Bioprocessing 4.0 – Where Are We with Smart Manufacturing in 2020?

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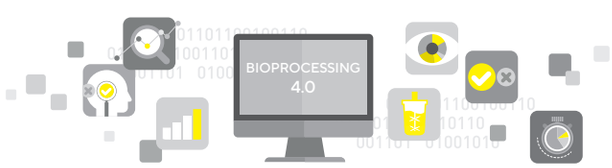
Introduction

The term Bioprocessing 4.0 has been tossed around since 2018 and is derived from Industry 4.0, a national strategic initiative from the German government launched in 2010 with the aim of driving manufacturing forward by increasing digitization and the interconnection of products, supply chains and business models.[1] Bioprocessing (or Bioprocess) 4.0 today is defined as a totally end-to-end connected bioprocess, where all systems and equipment in the process are connected digitally, forming the Industrial Internet of Things (IIoT) to run, control and even improve the process via feedback loops and artificial intelligence (AI) or machine learning. IIoT is redefining automation architecture and simplifying the automation pyramid by compressing many of the lower layers and also upper layers. Sensors, instruments, and other devices are interconnected directly to the cloud for data collection and analysis, as well as optimized process controls. Due to the need for real-time control capabilities of bioprocess workflows, Bioprocessing 4.0 relies heavily on integrated data management and analytics, modelling and automation, as well as cloud and edge-based computing for the vast amounts of data it produces.

The biopharmaceutical industry has lagged behind other industries, such as oil and gas, where they have been using integrated processing since 1995, as well as finance and the semi-conductor sectors, which have been using end-to-end digitization since 2000. One reason for the biopharmaceutical industry being behind is that



unlike many other industrial processes, bioprocessing is not binary and generally involves complex living cells where variability is high making measurement and predictions of bioprocess performance challenging. The industry is also heavily regulated, with special constraints around contamination and safety, where changes to a Good Manufacturing Process Compliant (cGMP) locked down process are viewed by bioprocess scientists as tricky to implement. Another reason is that process automation capable of culturing cells and purifying biologics in bioprocessing was in its infancy in 2000, as were scale-down models for predicting process performance and Process Analytical Technology (PAT) tools for real-time bioprocess monitoring.

Some might say that Bioprocessing 4.0 really began to take off after 2004, with the publication of the FDA's guidance on PAT and (Quality by Design) QbD, which aimed to reduce process variability and thereby improve quality, safety and/or efficiency in drug manufacturing.[2] The idea has been driven forward by a number of industry bodies including the Biophorum (BPOG)

with its Biomanufacturing Technology Roadmap in 2017.[3] This was followed by its plug and play initiative in 2018[4] and The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) with its ICH Q12 guidelines.[5] Each of these initiatives and guidelines has helped galvanize forward-thinking biopharmaceutical companies and life science equipment suppliers into action on standardization and integration of bioprocess automation.

Who's Embracing It?

Biopharmaceutical manufacturers are being driven to adopt Bioprocessing 4.0 by market pressures to produce biologics in a shorter timeframe without compromising product quality and safety. The SARS-COV-2 pandemic has magnified the need to do this because of the time-critical need to produce vaccines to prevent and therapies to treat this novel Coronavirus.

The ideal Bioprocessing 4.0 manufacturing facility for rapid, flexible production would include fully automated upstream single-use (SU) bioreactors designed for intensified processing using high cell density fed-batch culture or perfusion culture. The bioreactors would have associated SU in-line sensors, providing real-time information to determine or estimate Critical Quality Attributes (CQAs), such that scientists could gather data for release decisions while the process is running. These facilities would also have 'digital twins' of bioprocess equipment, such as bioreactors and chromatography columns, which are *in silico* simulations of the process, that can be used for improved process control or run simulations in place of physical experiments when needed. Using this type of Bioprocessing 4.0 set-up would mean weeks could be shaved off process runs because there would be less waiting for off-line data testing and feedback, we could run virtual process testing, and time for cleaning and cleaning validation of equipment would be virtually eliminated.

Companies such as Biogen are actively working towards Bioprocessing 4.0 with studies by Ahmed et al in 2019 where they have constructed a hybrid model or 'digital twin' of their cell culture process, which includes cell growth, glucose consumption, lactate, glutamine, glutamate and ammonia production, as well as titer data to simulate a high titer monoclonal antibody (mAb) production bioreactor.[6]

Sanofi has also embraced Bioprocessing 4.0 in its new biomanufacturing facility in Framingham, Massachusetts. The plant, which opened in 2019, is highly digitized with closed loop controls for intensified, continuous biologic production using automated data capture from a range of sensors. The cloud-based data can be accessed from anywhere in the world in real-time to assess bioprocess runs and make process changes if necessary. Sanofi has also generated 'digital twins' of its production bioreactors, so that bioprocess scientists can simulate manufacturing process changes.[7]

Bioprocessing 4.0 is not just about controlling process runs, and Amgen has recognized that actively managing the supply chain is an important piece in the puzzle and has set up a Supplier Relationship Excellence (SRE) program to create a feedback loop where electronic data is exchanged with raw material suppliers. The program aims to understand operational performance by developing data exchange standards, using predictive models to anticipate supply issues or identify any improvements[8] and thereby ensure biologics' quality is continuously achieved without any issues.

Game Changing Technology

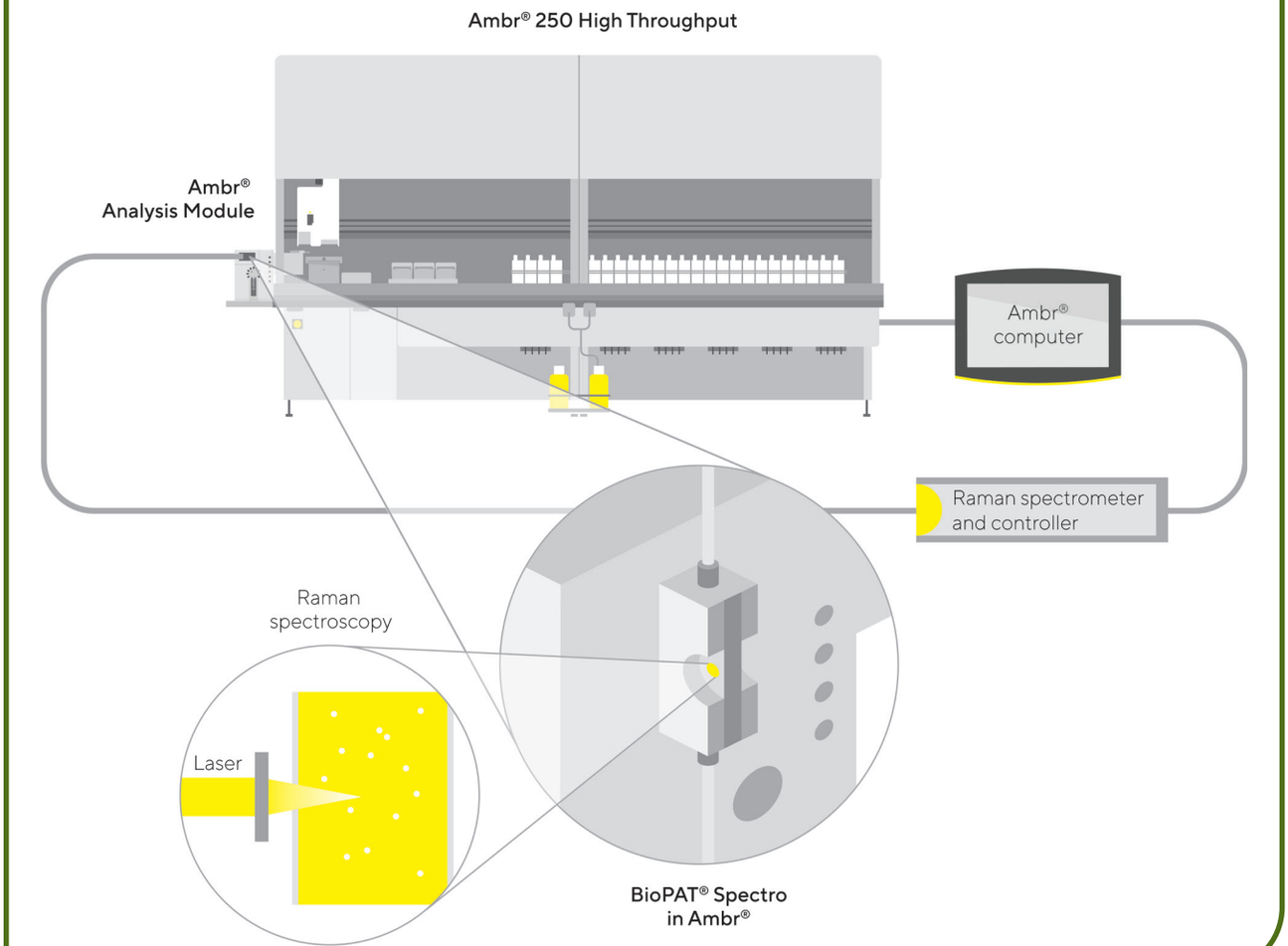
In the past decade, a technology platform that has been helping to move the biopharmaceutical industry closer to Bioprocessing 4.0 in the upstream is the high-throughput automated scale-down bioreactor mimic. These mini bioreactors have been shown to provide robust estimates of process performance and product quality from bench to pilot scale in studies by Lewis et al at AstraZeneca[9] and Hsu et al at Genentech.[10] They have also recently been used in 2019 as a qualified scale down model for process characterization by Manahan et al at Merck in large-scale commercial bioreactors (>10,000 L).[11] Using mini bioreactor technology with PAT tools that can be transferred between SU bioreactor scales offers a simpler method of integrating and digitizing an end-to-end upstream process.

Aligned with mini bioreactor technology, spectroscopy is an analytical technique that is helping move the upstream Bioprocessing 4.0 dial. Spectroscopy techniques such as Raman, Fourier-transform infrared (FTIR) and Near-infrared (NIR) are beginning to replace off-line HPLC and autosamplers because these off-line measurement methods are time consuming and cannot provide in-line feedback loops for real-time monitoring and control as Raman spectroscopy, for example, can. The use of spectroscopy techniques looks set to increase in the next decade as they are tackling some of the pain points of measuring cell culture and monitoring CQAs of biologics.

Currently in-line Raman spectroscopy is being used in pilot and manufacturing scale cell culture. But there are studies that indicate this technique has the potential to be used as an automated on-line method to measure multiple analytes simultaneously in mini bioreactors[12] (Figure 1). Biopharmaceutical companies such as

Digital twins of bioprocessing equipment are often used in Bioprocessing 4.0 facilities.

Figure 1. Mini bioreactor technology with an integrated Raman spectroscopy platform



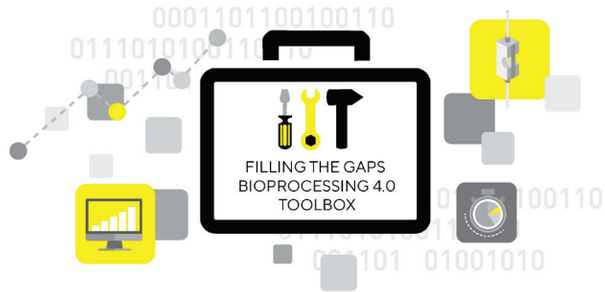
GlaxoSmithKline are working with integrated Raman spectroscopy from mini bioreactors through to manufacturing vessels to rapidly and more easily build models that can control their bioreactors.[13] Having this integrated real-time PAT technology from process development though to manufacturing scale will help to build Bioprocessing 4.0 upstream cell culture processes in many biopharmaceutical companies in future.

Where are the Gaps?

In general, upstream is further down the Bioprocessing 4.0 road in terms of connectedness and digitization than downstream. This is because downstream processing relies on more traditional, less automated equipment and techniques with fewer in-line sensors and it is often difficult to connect all the parts of the process, which means there is less opportunity to collect meaningful data and control processes, leading to high variability in downstream bioprocessing.

What is required now is the capability to connect downstream equipment together more easily, (the increasing use of ballroom style skids is helping here), as well as the use of more PAT sensors to collect data on process variables. Also design of Experiments (DoE) studies using scale down high throughput columns and filters and multivariate data analysis (MVDA) of the results are needed to predict the effects chromatography resins and filter pressures, for example have on processes and CQAs.

With the level of integrated SU technology and in-line sensors available in the upstream, it should be easier for many biopharmaceutical companies and CDMOs to be implementing Bioprocessing 4.0 here. Yet this is still not the case. One of the main reasons many companies are not implementing Bioprocessing 4.0 in the upstream or downstream is bandwidth and budget constraints. Many smaller biopharmaceutical companies and CDMOs simply do not have the money or the staff available with the right skill set that can spend



time making sure their processes and analytics are fully integrated. This is an area where equipment and software suppliers can assist, and they should try to ensure that their products are as ready to use for seamless integration and digitization in manufacturing facilities as possible.

Another reason why many biopharmaceutical companies are wary of Bioprocessing 4.0 is a lack of regulatory guidance. Although, the FDA has issued information on implementing ICH Q8, Q9, Q10,[14] which is beginning to put boundaries around processes and product quality, guidelines around some automation and sensor technologies are missing. For example, Raman spectroscopy sensors that measure multiple analytes in cell culture are not fully covered. Additionally, there is limited guidance on how to validate chemometric models generated from Raman spectroscopy with MVDA for use in GMP facilities. With the increase in use of continuous instead of fed-batch culture in the upstream, there is a much greater need to validate PAT methods such as Raman spectroscopy as these can be used for in-line monitoring and feedback control of processes that could potentially have much longer run times and where the definition of a "batch" is unclear. The FDA has given some good strategic guidance on spectroscopy; however, the biopharma industry needs more prescriptive guidance, which is likely to come when the ICH Q2/Q14 guidance (currently in draft) is published and should improve communications between regulators and the industry.[15]

Finally, there is a lack of skilled technical staff to run Bioprocessing 4.0 type facilities as many educational institutes are not providing the right kind of training with very few courses on advanced process control currently being offered. This gap could be plugged by equipment suppliers, if they can hire enough IT experts with a diverse skill set to develop software and automation that can be used intuitively with minimal training by operators on the shop floor. However, this means suppliers need to invest time in understanding the bioprocess workflow and how the different personas of people working along it interact with the equipment from a user experience point of view.

Conclusion

Despite Bioprocessing 4.0 with its integration and digitization promising better process consistency to improve quality and safety in biologics manufacturing, only a handful of biopharmaceutical companies are currently embracing this initiative. However, by leveraging technology advances including mini bioreactors for process development, SU scalable bioreactors, PAT tools for automated in/on-line spectroscopy and MVDA, Bioprocessing 4.0 in the upstream at least is becoming more widely achievable. In the downstream however there is still a way to go with automation, PAT tools and data analysis. If clear regulatory guidelines, improved access to the right type of training for scientists and delivery by suppliers of equipment and software that harmonizes with a plant's digital connectedness can be achieved, then a tipping point will occur, so that by 2030 Bioprocessing 4.0 manufacturing facilities, which can be operated from anywhere in the world, will become commonplace across the biopharmaceutical industry.

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