New Manufacturing Technology Platforms for Biosimilars

One of the main drivers for the pipeline growth in biosimilars is the number of originator blockbuster molecules coming off patent – 17 blockbuster molecules with annual peak sales worth $60 billion have or will lose exclusivity between 2020 and 2025. Global sales topped $15 billion in 2020, representing a compound annual growth rate (CAGR) of 56% since 2015. According to McKinsey's biosimilars market model, double-digit growth is set to continue with the market anticipated to double in size by 2025.[1]

There have also been several biosimilars approved, entering the market and gaining major market share – since the FDA approved Zarxio in 2015, a further 32 biosimilars have entered the US market[2] with Herceptin and Humira being the subject of most competition. An executive order from the Biden administration,[3] in combination with plans from the Department of Health and Human Services (HHS),[4] have made it clear that biosimilars are seen as a means to increase competition and reduce costs. There are also many developing countries and emerging economies that can't afford the originators – a high quality biosimilar, with the same efficacy and quality aspects, could open up entirely new markets.

Concurrently, advances in biosimilar development and biologics manufacturing have created the potential for companies to reduce the comparative production cost of drugs and to put these out to the market at significantly lower prices.

The sector then is poised for significant growth over the next ten years. Here, Dr. Gerrit Hagens Director at BioXpress and Simon Keen, Vice President Cell Line Development at Abzena, explore the technologies that will enable and drive this growth.

Upstream Process Development

One of the technological advantages that biosimilar developers have compared to originators are the advances seen in enhanced cell line productivity and upstream process development. Titers for example have increased tenfold in the last 10 years, and the move away from older adherent cell lines into suspension has allowed developers to grow larger cell culture volumes more efficiently and cost effectively.

As originators come off patent, they're 'stuck' using dated, less efficient systems. The development of more productive cell lines and processes offers developers the option to use these to manufacture biosimilars. The overarching impact is that cost of goods comes down, helping to reduce the financial risk associated with development and production. In addition, the cost of clinical trials and capital spending on research and development are reduced, through streamlined regulatory pathways. This drives down the overall costs associated with approving and manufacturing biosimilar molecules which permits a lower market price than the originator.

Single Use and Agile Manufacturing

There has been a simultaneous advancement in the innovation and adoption of single use technologies. Many biosimilar molecules will be manufactured at lower scales because these products are expected to have smaller market demands than originator drugs, as several biosimilars are expected to share each market as is the case. The Humira 'patent cliff' in the US for example will see at least six FDA-approved biosimilars enter the market in 2023.[5] Many producers in the biosimilar space are smaller innovators, some of them virtual, who may lack the capabilities to manufacture their product at any volume.

This requirement for lower volume capabilities and the rise in virtual companies, is invariably pushing manufacturing to contract partners (CDMOs). CDMOs in turn are using single use technologies to give them the flexibility and adaptability to take on multiple projects at a time so they can be much more cost effective.

One area of significant progress has been the adoption of single-use bioreactors (SUBs) – a market which is projected to grow at a CAGR of 19.36% from 2021 to 2028.[6] This technology is a key enabler, allowing manufacturers to flexibly handle small batch volumes and multiple biosimilars. Current SUBs are offering improved changeover times as well as better containment performance. Initiatives to enhance stirring mechanism precision, integrate process analytical technologies as well as key advances in disposable technology are all paying operational dividends. Because of their improved reliability and performance 2,000L SUBs are fast becoming the default bioreactor technology for small-scale biologics manufacturing.

Continuous Processing

The industry is also on the cusp of introducing continuous biologics processing to further improve the batch quality and production efficiency of biosimilars. For example, continuous processing reactors for cell culture perfusion are beginning to enter the commercial manufacturing environment. The technique incorporates a cell retention device and continuous media exchange, while the product of interest, spent media and waste are continuously removed. This allows the process to reach and sustain higher cell densities and viabilities, while increasing productivity over longer periods of time.

Long term, continuous perfusion compares favourably against shorter applications, such as High Productivity Harvest, that focus on intensifying fed-batch processes, as it provides reduced batch-to-batch variability. Continuous perfusion technologies may also be used to intensify the seed train with reduced steps and faster overall time to production.

When biosimilar developers effectively implement these technologies, they can further decrease CoGs and reduce timelines, while keeping productivity and quality extremely high. Innovation here will continue to control costs which supports competitive product pricing and other very tangible and marketable differentiators.

De-risking Development

Most pharmaceutical and biotech developers are now looking to control every aspect of their process from start to finish. To

support better process control in biosimilar development it is vital that developers characterise the reference molecules in every detail. Exceptional analytical capabilities are required to achieve the desired outcome – which is to be able to generate the data required to identify and match the critical quality attributes (CQAs) between biosimilar and originator. This needs to be tracked throughout development and subsequent manufacture of the biosimilar.

The resulting data allows for a more thorough analytical understanding of a product which de-risks development. In combination with lower processing costs, accelerated timelines and a lower compliance burden, resulting from taking advantage of advanced process technologies, incentives for pharma to pursue biosimilar development are becoming increasingly persuasive.

Sensing the Most Critical Aspects of the Process

As analytical technologies have become increasingly sensitive, what the industry has come to learn is that manufacturing and characterising the cell line has become the most important part of the process during the development of biosimilars.

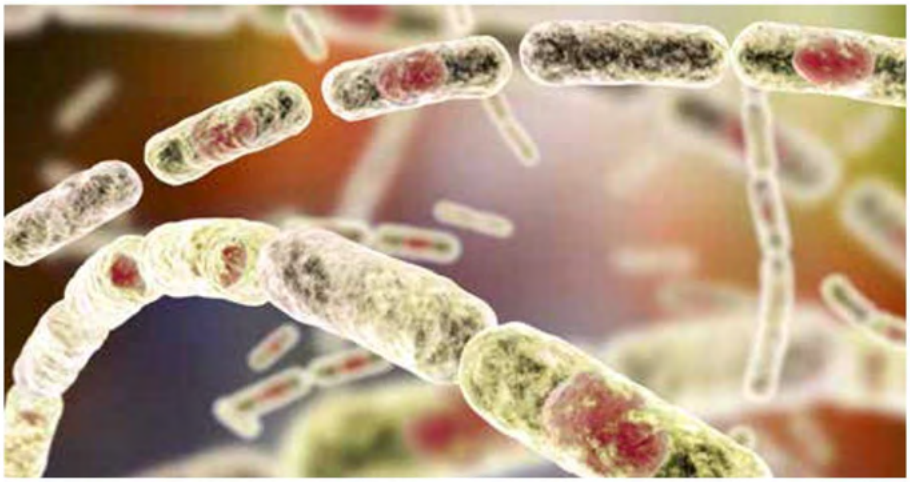
When the analytical capabilities of chromatography and mass spectrometry are aligned with cell line and process development, it can generate accurate data early in development. Equipped with precise analytical capabilities developers are achieving the appropriate product quality right from the beginning of cell line development which reduces the amount of work required downstream.

Studies show that glycosylation is a key factor in biosimilarity. As well as modulating mechanism of action through Fc-mediated effector functions, glycosylation may also impact a product's safety and efficacy. For these reasons, regulatory guidelines recommend an analysis of Fc functions in detail, including binding to Fc receptors and Fc-mediated cytotoxicity such as antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

Recent advances in innovative techniques such as *ex vivo* T-cell assays[7] and MHC-associated peptide proteomics (MAPPs)[8] have become powerful tools for assessing immunogenic potential and demonstrating similar safety profiles between originator and biosimilar molecules when it comes to their immunogenic profiles.

Analytics and Regulatory Innovation

The industry is also pushing for regulatory innovation with one area of note being in removing the need for clinical efficacy studies where it is justifiable. In 2021, the UK's Medicines and Healthcare Regulatory Authority (MHRA), dropped the requirement for biosimilars to pass through comparative efficacy trials in most cases. The guidance 'encourages a stepwise approach to development of biosimilar products, with emphasis on the comprehensive physicochemical and biological comparability studies, functional (*in vitro*) analysis and a confirmatory clinical PK (pharmacokinetic)'.[9] The World Health Organization (WHO) is also consulting on whether regulators should remove these requirements. This could significantly



reduce the costs and time of biosimilar development but does raise questions around regulatory robustness – the MHRA made it clear that its decision to removing the requirement was a means of attracting biosimilar manufacturers to the UK.

The decision has a secondary effect of highlighting the importance of robust physicochemical and biological characterisation of the product and pharmacokinetic (PK) studies which remain essential. Quality, safety and efficacy remain the most important metrics against which manufacturers are judged and assuring this with comprehensive analytics and data is essential. Packages showing high biosimilarity are key to convincing authorities that smaller clinical studies are sufficient.

It's another area where there has been notable progress as the analytical techniques used to demonstrate a clear structural and functional links between biosimilars and their originator molecules have advanced significantly.

Analytical techniques in biologics are becoming more routine – the equipment is also becoming higher throughput, smaller and less expensive. Importantly, there has been a broad acceptance and increasing use of advanced in-process analytical testing, which gives manufacturers better control and invariably lowers failure rates and other poor batch outcomes.

Summary

Innovation in process and bioreactor technology – better understanding of cell lines, advances in analytical methods and equipment, continuous processing, single-use technologies – has accelerated, de-risked and lowered the cost for biosimilar development. Regulators are similarly clearing the path for biosimilar developers to enter the market.

As a result, biosimilar developers and CDMOs operating in the space that have invested in the appropriate technologies and have the expertise in handling other biologics have an immediate, inherent advantage over reference molecule owners.

But as more biosimilar products clear the final commercial hurdle, it becomes vital that manufacturers maintain focus on quickly and efficiently moving through development and stripping costs from their processes wherever possible – especially where they will be competing against the originator and multiple other biosimilars. Getting a product to market first and making it more affordable for patients in comparison to the originator and competing biosimilars will define a product's commercial success.

REFERENCES

1. https://www.mckinsey.com/industries/life-sciences/our-insights/an-inflection-point-for-biosimilars
2. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information
3. https://www.whitehouse.gov/briefing-room/presidential-actions/2021/07/09/executive-order-on-promoting-competition-in-the-american-economy/
4. https://aspe.hhs.gov/reports/comprehensive-plan-addressing-high-drug-prices
5. https://www.healio.com/news/rheumatology/20210617/market-gears-up-for-biosimilar-boom-in-2023-as-humira-exclusivity-draws-to-a-close
6. https://www.globenewswire.com/news-release/2021/11/24/2340673/0/en/Single-Use-Bioreactors-Market-size-worth-11-603-32-Million-Globally-by-2028-at-19-36-CAGR-Verified-Market-Research.html
7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7338774/
8. https://www.frontiersin.org/articles/10.3389/fimmu.2020.00698/full
9. https://www.gov.uk/government/consultations/mhra-draft-guidance-on-the-licensing-of-biosimilar-products

Gerrit Hagens

Gerrit Hagens is director at BioXpress Therapeutics and Professor at the University of Applied Sciences HES-SO, Sion, Switzerland. Gerrit Hagens gained a strong manufacturing process development experience during more than 20 years in the industry. Before joining BioXpress where he leads biosimilar development projects, he was member of Serono's core team managing the Neurology Business Unit bringing Rebif for treating multiple sclerosis to a blockbuster status. He then took over executive roles at ExcellGene and RiboVax as COO and President and helped developing manufacturing processes for biologics. Gerrit has a PhD in molecular biology from the University of Berne and an MBA from the University of Lausanne and co-founded several start-ups in the biotech arena.

Simon Keen

Simon Keen has over 25 years of experience in molecular biology and cell line development in the biotechnology industry. His career began with him working on antibody humanisation technologies at the Medical Research Council (MRC) antibody engineering group, before moving to work for multiple small and mid-size biotech companies in the Cambridge UK ecosystem. Simon has developed a deep expertise in different production systems for vaccine, antibody and fusion protein therapies. Having spent the last 15 years at Abzena, Simon has helped to develop mammalian cell line development technologies suitable for the manufacture of biological drugs and is now VP of Cell Line Development. He sits on Abzena's Scientific Leadership Group, working with clients to shape projects to meet the demands of pre-clinical and clinical development for their drug candidates, to guide them through to regulatory submission.