Biologics Roundtable: the current landscape and future developments

In this joint discussion, we hear from Alex Del Priore at Syngene and Subodh Deshmukh at Aragen on why the biologics landscape has developed how it has, why India is such a hotbed for it and how might it grow in the future?

***EBR*: What is the current biologics-based treatment landscape, and how has it developed over the last five years?**

Alex Del Priore (ADP) at Syngene: Over the past five years, the biologics proportion of new drug approvals from the FDA has steadily grown, reflecting both the changing R&D pipeline but also the increasing demand for precision medicine and targeted therapies. This expansion encompasses a wide array of biologics, including monoclonal antibodies (mAbs), bi- and trispecific constructs, antibody-drug conjugates (ADCs), mRNA, plasmid DNA (pDNA), and cell and gene therapies.

What has also been seen alongside this however is that bioproduction technology is improving, which has driven improved efficiency and yield. For example, new technologies have been developed to deliver step-change improvements in titers, thereby significantly lowering costs per gram of product. As part of this, the use of batch-fed n-1 perfusion helps achieve far higher cell densities and titers by three- to four-fold. This leads to improved cost of production, ultimately lowering the cost of treatment involving mAbs.

Consequently, outsourcing and demand for CDMOs has expanded in parallel to the industry. Trust in sending commercial biologics projects to India is another big development – and reflects the fact that hubs of expertise open up here. There are three other main reasons for this: one, is it's a hedge against other macro manufacturing issues that are occurring; two, it's a reflection of the success of recent deals in the region; and most importantly, it's clients coming to the region with complex molecules and problems, and the region building a strong reputation as a developer for biological targets and solving these problems.

Subodh Deshmukh (SD) at Aragen: The biologics-based treatment landscape has witnessed significant growth and advancement over the last five years. Biologics, which are drugs derived from living organisms or containing components of living organisms, are increasingly being used in treating complex diseases, including cancer, autoimmune disorders, diabetes and chronic inflammatory conditions.

With the increasing focus on biologics drugs and the advancement in biologics research, there is also seen a notable expansion in the indications for which biologic drugs

are being used. Many such drugs, originally approved for one condition, have seen their use extended to treat other diseases. This expansion reflects the growing recognition of the effectiveness and versatility of biologic therapies across different medical domains.

Increasing acceptability of biosimilars is further accelerating the growth of the biologics market. In 2023, the US Food and Drug Administration (FDA) approved five new biosimilars, bringing the total number of FDA-approved biosimilars in the US to 45.

Additionally, advancements in technology and understanding of disease mechanisms have led to the development of novel biologic therapies with improved efficacy, safety and targeting capabilities. Monoclonal antibodies (mAbs) continue to dominate the biologics landscape, with advancements in mAb technology leading to the creation of more potent and targeted therapies.

***EBR*: When working with biologics, is there much variation between a molecular biology approach and a protein sciences approach?**

ADP: There can be significant variation between a molecular biology approach and a protein sciences approach. Typically, a molecular biology approach involves the manipulation and engineering of DNA or RNA molecules to produce desired proteins or biologics. On the other hand, a protein sciences approach focuses on the study and manipulation of proteins themselves, including their structure, function and interactions. While both approaches are integral to biologics development, they represent different stages and aspects of the overall process.

In the molecular biology approach, CDMOs manipulate genetic material, such as DNA or RNA, to generate cells capable of producing the desired biologic. This involves techniques like gene cloning, where the gene of interest is inserted into host cells, and expression systems, which control the production of proteins from the inserted gene. These manipulated cells are then cultured in bioreactors, where they multiply and produce the biologic of interest.

On the other hand, the protein sciences approach focuses on purifying and modifying the biologic once it's produced by the cells. This includes processes like protein purification, where the biologic is separated from other cellular components, and protein modification, which may involve altering the structure or adding certain molecules to enhance the biologic's properties.

At a large scale, CDMOs utilise specialised equipment and facilities to handle the high volumes of biologics production. This can include large-scale bioreactors for cell culture, purification systems capable of processing large quantities of protein, and advanced analytical techniques for quality control.

***EBR*: How is biologics research impacted if laboratories and manufacturing centres are not kept up to date?**

SD: Keeping R&D labs and manufacturing facilities updated with the evolving advancements in technology and instrumentation is absolutely critical and biologics is no exception. Failure to do so can have multiple implications:

- Outdated facilities lack the latest equipment and technology needed for efficient biologics research. This can hinder the adoption of innovative techniques and limit the ability to perform advanced experiments or analyses
- Older manufacturing facilities may not meet current regulatory standards for biologics production. This can lead to quality control issues, such as variability in product quality, purity and safety, which are crucial considerations in biologics development
- Such facilities can be less efficient and productive due to slower processes, increased downtime for maintenance, and higher likelihood of errors. There can be increased safety risks and challenges. This can result in delays in research timelines and increased costs
- Regulatory agencies such as the FDA and Europeans Medicines Agency (EMA) have stringent requirements for biologics manufacturing facilities to ensure product

safety and efficacy. Failure to meet these standards due to outdated facilities can result in regulatory hurdles, including delays in approvals or even rejection of products.

At the same time, continuous maintenance and upgradation of R&D and manufacturing facilities require heavy capital investments. That is where collaborating with established contract R&D and manufacturing solutions providers can offer advantages.

***EBR*: What can be done to encourage more biologics research to be conducted around the globe, beyond the currently established research hubs?**

ADP: Bangalore, India, has become a powerhouse for biotech because of the incredible talent it attracts. But getting the talent here has taken a concerted effort and so this city is great example of building a new research hub. Infrastructure plays a huge role too. Places like Hyderabad's Genome Valley are leading the way by providing world-class facilities for biologics manufacturing. Additionally, supportive government policies, like patent protections and tax incentives, can really spur innovation in new regions.

***EBR*: What challenges arise when developing therapies using large molecules like biologics compared to small molecules?**

SD: While there is an increasing shift towards biologics, developing therapies using large molecules presents some unique challenges. These molecules are typically produced in living organisms, necessitating complex and costly manufacturing processes. Additionally, their intricate structures render them more susceptible to degradation, demanding specialised handling and storage conditions to maintain efficacy and safety.

Biologics face challenges related to immunogenicity, as they can provoke immune responses in patients, resulting in the formation of anti-drug antibodies that may affect both safety and efficacy. Moreover, obtaining regulatory approval for biologics entails navigating stringent requirements to demonstrate their safety, efficacy and consistency, often necessitating extensive preclinical and clinical testing to meet regulatory standards.The cost and accessibility of biologics pose significant challenges, particularly in resource-constrained settings, where the high expenses associated with manufacturing and development can limit patient access.

***EBR*: Do biologics hold any potential for the development of antibody discovery and therapies?**

SD: Biologics hold tremendous potential for antibody discovery and therapies. Biologics, particularly monoclonal antibodies (mAbs), have revolutionised the treatment landscape for various diseases, including cancer, auto-immune disorders and infectious diseases. Techniques such as phage display, hybridoma technology, and recombinant DNA technology enable the creation of mAbs with desired specificity and affinity for therapeutic targets.

The specificity and potency of antibodies make them valuable therapeutic agents, capable of targeting specific disease-causing molecules or cells with high precision leading to improved treatment outcomes and reduced side effects. Additionally, advancements in antibody engineering and screening technologies have facilitated the development of novel biologics with enhanced efficacy and reduced immunogenicity.

Large molecules as such can offer advantages such as increased half-life, improved tissue penetration, reduced off-target effects, and the ability to modulate immune responses, making them promising candidates for the development of next-generation antibody-based therapies.

Alex Del Priore has three decades of experience in developing, commercialising and life-cycle management of products in various life science industries. Holding positions in both the US and Europe, his experience includes senior roles with global P&L responsibility. As a member of the executive committee, at **Syngene**, Alex plays a techno-commercial role providing technical expertise to the API plant at Mangalore while building a sustainable client base for the business in collaboration with the commercial and business development teams. Alex is also responsible for biologics operation.

Subodh Deshmukh is the CEO of biologics and president of development at **Aragen**. He has over two decades of rich experience in drug development across small molecules and biologics. Prior to joining Aragen, Subodh was the chief development officer at Zymergen in California. He also held various leadership roles at Bristol-Myers Squibb, Pfizer, Sun Pharma and Novartis.