimes and manufacturing improvements can all lead to enhancements of the patient experience and their outcomes, increase a product's attractiveness, extend its patent life and ultimately its sustainability in the marketplace[12] (Moorkens et al., 2020). Again, time afforded by entering the market as quickly as possible after a biological entity has been registered with the authorities can have significant commercial advantages in terms of IP extension or expanding indications after a license to market has been granted.

Top 10 mAb Global Bestsellers: Primary Registration and Supplementary Registrations



Supplementary registrations of top-selling mAbs, data extracted from Lu et al., 2020.

What about process development?

It is widely accepted that progress of biopharmaceuticals through the development process is slowed by three factors: demonstrating efficacy in clinical trials, developing an acceptable manufacturing process and manufacturing sufficient material of acceptable and proven quality to support clinical trials themselves – particularly at the later stages of development. It has been advocated that a continuation in the shift of empirical to science-based understanding of cell culture could chiefly be achieved by a deeper understanding of cellular physiology and detailing the input process parameters, how they interact and ultimately impact product yield. Such an approach is necessarily complex and scientists need to seamlessly and efficiently exploit technology, data and in-silico methods to assist in the development of their manufacturing processes, and hence their product. One such approach is the application of multiple experiments run concurrently or HTPD which can significantly reduce time to develop a process and necessarily requires data management to provide an audit trail for discovery and insight[13].

Collaboration among competitors

In a review of the strategies adopted by 25 of the largest global biopharmaceutical companies in 2017 Moorkens recognized[14] a number of strategic imperatives across the industry – often implemented in the face of diminishing IP life. Those strategies included the development of novel biologics, investment in biotechnology and, interestingly, one area seen as critical to success was the development of collaborative programs between the biopharmaceutical companies themselves. This again resonates with the proposal of Cha and Yu from Mckinsey – that organizations risk losing market share if they do not have domain experience of their product – a risk that can be mitigated by collaborative arrangements during the drug development phases. As a component of strategy, this may result in a significant advantage to the collaborating parties. Such arrangements would clearly benefit from having a digital platform to communicate the development protocols and status of any research programs.

Biopharmaceuticals — now more than ever before — represent an ability to transform global health.

Summary

Biopharmaceuticals — now more than ever before — represent an ability to transform global health. Yet the cost and speed of bringing these life changing drugs to market remains one of the biggest industry challenges of the new decade. The opportunities are enormous for those who are organized — those with know-how and cutting-edge tools to develop processes and therapies quickly. Monoclonal antibodies, recombinant proteins, vaccines and cell and gene therapy have sustained an arc of growth previously unencountered in our perpetual challenge to conquer disease states.

But with this explosion of therapeutic possibilities comes complexity. The complexity of navigating multiple systems. Regulatory systems, research and development centers in multiple sites, cities or even continents, drawing together information from diverse departments — clinical data, process data, analytical data, development data — all contribute to a multi-faceted eco-system that represents an immense challenge to corral and take meaningful insight from.

It is clear that there is no one factor that will determine the success of a molecule as it moves through the clinical pipeline or even if a biologic has therapeutic benefit, but it is clear that navigating this complex landscape with legacy tools is not a sustainable option. We position a biopharmaceutical lifecycle management (BPLM) platform as the digital enabler and partner in navigating the drug development lifecycle with speed and agility.

References

1, Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA. 2020;323(9):844. doi:10.1001/jama.2020.1166

2, Calvo, Jorge. Digital Transformation - is your Supply Chain ready to compete? The Future Factory. Published 2020. Accessed November 1, 2020. https://www.thefuturefactory.com/blog/22

3. Hammond M, Marghitoiu L, Lee H, et al. A cytotoxic leachable compound from single-use bioprocess equipment that causes poor cell growth performance: A Leachable Compound Causing Poor Cell Growth. Biotechnol Progress. 2014;30(2):332-337. doi:10.1002/btpr.1869

4. Danaher Market Research

5. Mak K-K, Pichika MR. Artificial intelligence in drug development: present status and future prospects. Drug Discovery Today. 2019;24(3):773-780. doi:10.1016/j.drudis.2018.11.014

6. Hummel, J. Pagkaliwangan, M. Gjoka, X. Davidovits, T. Stock, R. Ransohoff, T. Gantier, R. Schofield, M. Modeling the Downstream Processing of Monoclonal Antibodies Reveals Cost Advantages for Continuous Methods for a Broad Range of Manufacturing Scales. Biotechnol J, . 2019 14(2): doi: 10.1002/biot.201700665

7. Danaher Market Research

8. Philipson TJ, Sun E. Cost of Caution: The Impact on Patients of Delayed Drug Approvals. Published online June 2010. https://media4.manhattan-institute.org/pdf/fda_02.pdf

9. Cha M, Yu F. Pharma's first-to-market advantage. Published online September 2014. Accessed November 1, 2020. https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/pharmas-first-to-market-advantage

10. Jain S. Achieving Competitive Advantage in the Biopharmaceutical Industry. BioProcess International. 2016;14(4):3.

11. Lu R-M, Hwang Y-C, Liu I-J, et al. Development of therapeutic antibodies for the treatment of diseases. J Biomed Sci. 2020;27(1):1. doi:10.1186/s12929-019-0592-z

12. Moorkens E, Vulto AG, Huys I. An overview of patents on therapeutic monoclonal antibodies in Europe: are they a hurdle to biosimilar market entry? mAbs. 2020;12(1):1743517. doi:10.1080/19420862.2020.1743517

13. Shukla AA, Rameez S, Wolfe LS, Oien N. High-Throughput Process Development for Biopharmaceuticals. In: Kiss B, Gottschalk U, Pohlscheidt M, eds. New Bioprocessing Strategies: Development and Manufacturing of Recombinant Antibodies and Proteins. Vol 165. Advances in Biochemical Engineering/Biotechnology. Springer International Publishing; 2017:401-441. doi:10.1007/10_2017_20

14. Moorkens E, Meuwissen N, Huys I, Declerck P, Vulto AG, Simoens S. The Market of Biopharmaceutical Medicines: A Snapshot of a Diverse Industrial Landscape. Front Pharmacol. 2017;8:314. doi:10.3389/fphar.2017.00314

December 2020-1