CRDMOs Redefining Drug Substance Development with Platform Technologies

The development of biopharmaceuticals is expanding at an unprecedented rate, as the industry now comprises around 20 percent of the global pharmaceutical market.[1] This momentum stems primarily from an escalating demand for advanced therapeutic treatments for both previously untreatable chronic illnesses and conditions resulting from an aging population.[2] The appeal of biopharmaceuticals also reflects a shift toward precision medicine, as the unique molecular complexities of biotherapeutics tend to offer greater targeting capabilities and fewer side effects, aligning with growing consumer demand for better healthcare outcomes.[1,3]

This combination of factors means that biopharmaceuticals are opening doors to therapeutic approaches that were once out of reach with traditional small-molecule drugs. However, the impressive advances made in the sector often come with a range of critical challenges in process development. Even though each drug substance is unique, there is a common set of hurdles that each biomanufacturer faces during every process development journey. These can sometimes be related to the stability, solubility and purity of candidates, as well as bioprocessing hurdles, such as difficulty scaling up, low yields, the high cost of goods and even the need for complex characterisation methods. Taking just one of these factors as an example, scaling up production demands a high level of technical expertise and often imposes considerable constraints. These challenges can make the journey to the clinic a complex and resource-intensive process every time a new drug candidate is investigated, especially the complex ones. For instance, proteins are a highly diverse molecule class, defined by unique amino acid sequences, complex three-dimensional structures, specific post-translational modifications and, sometimes, specific cofactor requirements.[4,5,6] This variability demands a highly customised approach to protein production, which often results in prolonged development timelines and elevated costs, and hinders the transition from discovery to larger-scale production.

Core Bioprocessing Challenges

As the biopharmaceutical sector grows, tackling the complexities of bioprocess development has become essential, and among the most pressing challenges for biomanufacturers are instability, low yields, and issues with purity and solubility.

Instability

Stability is a crucial factor in biopharmaceutical production, not least because instability of the final product frequently results in a shorter shelf life, limiting the timeframe within which biologics can be safely administered. Proteins can become biologically inactive or even provoke immune responses in patients when they lose their structural integrity, diminishing their therapeutic efficacy.[7] They are also susceptible to aggregation, degradation, denaturation, or other structural alterations that can arise at various stages of the manufacturing process, from initial fermentation to final drug formulation. These issues can be mitigated using various approaches, including optimising cell lines, adjusting expression conditions, modifying amino acid sequences, and incorporating excipients or stabilising agents. However, this inevitably adds layers of complexity to the development process and ultimately increases manufacturing costs.

Low Yield

Maximising output from recombinant expression systems is vital for producing biotherapeutic proteins, but many proteins demonstrate low expression levels, reducing the yield in each production cycle. Low yield means that more resources, including raw materials, time, and labour, are required to produce adequate therapeutic quantities, raising production costs. This may also extend timelines, potentially delaying clinical readiness. Yield can be influenced by several factors, including the choice of host – such as bacterial, yeast, or mammalian cells – protein stability, folding efficiency, and post-translational modifications, so careful consideration needs to be given to each step in the process. Overall, enhancing yield can be a complex process that calls for sophisticated bioprocessing methods and expert handling.

Poor Purity and Solubility

Ensuring high purity and solubility is also essential to the safety and therapeutic effectiveness of biopharmaceuticals. Poor solubility can result from some proteins having a tendency to aggregate or precipitate, which can affect a drug's bioavailability, restrict its therapeutic impact and complicate its formulation for clinical applications.[8] Any drug substance must meet stringent purity standards to prevent contamination by common impurities, including host cell proteins, residual DNA, endotoxins, or other byproducts from the production process. Such contaminants can undermine the product's safety and effectiveness, and may even trigger adverse immune responses in patients.

Addressing purity and solubility issues requires rigorous purification and filtration techniques, such as chromatography, depth filtration, and tangential flow filtration (TFF). However, these processes add considerable operational costs and often extend production timelines, posing additional challenges to large-scale biomanufacturing.

CRDMOs: Bridging Resource Gaps with Platform Technologies

Overcoming the complex challenges associated with bioprocessing requires considerable resources, and many biopharmaceutical companies find themselves constrained by limited time, facilities, and in-house expertise. This often makes it impractical to develop new cell lines or innovate manufacturing technologies internally and, as a result, companies are increasingly partnering with contract research, development,

and manufacturing organisations (CRDMOs) to bridge these gaps. CRDMOs provide deep expertise and advanced technological solutions across the entire biopharmaceutical production spectrum, offering support in areas from the selection of host cells to stringent quality assurance and control. CRDMOs are increasingly achieving this by establishing efficient, end-to-end platform technologies that quickly overcome the challenges faced during each stage of development, from host selection to analysis.

Advanced Technologies

Many CRDMOs incorporate state-of-the-art technologies like machine learning (ML) to precisely monitor and control numerous protein production stages.[9] For example, ML can be applied to refine and optimise gene sequences of recombinant proteins, thereby enhancing their expression and boosting overall yields. This approach addresses the inherent unpredictability in translating RNA to protein, resulting in more consistent production.

Host Selection and Screening

Selecting an appropriate host organism is the first pivotal step in biomanufacturing, as it directly impacts critical factors such as protein yield, solubility, and overall efficiency; the choice of host influences every subsequent stage of the process, including expression levels and scalability. Traditionally, biomanufacturers have favoured well-known hosts like mammalian cells and *Escherichia coli.* However, CRDMOs sometimes bring a wider variety of host options to the table, such as Gram-positive bacteria like *Bacillus subtilis* and yeasts like *Pichia pastoris,* which can be advantageous due to their rapid growth rates, simpler media requirements, protein secretion capabilities and genetic flexibility.

A skilled, platform-focussed CRDMO partner can use specialised strain and cell line engineering techniques to tailor the selected host for peak productivity. This includes offering an array of refined genetic components and expression vectors aimed at enhancing the solubility and expression of targeted proteins. Using ultra-high throughput systems also allows CRDMOs to swiftly identify high-performing 'jackpot' clones, greatly improving the efficiency of selecting ideal recombinant proteins for scaled-up manufacturing. Advanced capabilities in selecting and screening different hosts allow CRDMOs to help biomanufacturers overcome the challenges commonly experienced during bioprocess development, streamlining production with more efficient expression systems.

CRDMOs can refine the biomanufacturing process by optimising the strain or cell line. This iterative process enhances the target protein's stability, proper folding and overall yield. For instance, codon optimisation can promote the production of molecular chaperones that support correct protein folding and stability, or prevent the expression of proteins – such as proteases – that could interfere with or degrade the therapeutic protein.

Process Development

CRDMOs also apply design of experiments (DOE) methodologies to precisely adjust key parameters in upstream processes, like fermentation, and downstream steps, such as purification.[10] By meticulously adjusting these variables, they can create scalable, consistent and efficient processes that can be smoothly transitioned to scale-up, ensuring that materials for clinical trials are manufactured with precision and efficiency.

Advanced Analytics and Quality Control

Collaborating with a CRDMO provides biomanufacturers with access to advanced analytical technologies that lead to high quality and consistent biologic products. One powerful tool in this arsenal is quadrupole time-of-flight liquid chromatography-mass spectrometry (Q-TOF LC-MS). This technology separates, characterises and quantifies complex protein compounds, enabling precise analysis of their composition, structural integrity and biological activity. By evaluating critical quality attributes like purity, solubility and stability, Q-TOF LC-MS ensures that each batch meets stringent quality standards.

Case study of a Recombinant Subunit Vaccine[11]

Ingenza tackled the challenge of producing a recombinant pancoronavirus vaccine featuring eight distinct antigens displayed on a nanoparticle for cross reactive coronavirus immunity. Initially, the vaccine candidate required eight different mammalian cell lines for antigen production, while *Escherichia coli* was used for the nanoparticle, resulting in high production costs and endotoxin contamination. Ingenza used its knowledge of microbial host selection and process optimisation to move antigen production to *Pichia pastoris,* which grows in simple media, and nanoparticle production to *Bacillus subtilis,* which is naturally free from endotoxins. It also optimised upstream and downstream processes for the vaccine's nine components and established a QTOF-MS characterisation method to show batch-to-batch reproducibility. This approach accelerated vaccine development, positioning it for IND submission by 2026, and supports global accessibility through cost-effective production.

Conclusion

Biopharmaceuticals are evolving rapidly, the path from discovery to clinic presents significant challenges – including issues with developing a scalable and robust bioprocess – that make the journey both resource-intensive and technically demanding. Partnering with a CRDMO that integrates platform technologies and ML into a seamless process enables biomanufacturers to address these challenges effectively at each stage from host selection to downstream processing. With capabilities across diverse host systems, innovative bioprocessing techniques and advanced analytical tools such as QTOF-MS, CRDMOs provide the specialised expertise and resources to optimise drug substance development. This collaborative model allows faster, more efficient and scalable production of biopharmaceuticals, better positioning the industry to meet rising healthcare demands and improve patient outcomes worldwide.

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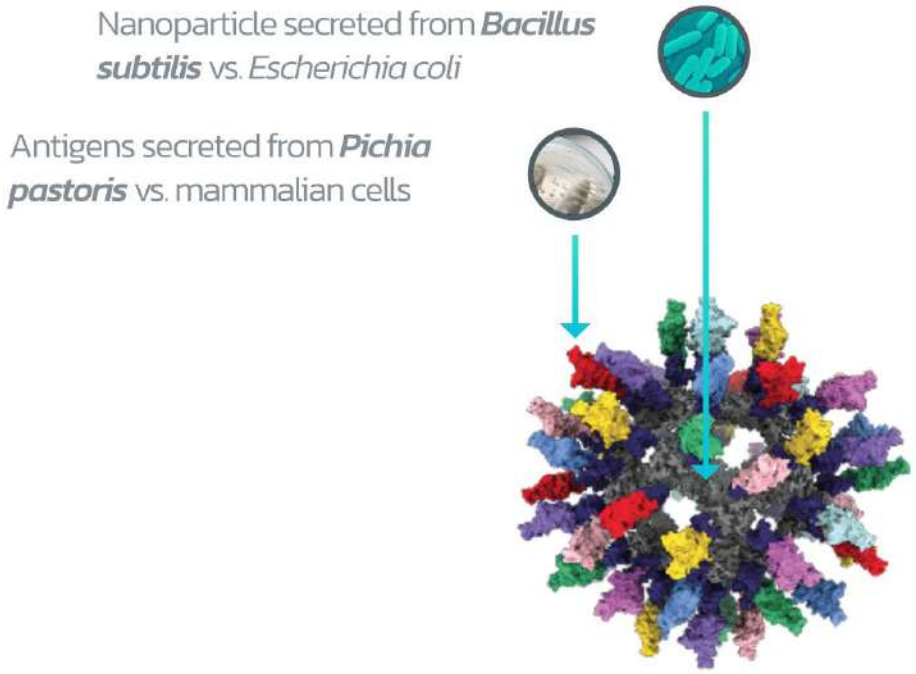

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