White paper

Biopharma 4.0: Navigating the future of biomanufacturing

How to embrace the transformative impact of Biopharma 4.0 technologies in a new era of biologic production

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The biopharmaceutical industry is undergoing a transformative shift with the adoption of Industry 4.0 principles, collectively known as Biopharma 4.0. This integration of digital communications, automation, and advanced engineering techniques into biopharmaceutical production is crucial for addressing the high costs and lengthy timelines associated with developing new therapeutics.

Driven by the need for operational excellence, rapid product development, and data-driven decision-making, Biopharma 4.0 requires trust in data and measurements, which hinges on proper training and knowledge in relevant manufacturing technologies.

This white paper explores the historical context of industrial revolutions, from the mechanization of the 1700s to today's digital connectivity, each paving the way for increased efficiency, production volume, and market reach. It also addresses personal drivers for adopting Biopharma 4.0, emphasizing career development opportunities and various training pathways to bridge the knowledge gap. By embracing Biopharma 4.0 principles, the industry can achieve greater agility, efficiency, and innovation to ultimately improve patient outcomes and address emerging therapeutic needs.

What is Biopharma 4.0?

Novel technologies have an important role in enabling industrial production. The four main industrial revolutions since the late 1700s were brought by advances in machinery, energy sources, and data availability technologies.[1] The first two industrial revolutions in the 1700s and 1800s were marked by simplified production of machinery and new energy sources of steam, coal, gas, and electricity. These enabling technologies spurred unprecedented mechanization of processes, improved production efficiency, higher production volume, and broader market reach. The third industrial revolution, starting in the 1950s, stemmed from advances in microelectronics which enabled computers and telecommunications. The use of computing and electronics then advanced fundamental knowledge and application development in many fields, including space exploration, biochemistry, synthetic chemistry, and analytical instrumentation.

We are currently in the fourth industrial revolution, also known as Industry 4.0. Industry 4.0 is marked by the widespread use of digital communications, digital connectivity, and advanced engineering techniques such as additive manufacturing or robotics, automation, and renewable energy. Industry 4.0 is changing most manufacturing practices, but it is profoundly impacting the discovery, development, and production of biopharmaceuticals. Industry 5.0 principles augment the pillars of Industry 4.0 via thoughtful interaction between humans and robots or smart systems. The integration of Industry 4.0 principles in the production of biopharmaceuticals is called Biopharma 4.0.

Biopharmaceutical development is an expensive and risky investment. On average, development of a single therapeutic can cost $2.6B and take 10-15 years to reach Phase I clinical trials.[2] Companies who have adopted Biopharma 4.0 practices realize faster time to patient for new therapeutics, more agile manufacturing, and lower costs. One example of faster time to patient is the unprecedented development of Covid-19 vaccines. An overview paper on the Comirnaty vaccine's development underscored the importance of a shared goal, extraordinary collaboration, and enabling technologies in the rapid development timeline to produce 2.5 billion doses/per year.[3] The use of automated laboratory systems and single-use technology was cited as enabling technologies in another Covid-19 vaccine development effort.[4] The operational flexibility demanded by the development and production of Covid-19 vaccines accelerated adoption of Biopharma 4.0 principles and established priorities to transform biologics manufacturing with digitalization in mind.

Many leading biopharmaceutical companies are carefully examining their Biopharma 4.0 readiness across the product development lifecycle. Mike Tomasco, Vice President of Digital Manufacturing at Pfizer, explains, "One of the ways we measure our level of maturity for each site is through the BioPhorum Digital Plant Maturity Model (DPMM)…It is a standards-based model that defines the stages of maturity for biopharma manufacturing processes as follows: Level 1: paper; Level 2: digital silo; Level 3: connected; Level 4: predictive; and Level 5: adaptive."[5] As the industry continues to adopt Biopharma 4.0 principles, digital solutions and evolve toward agile manufacturing, the next goals are to improve operational excellence and flexibility so that the industry can address new therapies in mRNA, cell and gene therapy, and personalized medicine.

Why adopt Biopharma 4.0 principles?

Operational excellence, rapid product development, and data-driven decisions provide clear value to biopharmaceutical manufacturers, and these motivations are the primary industry drivers of adopting Biopharma 4.0 principles. Scientists, engineers, and plant technicians interact with and use a variety of sensors, integrated data management tools, and large amounts of information in their daily jobs. It is therefore important to recognize personal drivers in adopting Biopharma 4.0, with stakeholders from R&D to manufacturing to operational support. At Pfizer, Tomasco states, "We are transforming into a data-driven organization, which means that we need our operators and managers to trust what the data [are] telling them to do."[5]

Across many industries, we have observed that the foundation for efficient process automation is trust in the measurement. But how can you trust the data or the measurement without the right training or knowledge? The gap in personnel knowledge in relevant areas of manufacturing technology–data science, robotics, regulatory compliance, and digital fluency–is a widely acknowledged challenge.[6] There are many avenues to address the knowledge gap, and Biopharma 4.0 offers upskilling and training opportunities not seen in the industry since the early 2000s with the onset of the FDA's process analytical technology (PAT) initiative.

10-15 years

how long it takes on average to bring a new active ingredient to market

$2.6B

how much it costs for a single therapeutic to reach phase 1 clinical trial

Table 1: Biopharma 4.0 training opportunities

Training avenue	Possible educational or career development topics
Internal training workshops	▪ Domain expertise in data science, PAT, spectroscopy, robotics, or automation ▪ Internal best practices
Professional organization memberships	▪ Domain expertise in risk-based manufacturing, quality, regulatory compliance, data security ▪ Mentorship ▪ Networking ▪ Scientific exchange
Online or in-person courses	▪ Domain expertise in automation, PAT, vendor-specific software, cyber security, and data science
Educational degree or certificate programs	▪ Domain expertise in focused topics including industrial communication protocols, project management, or enterprise solutions ▪ Networking

Embracing new opportunities for career development

Quite simply, an important personal driver to learning Biopharma 4.0 principles is career development. Did you know that the most in-demand talents in biopharma are in machine learning, artificial intelligence, process analytical technology, and data science?[7] Training can improve skills for current job roles, bring new opportunities within a company, or increase the likelihood of a successful transfer to another company. In most cases, training on Biopharma 4.0 topics is a job requirement. And, the successful use of Biopharma 5.0 principles that focus on human expertise relies on the skills and creativity of the biopharmaceutical work force.

There are a variety of pathways for training or continuing education, and it may be helpful to think of the avenues shown in Table 1 as an educational ecosystem. Internal training and talent nurturing, educational degree or certificate programs at the university or technical college level, and online courses all have an important role in continuing education. Professional organizations, such as the American Association of Pharmaceutical Scientists (AAPS) or International Society for Pharmaceutical Engineering (ISPE), have mentorship, online discussion boards, training workshops, leadership opportunities, and networking programs in addition to regional or international conferences. Membership in these professional organizations creates opportunities to learn about Biopharma 4.0, industry best practices and practical advice on implementing Biopharma 4.0 principles. Each of these training or education avenues provide the means for those currently in the workforce to learn new skills in digital twins, spectroscopy, sensors, and data analysis.

Biopharma 4.0 draws on new topics in digitalization, enterprise management, project management, continuous improvement, and data science. There are many ways to obtain new knowledge or continuing education, but limited guidance exists to help link these topics with the right tools necessary for practical implementation. Thus, a major hurdle in adopting Biopharma 4.0 for a scientist or process engineer is addressing the question, “where do I even begin?” Below is an overview of the tools to facilitate key areas in Biopharma 4.0. Also discussed is the role of PAT because it is so integral to technology readiness with a proven high impact on operational excellence.

A recent report by McKinsey highlighted ten key areas that offer biopharma companies high-value opportunities for innovation and operational excellence. These areas include:

- Disease understanding
- Disruptive product design
- Integrated evidence generation
- Operational excellence in development
- Medical impact
- Precise and real-time customer or patient engagement
- Industry 4.0
- New digital and data-driven businesses and business models
- Digital organization
- Technology modernization[8]

Not all of these are applicable to the daily job of a scientist or process engineer. However, we identified that disease understanding, disruptive product design, integrated evidence generation, and digital organization are most relevant to R&D scientists (whether their project is a novel target molecule, biosimilar, or charge variant). For process engineers or scientists working in early development, the focus is more on integrated evidence generation, operational excellence in development, Industry 4.0, new digital and data-driven businesses and business models, digital organization, and technology modernization.

Underlying all these concepts is something common to both R&D and process development–the increased use of process analysis. Incorporating process analysis into biopharmaceutical manufacturing has surged in the last two decades, driven by the advent of the PAT framework. Some tools to facilitate the items on McKinsey's list are shown in Table 2 below, encompassing a variety of laboratory and digital approaches.

Table 2. Tools to facilitate innovation and operational excellence in R&D and process development

Role	Key areas to create high values	Tools to facilitate key area
R&D scientist	Disease understanding	▪ Computational chemistry ▪ Next generation sequencing ▪ "Omics" technology ▪ Systems biology
	Disruptive product design	▪ Process Analytical Technology (PAT) ▪ Quality by Design (QbD) ▪ Cell line engineering ▪ Site-specific integration[9] ▪ *In silico* process development[10]
	Integrated evidence generation	▪ Digital twin ▪ Hybrid data+AI process models ▪ Artificial intelligence ▪ Machine learning
	Digital organization	▪ Electronic notebook ▪ Laboratory Information Management Systems ▪ Harmonized digital data protection, exchange, and storage strategy
Process development or process engineer	▪ Integrated evidence generation ▪ Operational excellence in development[11]	▪ PAT/QbD ▪ Process intensification ▪ Perfusion ▪ Continuous manufacturing ▪ Single-use systems ▪ Artificial intelligence ▪ *In silico* process development ▪ Digital twin ▪ Hybrid data+AI process models
	▪ Industry 4.0 ▪ New digital and data-driven businesses and business models ▪ Digital organization ▪ Technology modernization	▪ Digital data harmonization and storage strategy ▪ PAT / QbD ▪ Digital twin ▪ Automation ▪ Cloud-based data exchange

Key areas of focus for R&D and process development incorporate novel tools, such as cloud-based data storage, artificial intelligence, systems biology, and digital twins. More established tools such as PAT and hybrid models are used in new ways, as the emphasis in Biopharma 4.0 focuses on operational excellence from discovery to market to address new therapies.

The role of PAT in Biopharma 4.0

An important aspect of Biopharma 4.0 is inclusion of analyses throughout the discovery and development lifecycle. PAT provides real-time data on physical or chemical aspects of a process, but it is also a regulatory mechanism to enable trust of online measurements. PAT started in pharmaceutical manufacturing in the early 2000s with a regulatory framework of process knowledge and science-based development of manufacturing practices. The well-known 2004 FDA paper on Process Analytical Technologies (PAT) encouraged improved process understanding and manufacturing innovations in Life Sciences.[12] Support of the PAT initiative throughout the product lifecycle has been strengthened by continued guidance from regulatory agencies, such as the FDA, EMA, and ICH, and industry groups such as BioPhorum and ISPE.[13]

Integration of process analysis and increased use of automation in manufacturing started with small molecule pharmaceuticals soon after the 2004 FDA paper and has expanded to include upstream bioprocessing.[14] Later emphasis on Quality by Design (QbD) encouraged a risk-based approach to product and process understanding in a systematic and documented fashion.[15] Some elements of QbD that are familiar to PAT practitioners include using the quality target product profile (QTPP) to identify critical material attributes (CMA) and critical quality attributes (CQA), then linking critical process parameters (CPP) to the CQA and CMA. PAT is an important tool within the QbD framework, often fitting into the product or process control strategy. Today, the use of PAT and risk-based approaches are considered standard in biopharmaceutical production. These approaches are further enabled by adopting Industry 4.0 principles and are critical to innovative manufacturing approaches including continuous manufacturing, single-use systems, micro bioreactors, robotic cell and liquid handling, and real-time release testing.

The use of PAT varies throughout the product lifecycle. Analytical lifecycle development often runs concurrently with the product lifecycle, sharing considerations such as robustness, reliability, and scalability. Just as a QbD or risk-based assessment is valuable for product development, this framework can be used to improve robustness of a PAT throughout the analytical lifecycle.[16] The considerations for PAT will differ as it transitions from pre-clinical R&D to clinical and then commercial manufacturing.

Lab implementation of PAT: focus on scalability and miniaturization

Biopharma discovery is a stage where every molecule has potential to become a blockbuster. Thousands of candidate molecules or a myriad of high-producing clones vie for selection, but they are only available in vanishingly small volumes. With the limited availability of usable supply, studies in toxicology, pharmacokinetics, stability, and bioavailability need to be carried out quickly and judiciously using as little of the material as possible. With analysis being such an important aspect of the biopharmaceutical discovery process, non-destructive optical or spectroscopy techniques like Raman spectroscopy are highly valued.[17] For example, surface plasmon resonance can be used to understand molecular-target interaction, fluorescence for identifying GFP-tagged proteins in high producing cells for clone picking, and mass spectrometry for proteomics or next generation screening. Approaches supporting high-throughput discovery are standard tools with standard models that can be applied for the many candidate molecules. In addition to these high-throughput tools, there is some initial work to support process development. These initial studies typically involve small sample amounts and there is a growing need for the developed process to be scalable beyond the bench to accelerate product go-to-market timelines.

Miniaturization, robotic sample handling, and automation are not new to small molecule pharmaceuticals. Extension of these technologies to biopharma is most often used to build a scale-down model for bioreactors, and transferability is an important criterion for both the process and its analysis.[18,19] But it is only recently that mini- and micro- scale bioreactors have been integrated with Raman spectroscopy. Such an integrated system addresses the primary concerns of an R&D scientist who is working on process development: quickly build process knowledge, allow spiking experiments, and optimize the scaled-down process that can be transferred beyond the benchtop scale. An added value of using a mini- or micro-bioreactor is the possibility to scale directly to 1L - 20L glass bioreactors, as recently demonstrated by Bayer[20] and Sartorius[21] with the use of Raman spectroscopy. These integrated PAT-bioreactors address the Biopharma 4.0 key areas of disruptive product design, integrated evidence generation, and digital organization.

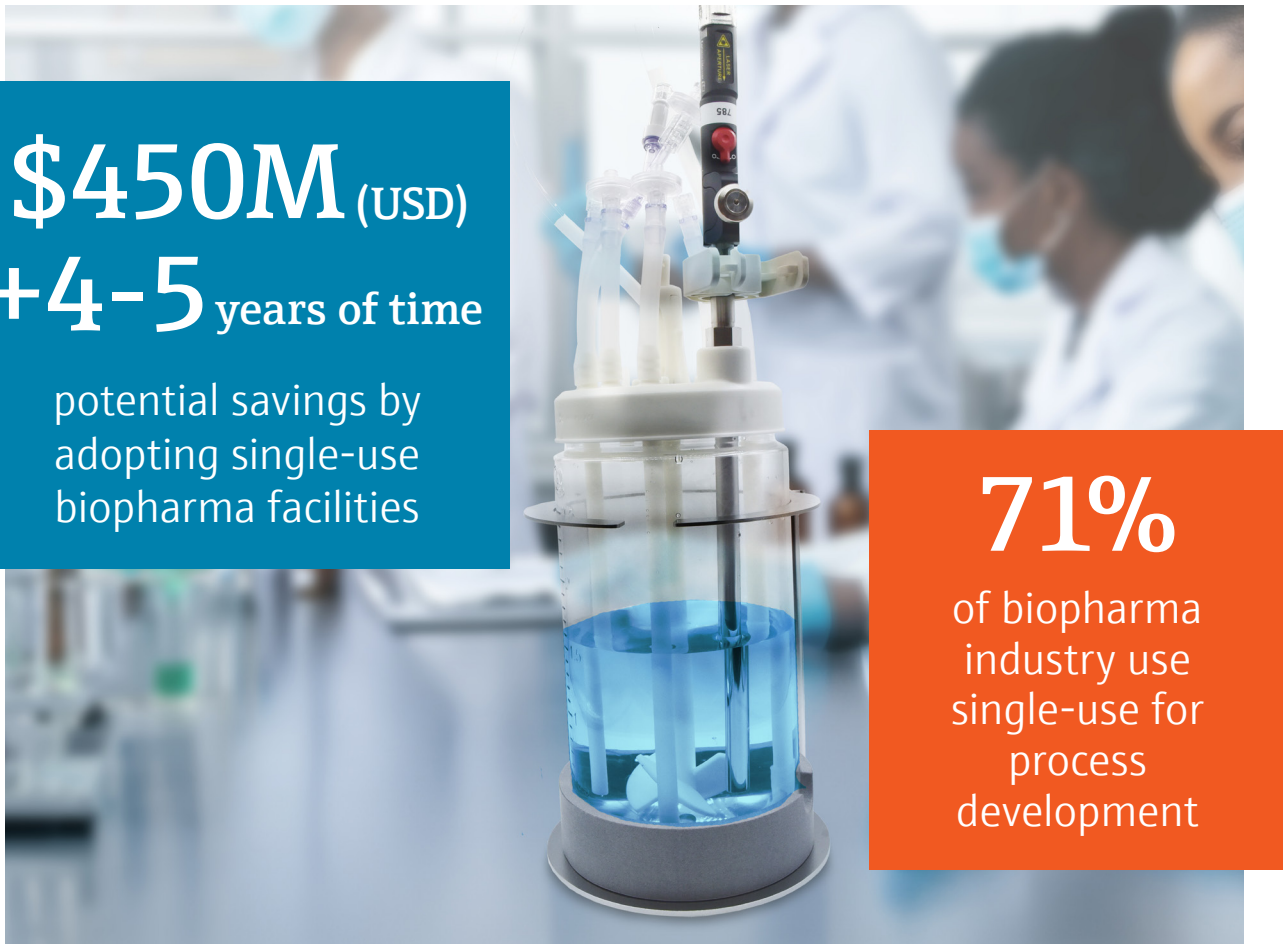
Raman spectroscopy, a specific PAT tool, is particularly valuable in Biopharma 4.0 due to its non-destructive nature and high molecular specificity. It allows for real-time, inline monitoring of critical quality attributes (CQAs) and critical process parameters (CPPs) such as glucose, lactate, cell density, and protein titer. This capability enables advanced process control and ensures consistent product quality throughout the manufacturing process. By providing detailed molecular information without the need for extensive sample preparation, Raman spectroscopy helps maintain the integrity of the biopharmaceutical products and supports the Quality by Design (QbD) framework.

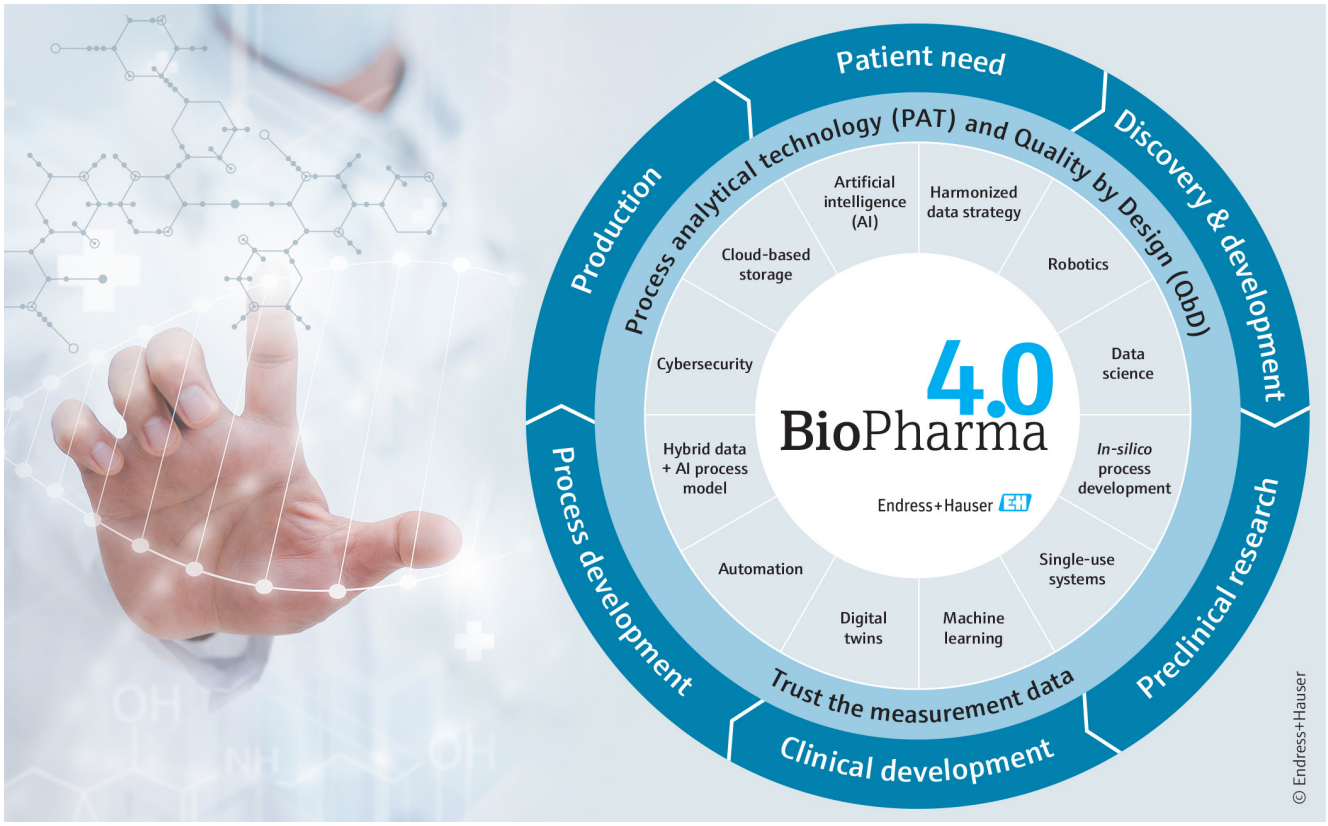
Tech transfer implementation of PAT: focus on flexibility, intensification, and sustainability

It is important to note that as the product is being developed, so too is the analytical/QA/testing approach. Analytical development can be part of a lead declaration, and it is here where PAT models and methods are developed for the bench scale or scaled from the micro scale. In discovery and early process development, there is a lot of flexibility to develop new analytical methods, write documentation, and learn about what works and what can go wrong. The open-ended flexibility in analytical development may seem overwhelming, since there are so many variables for data collection and analysis. Lessons learned from analytical development of a similar target may also be lost if data or group reports are not stored properly or accessible. This is where adopting the Biopharma 4.0 key target area of digital organization may help to accelerate process development. In a recent interview, Bethany Silva, Life Science Industry Manager for Endress+Hauser, identified PAT/QbD as one of the top three current trends in the biopharma industry today.

Even without the complication of developing a new analytical model or method, there is a staggering volume of data in the process development stage. The sheer volume of data from this myriad of tests and sources necessitates digitalization and a central repository for project teams to make accurate decisions rapidly. A harmonized digital data storage and archive strategy, electronic notebooks, and Laboratory Information Management Systems (LIMS) are tools that support the needs of the R&D group. Use of electronic notebooks for all R&D and process development teams has tangible benefits. One of those benefits is that the data or notes from relevant campaigns can be mined manually or by AI. The mined historical data can then form the basis of an initial PAT or QbD strategy.

Another trend on the rise is single-use technologies becoming more prevalent in process development to support process intensification and flexible manufacturing demands.[22] The use of single-use equipment also reduces cleaning requirements, shrinks the facility footprint, and does not require a new plant to be built, commissioned, and validated. Thus, the adoption of single-use facilities can represent savings up to $450 million dollars and 4-5 years of time.[23] Single use is used in 71% of biopharma industry for process development, and we anticipate that continued innovation in single-use equipment, sensors, and integration with PAT will facilitate continued adoption in process development and in commercial manufacturing in the next 2-4 years.[24]





cGMP implementation of PAT: focus on robustness and compliance

Clinical and commercial manufacturing requires production of a biopharmaceutical product with tight specifications and controls to ensure consistent product quality, safety, and efficacy. In this regulated environment, there is little to no flexibility for changes to documentation, instrumentation, data storage, and process protocols. Stability and consistency become paramount. Out-of-tolerance process targets or product specifications have costly ramifications for a clinical or commercial campaign. Batch losses can cost millions of dollars and drastically delay production. The strict regulations and expectations on product quality and manufacturing processes also applies to PAT, data analysis, and data communication. Benefits of a PAT-enabled bioprocess includes a well-defined design space for robust and predictable outcomes, real-time monitoring and control, fewer batch losses, increased yield, and faster product releases.

The role of data digitalization in Biopharma 4.0

Digitalization has been a boon for industrial manufacturing, as it has enabled a unified output for plant sensors and instrumentation. Engineers no longer need to physically walk through a plant and understand how to read thousands of dials, sensors, gauges, or voltages. Output from a variety of sensors is now digitized and integrated into distributed control systems (DCS) and supervisory control and data acquisition systems (SCADA). The ecosystem that turns the data into useful information includes model development and maintenance, integration into control systems, data integrity and compliance, and instrumentation qualification, maintenance, and service. On top of that, the PAT ecosystem adds requirements of documentation, vendor qualifications, and audits in cGMP environments.

Adoption of Biopharma 4.0 principles is an ongoing effort to focus on digitalization tools to affect operational excellence. Soon after Biopharma 4.0 was introduced, it was widely recognized that several important factors needed to be integrated. Those factors are sustainability, the human-machine interface, and human creativity. Thus, Biopharma 5.0 is a concurrent paradigm that recognizes the important role of human experience. The need for knowledge development, upskilling, and ongoing training in digitalization, artificial intelligence, and machine learning are reinforced in Biopharma 5.0.

Digitalization is a framework to bring in more data, turn it into useful information, and then disseminate and store it safely. Specifically for PAT, digitalization enables in situ analyses to be used to support operational excellence throughout a facility in the form of centralized process control, multivariate analysis, and digital twins. PATs are a “big data” source and provide real-time information on multiple process and quality attributes. The use of multivariate analysis to interpret spectroscopy data and use it for qualitative and quantitative predictions was

Companies adopting Biopharma 4.0 practices realize:

1. Faster time to patient

2. More agile manufacturing

3. Lower costs/ most savings

the first step in PAT data digitalization. Now, PAT data are used as an engine for digital twins. Digital twins differ from mathematical models such as Monte Carlo simulations in that they run in conjunction with a physical system and data from the physical system reports to the DCS and the digital twin.[25] A digital twin can handle bidirectional data flow, and is readily integrated into AI or machine learning.[26] Digital twins are especially useful in modeling upstream production because of the complex interaction between process conditions and cell metabolism.

Digitalization has proven benefits on operational efficiency. The wealth of data generated by PAT can be used for physical process control and as input into digital twin models. An important part of the digitalization is to contextualized the information. This is often achieved with a combination of AI or ML models and human expertise. This integrated approach is an example of putting Industry 5.0 principles into action.

Conclusions

Biopharma 4.0, inspired by Industry 4.0, represents the digital transformation of biopharmaceutical manufacturing. This paradigm shift leverages advanced technologies such as AI, machine learning, the Industrial Internet of Things (IIoT), and big data analytics to create smart, automated factories. The goal is to enhance efficiency, reduce costs, and improve product quality by enabling real-time monitoring and control of manufacturing processes. Operational excellence in Biopharma 4.0 is achieved through the integration of digital technologies and advanced analytics, which streamline processes and enhance decision-making. By adopting a holistic approach that includes automation, real-time data analytics, and continuous improvement practices, biopharmaceutical scientists and engineers can improve operational efficiency through open and easy access to data and the knowledge it yields about multiple processes. Embracing these principles not only drives innovation but also ensures that biopharmaceutical manufacturing remains agile and responsive to market demands.[27]

PAT plays a crucial role in Biopharma 4.0 by providing real-time data to monitor and control manufacturing processes. Raman spectroscopy is a proven PAT for upstream bioprocessing, from the micro-bioreactor to cGMP, and strongly supports Biopharma 4.0 key areas in disruptive product design, integrated evidence generation, digital organization, and operational excellence in development. PAT enables the continuous assessment and adjustment of critical process parameters, ensuring that products meet quality standards throughout production. PAT also supports innovative approaches to process development including miniaturization, single-use bioreactors, process intensification, continuous processing, and micro-to-pilot scalability. These approaches not only enhance process understanding and increase yield but also reduce the likelihood of batch failures and improve overall efficiency. By incorporating PAT, biopharmaceutical companies can achieve greater precision and reliability in their operations, aligning with the principles of Biopharma 4.0. Integrating PAT into digital twins also enables manufacturers to simulate and optimize operations, predict maintenance needs, and ensure consistent product quality.

Biopharma 5.0 recognizes the need to integrate human creativity and input into digital systems. Learning new skills in digitalization, data science, and AI is critical for the successful adoption of Biopharma 4.0 and Biopharma 5.0 principles.

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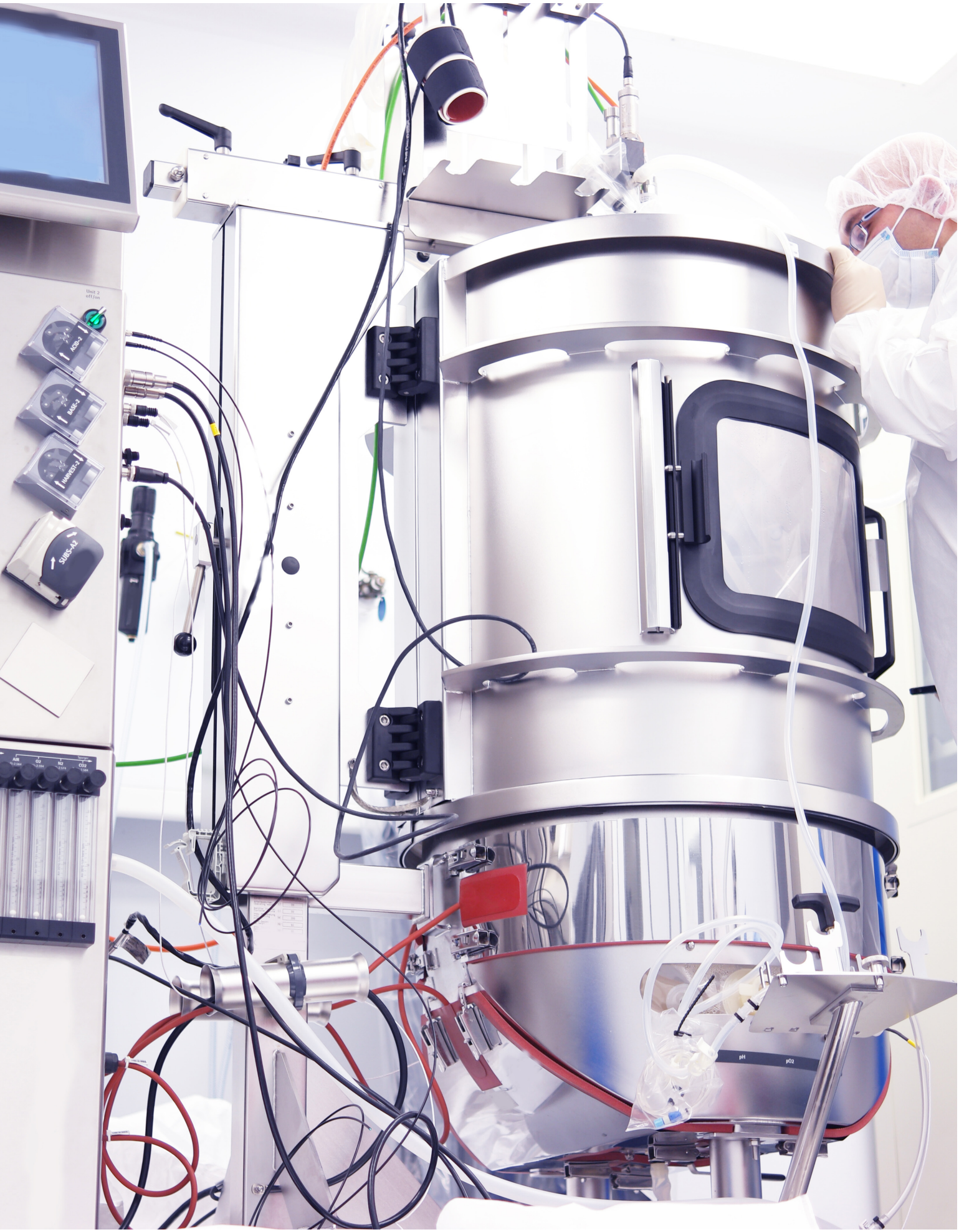
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