Capgemini engineering

THE BIODRUG REVOLUTION

Accelerating bioproduction towards high performance and scale

CONTENTS

INTRODUCTION

Life Sciences is experiencing a huge transformation caused by the innumerous innovations in technology. More than ever, society is hearing about biological treatments (Biodrugs) and their therapeutic advantages.

Biodrugs are drugs with active ingredients that are complex biological molecules, or which are produced from living systems, such as cells or tissues. Examples include antibody therapies, vaccines, gene therapies and cell therapies.

Many Biodrugs represent the cutting-edge of biomedical research and offer potential to treat a variety of medical conditions for which no other treatments are available. In recent years - as knowledge, interest and investment in Biodrugs has increased - the pharmaceutical biomanufacturing industry has grown significantly. Biotherapies now represent half of the top two hundred medicines sold[1].

Some Biodrugs are global therapies: for instance, the therapeutic proteins and monoclonal antibodies (mAbs) commonly used for treatment across large populations.

On the other hand, some cell and gene therapies are highly personalized and developed to be able to act at genome or cellular level in specific host patient human cells – this means that an individual therapy will be the one that best fits best each one of us, improving the therapeutic success and decreasing the probability of side effects.

Finally, nucleotide technologies such as mRNA, developed from gene engineering combined with whole genome sequencing, are now within our reach and show great promise for personalized medicine and for diseases that were previously considered untreatable.

Thanks to emerging biotechniques and a growing knowledge in omics (biological sciences that includes genomics, transcriptomics, proteomics, or metabolomics), scientists are enlarging the scope of this powerful technology. The challenge now is to produce them at scale and at an acceptable price. We will discuss these challenges in the next section, before looking at how digital technologies and intelligent industry will boost this industry.

Society is hearing about biological treatments (Biodrugs) and their therapeutic advantages.

MEETING THE CHALLENGES OF SCALING BIODRUGS

Whilst excitement about biologics-based therapeutics is high, Biodrugs remain hard to produce at a large scale, whilst ensuring they maintain targeted Critical Quality Attributes (CQAs).

Bioproduction remains highly complex, mostly due to the nature of the bioproduct itself (mRNA stability, mAb folding, and protein glycosylation, for example) or the difficulty in deploying powerful monitoring sensors that enable full control of bioprocesses at scale. Existing bioprocesses usually rely on conventional batch processing which comes with size and time limitations. Continuous and intensified manufacturing are key to delivering more product in a shorter time frame. Perfusion technologies are out there, however, allowing continuous production over a longer period of time, leading to higher productivity.

Moreover, both process and bioproduct are inseparable in regulatory standards. Authorities recognize a certain level of variability on bioproduction, but push the manufacturer to explore this variability, control it and make sure the process - and the eventual patient - is not at risk. Reduction of human introduced variability is key. Each process needs to be handled efficiently and automated where possible, helping to increased robustness and quality.

Bioproduct definition and bioproduction can be divided into several phases, including bioproduct engineering, and Biodrug production (Biodrug manufacturing), composed of UpStream Process (USP), DownStream Process (DSP) and Fill and Finish.

Each step of the bioprocess has very different challenges to more established chemical-based drugs manufacturing, and these need to be addressed to deliver optimal product with optimal yields.

Bioproduct engineering

At the beginning of the bioprocess, the product is designed, engineered, screened and tested. Design of Experiment plays a key role in the success of the journey. The selection of expression cell lines or vectors (e.g., Chinese Hamster ovarian cells, Vero cells, Human Embryonic Kidney 293 cells, Escherichia coli for bacteria...), and the molecule of interest itself (DNA, mRNA, cDNA...) are key (see Figure 1 – step 1) to drug success. Cell culture, transformation of cells, clone screening and selection and amplification remain the start points to ensure a reproduceable and safer bioprocess.

Organisms used in biomanufacturing are selected for their stability, which is critical for reliable scale-up. Nevertheless, sub-optimal conditions may lead to changes over time as the cells divide. Cell lines are selected based on their known stability or likelihood of stability, as they may occasionally see natural genetic mutations. When produced in sub-optimal conditions in a bioreactor, a change could lead to a mix of the targeted biomolecule and its variants – which would potentially mean that the entire batch would need to be scrapped. Even when bioproduction occurs in optimal conditions, a certain degree of truncated or diverse products is expected, requiring further processing for purification of the target bioproduct.

The possibility of these genetic alterations creates a need to understand, control and define these complicated interactions to ensure product manufacturing reproducibility and consistency, stability for safety and efficacy - and to provide reliable data for regulatory authorities' approval.

In silico modeling

Data and technology allow for Biomolecules to be reverse engineered, via in silico modeling that allows the design of molecules that are more prone to be stable, and have higher affinity and efficacy. Nowadays, engineers have the tools to overcome several Biodrugs' development challenges through AI, data science and modeling.

Through the better design and improved stability of Biodrugs, it is possible to address current complex supply chain challenges, such as by designing robust Biodrugs that maintain quality with less restrictive temperature requirements.

Biodrug production: UpStream process

UpStream processing is the first step of the bioprocess, where Biodrugs are produced or amplified. It requires cell cultivation steps to scale up culture size to produce sufficient quantities of product.

At the bioreactor level, several key challenges need to be addressed. Some expression cell lines require adherent cellular growth in medium with microcarriers (e.g., Vero cells), while others can be produced in single cell suspension in a liquid medium (e.g., CHO). For the latter, the main challenge is the monitoring and control of what is happening in the bioreactor.

In 2002, the Federal Drug Administration initiated the Process Analytical Technology (PAT) approach, dedicated to supporting innovation in pharmaceutical processes with a view to improving production and quality criteria. Its objectives include a better understanding of the process through greater knowledge of cell physiology and metabolism, as well as the implementation of new tools for on-line control of key parameters of the culture process (Critical Process Parameters, or CPPs). The ultimate goal is to predict, optimize and control the evolution of the process with appropriate tools, in order to ensure the final Biodrug CQAs.

CPPs are often monitored with a wide range of sensors to observe cell viability and Biodrug production. However, these are often displayed along the bioprocess, off-line, at line, and on-line. Only a few are displayed in-line, which is the only way to allow real-time monitoring.

Quality by design

Real-time monitoring of reactions in the bioreactor would have a number of benefits, including (1) tracking a Biodrug through production and preventing its degradation, (2) identifying the best CPPs for an optimized yield, (3) predicting the best CPPs for the best CQAs. Quality by Design is essential for manufacturers that need to scale up their bioproduction. Indeed, the identification of CPPs among the wide range of input parameters (temperature, oxygen, pressure, etc) remain key to ensuring the best conditions for scaling-up and therefore reducing time to market.

Biodrug production: DownStream process

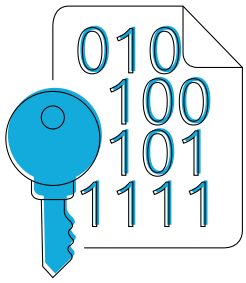
DownStream processing refers to the recovery and purification of a drug substance from natural sources, such as animal or bacterial cells.

Biodrugs, especially mAbs, are complex molecules and can only be made, extracted or replicated through processes equivalent to the those present in living systems. They cannot be artificially formulated in the way small molecule chemical drugs are.

This represents a huge challenge as the DownStream Process purifies molecules obtained in UpStream processing. Post-production reactions, such as glycosylation, need to be correctly achieved to ensure their full efficiency in biotherapies. The choice of the cell line in USP, combined with post-translation engineering possibilities by process optimizations will be the key to overcoming this limitation.

Storage conditions are also challenging. Some vaccines require controlled temperature for storage, such as ambient, refrigerated, or sub-zero conditions. As such, biopharma faces issues in guaranteeing the temperature requirements in storage and transit.

MOVING TO AN INTEGRATED DIGITAL STRATEGY AND DATA-DRIVEN APPROACH



Data is the key to unlocking scientific and technological issues.

New cutting-edge technologies, when deployed by people with knowledge in omics, can bring significant breakthroughs.

In respect to guidance methodologies (PAT[2] and ICH[3]), data-driven approaches are becoming key in bioproduction and more generally in life sciences. Data governance, automatization, digitalization and data science, along with the use of Artificial Intelligence, are able to boost not only bioproduction processes but also revolutionize the way that scientists think about their whole Design of Experiment.

Data is the key to unlocking scientific and technological issues. Historically, data has been seen as a collection exercise for regulation, but now that same data is being used to take data-driven approaches to the Design of Experiment, modelling design and scale up, and using that to fine tune the initial design to ensure a smooth journey through the entire process, not just to get it over the line to the next stage. The Quality by Design paradigm starts with building quality into the product rather than testing quality.

At the early step of the biomanufacturing process, high throughput sequencing platforms allow scientists to identify molecule alterations. High PCR amplification platforms are used to boost their early stage R&D journey, leading to time and cost savings in the identification and production of gene targeting molecules. Automation can be applied to ease the cell line selection, thanks to spectrophotometry analyses or by direct screening of positive clones[4].

In the mRNA approach, optimization of the mRNA nucleotide composition should be prioritized to improve the stability of mRNA-LNP vaccines[5]. Data science linked to analytics such as spectrometry are used in a win-win combined approach to monitor and predict mRNA stability – allowing the real-time identification of unexpected behavior and using the data collected to feed models that predict bioproduct degradation. Here, automation and digitalization reduce manual operations and tedious analyses.

At the USP/DSP levels, each batch process leads to a unique bioproduct – where small variances may actually

Success Story: Moderna

Moderna, now known for its COVID-19 mRNA vaccine, has built all its biomedicine solutions from scratch thanks to an integrated digital strategy. The company invested €100 million to combine its RNA-based technologies with innovative digital assets such as robotics, automation, analytics, data science, and AI. This data-driven R&D approach allowed Moderna to accelerate its go-to-market timeline from R&D to market access.

change the final product and the yield (unlike in chemical processing where small changes will likely just impact the yield). That means lots of overlapping parameters and variables must be very precisely understood, monitored and controlled (such as temperature, pressure, agitation power, pH, cell morphology and variability, cellular composition, etc) and in-process changes are often impossible. Batches often spoil because conditions deviate from optimal. As a result, they are more likely to find variation between batches, low yields or, in the worst case scenario, batches spoiling, creating huge amounts of waste and potentially risk and regulatory hurdles.

New data-driven approaches are needed to carefully track, model and control optimal conditions for production and stability in manufacturing. Due to that, implementation of continuous manufacturing as well as prediction based on AI and experimentation using Digital Twins might represent a critical advantage.

A holistic approach

Digital Twins and Data-Driven R&D approaches are today used for multilayer purposes.

First, we need sensor technologies to monitor the parameters that can be captured in the bioprocess, either inline or at/offline, at appropriate frequency, and in real-time. This data-driven approach allows mathematical models combined with mechanistic and biological approaches to generate a holistic view to understand what is happening in the process.

Then, Critical Process Parameters (CPPs) are identified, and Design of Experiment can be improved for updated experimentation design. Moreover, graph-based technologies have been recently implemented to visualize data interactions and better identify both potential CPPs, and interdependencies that were previously unpredictable. This new methodology in bioprocessing is essential for continuous biomanufacturing since it allows a robust database that can be fully explored and lead to a quick data-driven decision-making process. The integration of AI and Machine Learning is also key to predicting CPPs. Some data models are implemented after several runs and can be applied to address future similar experiment or new Biodrugs.

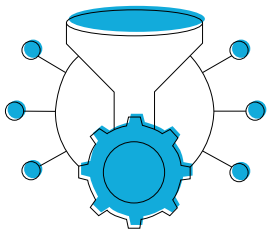
Finally, Digital Twins can be used to build feedback loops, allowing real-time modifications in the bioreactor to improve yields or prevent spoilage. These feedback loops also offer potential for reverse engineering to improve the Design of Experiment itself.

Some data models are implemented after several runs and can be applied to address future similar experiment or new Biodrugs.

BOOSTING BIOPRODUCTION THROUGH INTELLIGENT INDUSTRY

It is highly valuable to bring automation, AI and data management to manufacturing plants. However, right now, data collection, data management practices, analysis technologies and skills are often lacking or insufficiently centralized in bioproduction. Bioproduction plants have people who are highly skilled and experienced in bioprocess, but who rarely have sufficient expertise in digitalizing processes and extracting and analyzing data.

Although in silico analyses are not new, scale-up models have proven hard to do well. The primary problem has been a lack of quality data on bioprocesses. But thanks to advances in measurement sensors that can be deployed into bioreactors and other process steps – and the tools to turn their data into meaningful insights such as AI, modeling, compute power, and data management improvements – modeling bioprocesses is increasingly possible.



Prepare the data capture and management environment to take advantage of growing opportunities from Real World Evidence.

To take advantage of this opportunity, we recommend biopharma take the following steps:

Data first

Integrate a data-driven R&D approach into the Design of Experiment. This requires robust data collection and governance that allows data collected at each step of the biomanufacturing process to be exploited. This is especially true in personalized biotherapy, where data is limited and not always reproducible, so collecting data specific to each experiment is highly important.

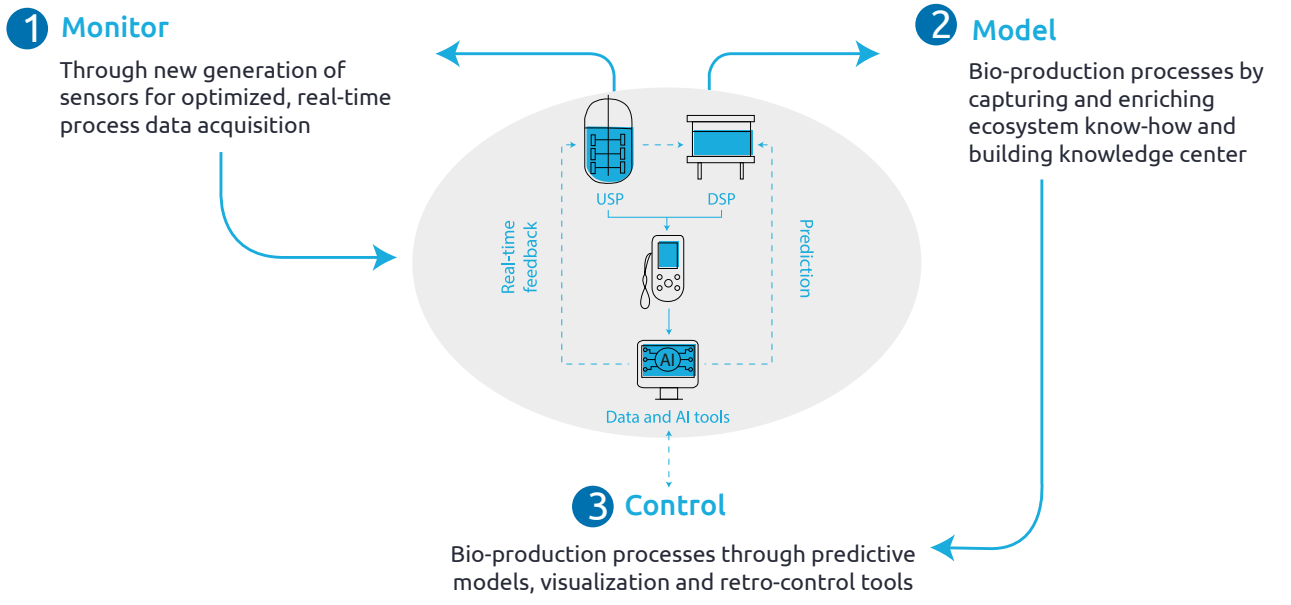
Continue the acquisition of data in subsequent manufacturing steps to create ongoing insight, monitoring, and feedback loops.

Address the traceability of data in the Design of Experiment, since minor changes can have a huge impact on the bioreactor (USP) or in the Biodrug purification step (DSP) and therefore on the yield performance. Create standardized data capture and management approaches (data governance, FAIR data) and data piping to feed to models or data science teams.

Prepare the data capture and management environment to take advantage of growing opportunities from Real World Evidence, allowing companies to capture Real World Data and apply data science to gather fresh insights.

DATA JOURNEY FOR BIO-PRODUCTION

Revolutionize the development and mastery of tomorrow's bioprocesses



Source: Capgemini Engineering

Automatization and digitalization

Design processes into the Design of Experiment to automate documentation and data collection - these are easy to design but hard to retrofit.

Use or build Natural Language Processing tools to automate documentation and reports, reducing low value tasks and limiting manual errors.

Improve batch record execution and verification to support Quality Assurance review. Deploy intelligent compliance through digital tools (MES, eBR, release by exception). This digitalization saves operational time and ensures compliance for all stakeholders.

Implement data visualization to present data insights in ways aligned to user knowledge and requirement (for example, this may be complex multi-layers charts for research scientists or simple dashboards for bioreactor operators) to improve decision making.

In all of these, consider and address the interoperability of equipment, and integration with LIMS and data platforms as appropriate.

Build intelligent-by-design manufacturing units, ensuring that AI and automation is considered and included in the technology roadmap of the company.

Bioprocess robustness

To understand CPPs with precision, it is usually recommended to limit the number of variables. AI allows a far higher number of variables and their effects to be understood, reaching conclusions based on what it learns from the input data. Thus, controlling parameters and experiment variability is key to ensuring reliable data feeds into the AI model.

Taking a holistic view

Build multi-functional teams to open new doors in bioproduction. Few lab scientists are familiar with the complexities of AI, whilst not all AI experts know the complexities of bioprocesses. The integration of research scientists, data scientists, business analysts, bioinformaticians and mathematicians will help breaking these barriers.

Conclusion

To boost the potential of Biodrugs to improve human health, bioprocesses need to be scalable and their challenges must be simplified. Challenges are mostly technological, and many can be improved through a joined-up approach to digital technology, incorporating better data collection and processing using cutting edge tools.

Better sensors, data-driven approaches, the use of new disruptive mechanistic models and AI to analyze data, and process automation technologies will allow biopharma to optimize R&D and manufacturing processes through data insights. As Biodrugs become more and more complex, biotechnologies and cutting-edge technologies have to be considered in one holistic approach, combining omics know-how and AI within multi-functional teams. The implementation of this new methodology has already saved time and cost, reducing the time to market, and ultimately improving health and saving lives.

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