A Look into the Future of Bioprocessing

by Dr. Svea Grieb, Kai Touw and Dan Kopec

The internet of things and robotics are already the working standard in fast-adapting industries. These technologies are now also being implemented in the biopharma industry, which is more conservative due to strong regulations and intrinsically complex processes. How is this change going to proceed and how does it change the industry? Does it provide a bigger benefit than its risk? We asked three experts for process analytical technologies, automation and data analytics from Sartorius about their view on the future of bioprocessing.

Advantages of Next Generation Manufacturing

We would first like to discuss the main advantages of implementing Process Analytical Technology (PAT) and advanced data analytics, which enable automation of bioprocesses. This allows for the production of higher quality and more consistent biologic drugs and regenerative therapies at reduced costs of goods (CoGS), with higher flexibility and faster time to market[1,2]. We consider the five main advantages of the implementation of PAT, automation and data analytics to be the following:

Consistent, High Product Quality

Consistency in product quality and quantity is achieved, as variations of critical process parameters (CPPs) are reduced and process robustness is increased. This is summarized in figure 1.

Reduced Risk of Lost Batches and Increased Process Safety

Reduced risks of operator errors and of contamination through manual sampling. The timely identification and correction of process irregularities reduces the risk of lost batches.

Fast and Predictive Up- and Down-Scaling

A well characterized and monitored process together with scalable hardware can significantly reduce the cost and efforts of process scale up | down, as scale variations can be accounted for in an automated and predictive fashion.

Freeing up Operators

Advanced Automation reduces the requirements of operator interference, which on the one hand reduces the risk of operator errors, and on the other hand allows the operators to focus on other tasks.

Account for Cell Variation from Different Sources

The field of personalized medicine benefits greatly from automation. In regenerative medicine applications, the autologous nature of the treatment demands a process that is flexible, and can dynamically adjust to wide variations in starting material. PAT can account for the variations and peculiarities of the cells from different patients in an automated fashion. This result in a high process consistency irrespective of the starting material.

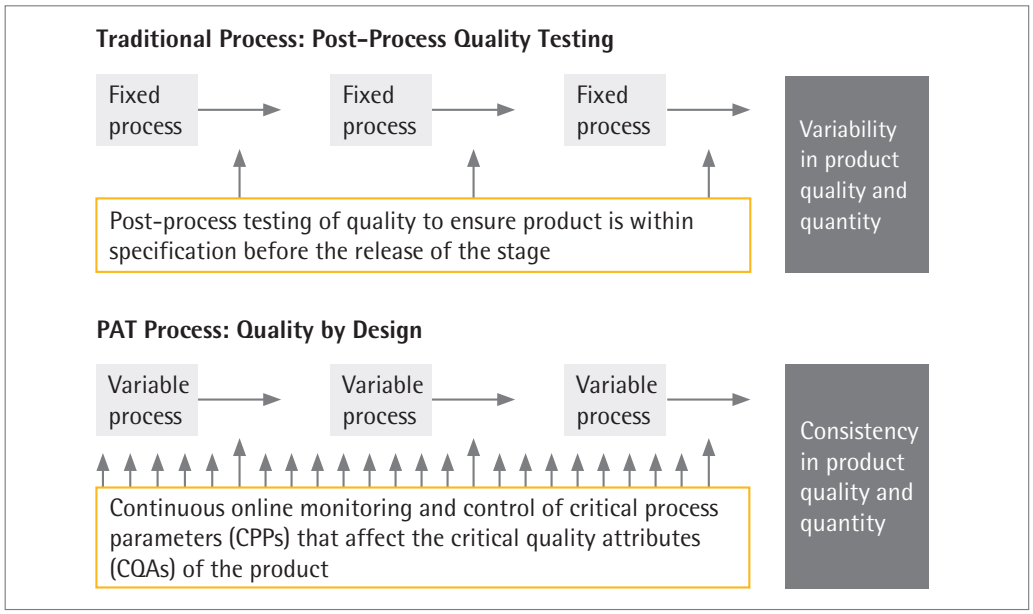


Figure 1: PAT and automation result in consistent, high product quality

Key Technologies of Next Generation Manufacturing

We would like to discuss three key players of next generation manufacturing that are currently driving the change.

Flexible, Automated Skids

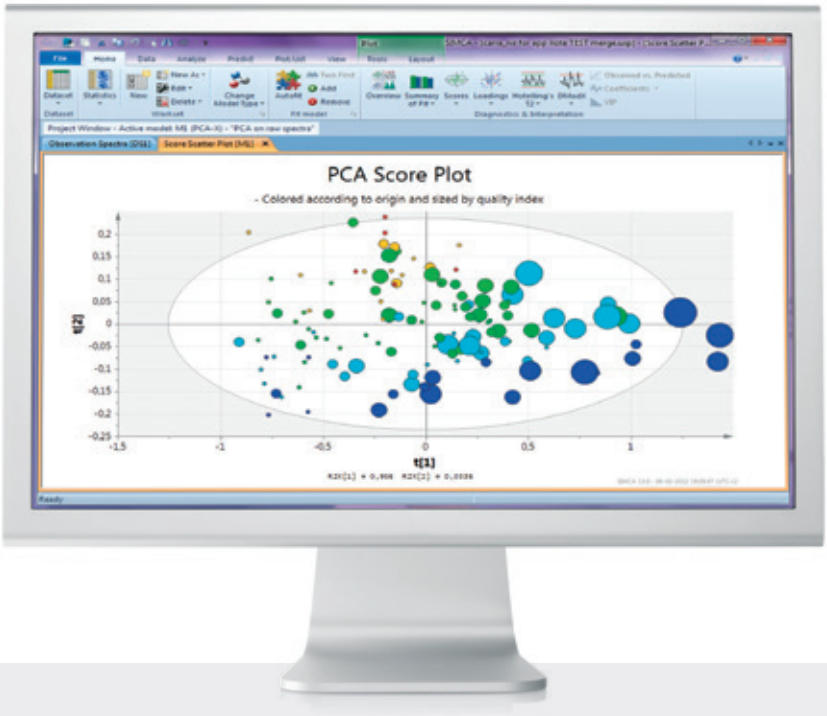
A technological development, which is key for use in down-stream processes are flexible automated skids, capable of handling different type of unit operations, all based on S88 compliant recipes. These type of process skids make it possible to run standardized and automated processes in facilities making use of a 'ballroom' concept.

Spectroscopy

We believe that spectroscopic techniques will become more abundant in both upstream and downstream bioprocessing, due to its capability of label-free, online measurements of several analytes, cell properties and product quality attributes. Hence, spectroscopy has the potential to replace offline measurements during the bioprocess. We envision the use of a combination of different spectroscopic techniques, such as NIR, Raman and UV-Vis to be required for this. That said, there will be a continuing need to use and further develop other technologies, such as bio-capacitance, and dedicated nutrient | metabolite sensors, for application for which spectroscopy does not provide a solution. Furthermore, to propagate the use in GMP, we envision a combination of sensors which crosscheck each other.

Multivariate Data Analytics

The application of sophisticated PAT tools in combination with multivariate data analytics has a high impact on commercial processing. Measurements are moved forward in the process to the point of controllability. Using process fingerprints, the state of the process can be assessed at any time. Furthermore through real-time univariate and multivariate process monitoring, data can be used for simulation and modelling of process design and control and ultimately lead to prescriptive analytics of product quality.



On the Challenges of Next Generation Manufacturing

When speaking about automation of bioprocesses, we need to evaluate technical feasibility and cost-benefit analysis. Furthermore, there are regulatory, logistics and safety issues that have to be solved before automation can really be adopted widely in the biopharma industry.

Processes Challenging to Automate

While we do not think that there is an application in the process of biopharmaceutical drug production that would not benefit from automation at all, we do not envision that we will see a high degree of automation added to already existing pipelines, such as well-established fed-batch processes. Unless, of course, the automation adds a significant improvement to the process, as we have seen it for automated temperature shifts at a certain viable cell density, for example. Further, there are processes that are possible to automate but do not benefit massively from the automation, as the manual interference is very limited, such as dead-end filtration. Finally, there are processes that will be quite challenging to find an automation for. Product quantification with a background of many other proteins could be one such example.

Compatibility and Infrastructure Challenges

The seamless integration of process equipment and process skids into the automation system, especially when considering flexible manufacturing facilities, is an issue. Communication between competitor solutions is not always given and there is a lack of standards that still need to be established. Further, there is the challenge of aligning the process automation concept of a supplier to the facility automation concept in terms of environmental monitoring, building monitoring and a certain level of integration into resource planning systems.

Regulatory Challenges

Some concepts of modern automation technologies and sensor technologies are not yet covered by regulatory guidelines. This is especially true for multivariate data analysis that takes all available data and integrates them into a fingerprint. The adoption of such batch-fingerprinting concepts must be considered by the regulatory bodies. The same questions arise for multi-analyte sensors that are based on computational models, as it is the case for spectroscopy, for example. How do we validate a model for the use of GMP? What are the characteristics of a 'good and robust' model? These questions have to be addressed. A last case we want to mention is the definition of 'a batch' for continuous processing. Regulations that were once established for a 2-weeks process have to be adjusted to processes that can potentially run for months without interruption. The Regulatory Agencies are well aware of the challenges which come with modernizing the industry, but are open and cooperative to new concepts coming from technical advances in the field of automation, PAT and advanced analytics, as is shown by the creation of the 'Emerging Technology Program' by the FDA[3,4].

IT Concerns | Data Integrity

A comprehensive automation strategy for an entire bioprocess, and potentially an entire production site, requires connectivity of all components and a centralized control unit. However, that would require data sharing and access that implies safety risks. We experience reluctance among our customers to adopt new technologies such as cloud computing and wireless communication of PAT components.

We are convinced that the task of meeting the requirement of next generation manufacturing in terms of hardware, software, data analytics and infrastructure is too demanding and complex to be addressed by just one supplier. It requires the collaboration of several industries in strong exchange with the customers to guide new developments. Sartorius has realized this need, as reflected by the integration of Sartorius Stedim Data Analytics (former Umetrics®) and the collaboration with Siemens for our newest automation platform NewAP.

On the Potential of Next Generation Manufacturing

We expect the upstream processes to benefit the most from automation, due to the highly variable nature of the biological process. A higher degree of automation and standardization of the process steps will lead to improved batch-to-batch consistency, and in turn, product quality. There are three application areas that will benefit the most from automation and therefore drive the development of PAT integration and advanced data analytics.

Intensified Processing | Continuous Processing

Intensified | continuous bioprocessing is a very hot topic in the biopharma industry at the moment, as it increases the productivity of single-use (SU) facilities, while decreasing the footprint[5]. This renders SU facilities competitive to conventional stainless steel plants for commercial supply of biopharmaceutical drugs. However, intensified processes are much more complex than conventional fed-batch processes and therefore require a tighter monitoring and control. PAT and automation do not only provide this, but also reduce the complexity for the operator. Another reason for why we think intensified | continuous processing will boost novel solutions, is that establishing new manufacturing pipelines with unique requirements justifies the costs and efforts of going through the approval for commercial manufacturing.

Viral Processes

When producing viral vectors for novel vaccines or gene therapy, the product is no longer a well characterized molecule, such as a monoclonal antibody, but a complex of various proteins, DNA | RNA and in some cases lipid membranes. This complexity makes it hard to identify and understand the factors influencing the product Critical Quality Attributes (CQAs). Hence, these processes benefit from a stricter control strategy, where high levels of automation and implementation of PAT and advanced data analytics play a key role. Another crucial aspect to consider when setting up a viral vector production process is the operator safety. Using PAT and automation minimizes the need of manual sampling and off-line monitoring, hence reducing the risks of spills or leakages.

Cell and Gene Therapy

In personalized medicine applications in the field of cell therapy, every process is unique. As the starting material are the patient's cells, there naturally is a high variation. Furthermore, these processes run at very small scales, with terrifically high costs per batch and high risk[6]. In these cases, lost batches must be prevented in any way possible. Online sensors for monitoring and control reduce the contamination risk of manual sampling and account for process variabilities. Because of the small batch size, these type of processes will also greatly benefit from parallelization, where a refined automation concept is of vital importance to lower the costs of goods (CoGs) and enhance patient safety. Advanced data analytics in CAR-T processes can improve process robustness by, on the one hand, controlling the quality of viral vectors and, on the other hand, account for the intrinsic variation in raw material attributes and their effect on the patient's response.

A look Into the Future

2 Years from Now

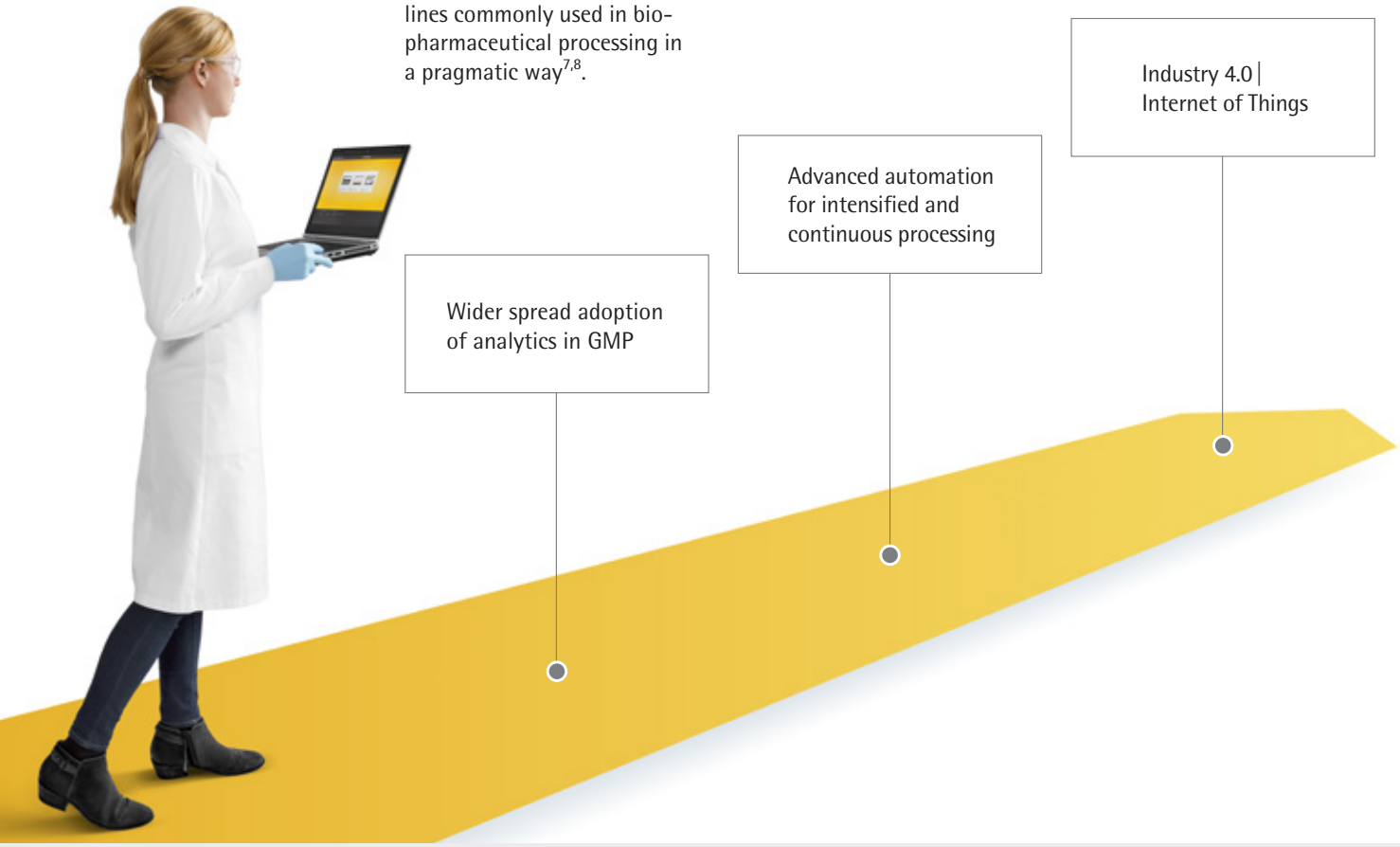
In the near future, we expect a wider spread adoption of analytics in GMP that are already available nowadays, such as spectroscopy for metabolite control and bio-capacitance for viable biomass. We also foresee that multivariate data analysis (MVDA) and design of experiments (DOE) are adopted by more users. Furthermore standardization has been realized to allow a real plug & produce scenario in a (multi-product-) facility setup. Also the field of hybrid modelling, where statistical and deterministic modelling principles are combined, will advance within the biopharmaceutical industry, further improving process understanding and simulation. Within systems biology, for example, these approaches are starting to be applied to enhance the production cell lines commonly used in biopharmaceutical processing in a pragmatic way[7,8].

5 Years from Now

In the mid-future, we expect that modern facilities will apply intensified and continuous processing with advanced automation. They will be using state of the art automated process batch management and S88 compliant batch recipe control functionalities, as well as plant-wide visualization and electronic batch records. Furthermore, sophisticated analysis tools, such as HPLC and mass spectrometry will be automated and integrated in the bioprocess. Together with an increased use of data science, quality by design approaches can be applied allowing real-time release testing of product quality based on batch finger printing. Robotics will take over tasks, which cannot be automated otherwise. E.g. materials are transported to and from the production location in-time.

10 Years from Now

The far-future vision is highly influenced by the industry 4.0 approach and related concepts such as machine learning and the internet of things. We will see fully automated, continuous bioprocessing pipelines that require no operator interventions. Processes can be monitored and controlled remotely. Every process will have a digital twin that can be used for process simulation and prediction. More and different data will be gathered and will reside in the cloud, where data analytics can be applied easily to improve processes, regardless of manufacturing location.



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Dr. Svea Grieb is product manager for Process Analytical Technology (PAT) for upstream processes at Sartorius Stedim Biotech. In this role, she has global responsibility for sensors and analytical systems. Before joining Sartorius in 2017, Svea did her PhD at the TU Dresden in single-molecule spectroscopy. Throughout her education Svea has worked at the MIT in Boston, US, the Max Planck Institute in Stuttgart, Germany, and the Pasteur Institute in Paris, France.

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Kai Touw works as (Bio)Pharma Market Manager at Sartorius Stedim Data Analytics.
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Dan Kopec is a PAT Technology Expert for Sartorius Stedim Biotech, covering the North American region. Dan is based out of Denver, CO and has over 10 years with Sartorius Stedim and 20+ years' experience in process sensors for monitoring, control, and automation in biopharma, food, and chemical industries.

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