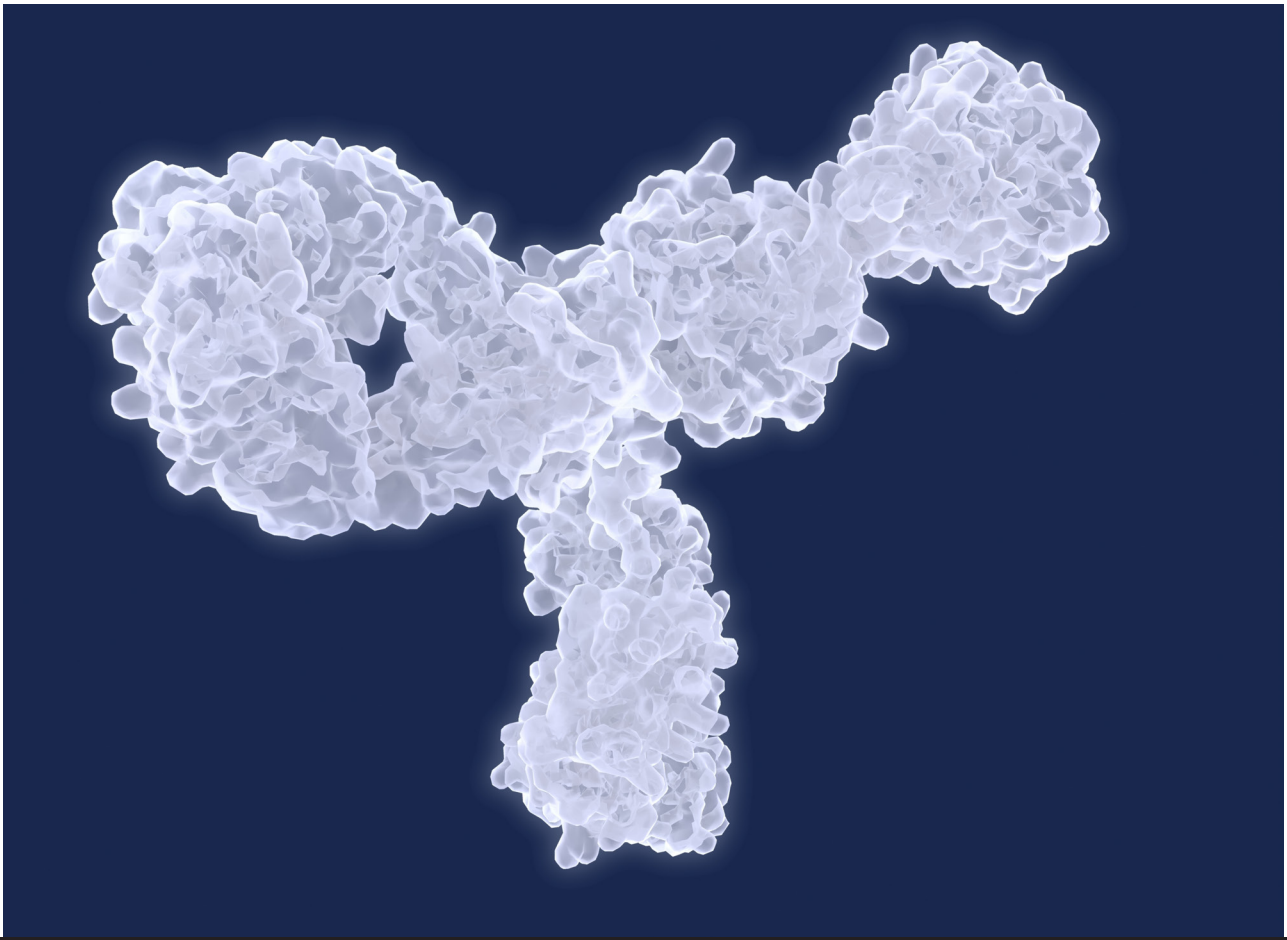

Meeting the global demand for non-monoclonal antibody biosimilars

Dr Frank Detmers gives us an overview of how new approaches to the manufacture of biosimilars have the potential to support sustainable access to critical non-monoclonal antibody biosimilars such as human growth hormone, follicle stimulating hormone, tissue plasminogen activators and many other protein therapeutics.

Biologics or biotherapeutics have transformed patient treatment by offering new and effective medicines for a range of chronic and acute conditions including neutropenia, cancer, a wide range of inflammatory and autoimmune diseases, and enzyme or hormone deficiencies. They represent the fastest growing segment of the pharmaceutical market with seven of the current top 10 blockbuster drugs by revenue being biotherapeutics. Indeed by 2020, biologics are predicted to generate US $290 billion in revenue and comprise 27% of the global pharmaceutical market[1].

The first wave of biologics to be approved/licensed included recombinant insulin, erythropoietin (EPO) and

hormones such as Human Growth Hormone (HGH), follicle stimulating hormone (FSH) and thyroid stimulating hormone (TSH). This was followed by relatively more complex biologics such as monoclonal antibody-based products, cytokines and therapeutic vaccines.

Notably, a number of these original "innovator" products are either off-patent, or going off patent in the next few years[2]. One strategy that manufacturers of these originator products have taken to attempt to mitigate the negative financial impact of this is to develop “biobetters”, an improved version of the therapeutic. By building on the knowledge and data around the target and the existing therapeutic, the risk of developing these biobetters is reduced compared to the development of a new innovator product. This route is open to both the developer of the originator and other manufacturers looking to reduce their development risk[3]. Patent expiry also opens up the opportunity for other manufacturers to create their own version of the original molecule, known as a ‘biosimilar’, to offer an alternative to expensive branded biologics[4].

Many originator molecules are manufactured by large biopharmaceutical companies in the purpose-built facilities that were designed around the manufacturing processes originally developed when the products were initially licensed for in-patient use. Once approved by the appropriate regulatory bodies, the methods and production processes are fixed and any changes can involve considerable amounts of time, cost, and potential lost production, ahead of receiving regulatory approval of any process modification. Whilst state-of-the-art at the time of inception, these established manufacturing processes often struggle with poor final yields. Having been set up often more than 20 years ago, these approved production processes do not take advantage of the incredible number of technology innovations that have been developed and commercialised in recent times and which are able to contribute to significant increases in yield and corresponding process economics.

The global demand for non-monoclonal antibody (non-mAb) biotherapeutics such as HGH, FSH, tissue plasminogen activators (tPA) and many other protein therapeutics, is increasing significantly. This is especially true in the Asia-Pacific (APAC) region, where the demand is directly linked to an increase in income levels and various government initiatives to enhance patient access. There is often a reluctance by originator molecule manufacturers to focus valuable limited resources on revisiting established production processes. The pace and demands of the industry are such that the focus is dominated by the pipeline of next generation therapeutics.

The outcome of this is a gap in the market and an opportunity for those manufacturers looking to produce these critical biotherapeutics to satisfy local demand, cost effectively. Development of biosimilars in parts of the APAC region is an established industry, however, even those countries with well-established biosimilar manufacturing capacity are facing the challenges of increasing demand and cost pressures, to drive down costs of goods. Focusing on regions such as APAC, where there is high demand for large molecule therapies, manufacturers looking to capitalise on this opportunity and stake a claim in this industry will need to ensure that manufacturing processes are fully optimised. Investing in improving the production process to increase efficiency and ultimately process yield is vital to remain competitive and justify the initial investments required[5].

Opportunities for process improvement

Manufacturing locally provides the opportunity for countries to produce these therapies for their own use, improving access and affordability, and also to export to the rest of the world. Irrespective of whether biosimilars are produced for local supply needs or to serve the global market, manufacturers in any country want fool-proof processes that effectively leap-frog the existing originator processes.

For companies in APAC, creating new manufacturing capacity locally is often not constrained by existing facility layout, hardware, or manufacturing processes. Therefore, there is opportunity to create completely new production processes and to incorporate the latest biomanufacturing developments with the primary objective to maximize the efficiency of the processes, increase yield and drive down cost of goods.

New manufacturers also have the opportunity to develop their own production processes, whilst learning from the challenges encountered by the originator product’s manufacturer.

There are three main steps to making biologics: cell production; purification and formulation. For cell production, it is important to determine the right conditions to express the target biological molecules and grow the cells containing these molecules at scale. Once the biotherapeutic has been produced, a suitable method is required to capture and purify the target molecules. With the target molecules in hand, these must then be formulated with the right combination of non-active compounds to help deliver the therapeutic to the target site.

For each of these steps, many tools and techniques have been developed with the aim to increase efficiencies at both the unit operation and process levels. Purification in particular has been a key focus for significant innovation in the tools available. Protein A affinity chromatography has become the gold standard for purifying mAbs, because of its broad applicability and therefore suitability as a platform approach to purification of this particular group of biologics. However, for non-mAb protein targets, such as the hormones FSH and HGH, other purification methods are required.

The output of each unit operation in the manufacturing process has an impact on each subsequent unit operation in the chain. Reducing the number of steps in the various unit operations is one way to increase process efficiency, another is to enhance the output of each step. A step-change in purification can be achieved with the use of the latest affinity chromatography purification resins specifically designed for recombinant protein therapeutics.

Improving downstream processing – a case study for purification[5]

FSH is one of the most important non-mAb biosimilars, and had a US $1.3 billion market in 2013 which is expected to grow to approximately US $2 billion by 2024. The original manufacturing process for producing FSH contains a 7-step purification process with has a significant negative impact on overall process yield.

With the specific objective of understanding and then improving the purification process in particular, the Purification team at Thermo Fisher collaborated with an Egyptian-based biotherapeutic manufacturer to develop a specific affinity purification resin for FSH. Working in close collaboration to fully understand the downstream process requirements, the team deployed their in-house techniques to create a bespoke camelid-derived single domain [VHH] antibody fragment affinity ligand, Figure 2, to directly capture the recombinant FSH.

Figure 1: Downstream processing of biological products using large scale chromatography.

Subsequently, the team took this ligand and developed a CaptureSelect FSH resin for wider commercial use. This resin was designed to specifically bind to intact FSH, having affinity for the interface between the alpha and beta chain of the FSH, and elute under mild conditions. Incorporation of this product into the purification workflow enabled the reduction of the number of purification steps from 7 down to 2-3 steps, which resulted in an overall 3-fold increase in process yield.

Improving upstream and downstream processing – a case study to maximise unit operation outputs[6]

Recently there has been a marked increase in the incidence of thyroid cancer globally. With only one in-market recombinant human Thyroid Stimulating Hormone (rhTSH) available, not all patients are able to access this vital medication, often because of the prohibitive relative cost.

The scientist and production engineers at SL BiGen, Inc and ProGen, Inc in South Korea were acutely aware of this challenge and so they initially developed a novel cell culture process which was able to increase the productivity of this stage of the production process 20-fold compared to the culture process used for the in-market product.

Unfortunately given the wide pH range of TSH, they were unable to remove sufficient unwanted host-cell protein (HCP), a crucial step before the resulting protein can be formulated for pharmaceutical use. Therefore, they decided to explore different purification approaches to address this issue.

With the use of a TSH antibody specific affinity chromatography resin (CaptureSelect TSH), they were able to develop a novel purification process that was able to successfully remove HCP contamination to less than 20ppm as compared to no less than 100ppm for the conventional purification process. In addition, they were able to reduce the number of purification steps with this resin and maintain the required high purity levels. Overall, the adoption of a new cell culture approach coupled with a new purification approach, enabled the team to achieve removal of the HCP to a level well within the limit allowed for pharmaceutical grade substances with a markedly increased yield.

In summary

Key technological developments in manufacturing tools and technologies are fuelling the significant process improvements possible in all stages of the biotherapeutics manufacturing process, all of which have the potential to contribute to manufacturing efficiencies. Simply decreasing the number of downstream processing steps reduces the

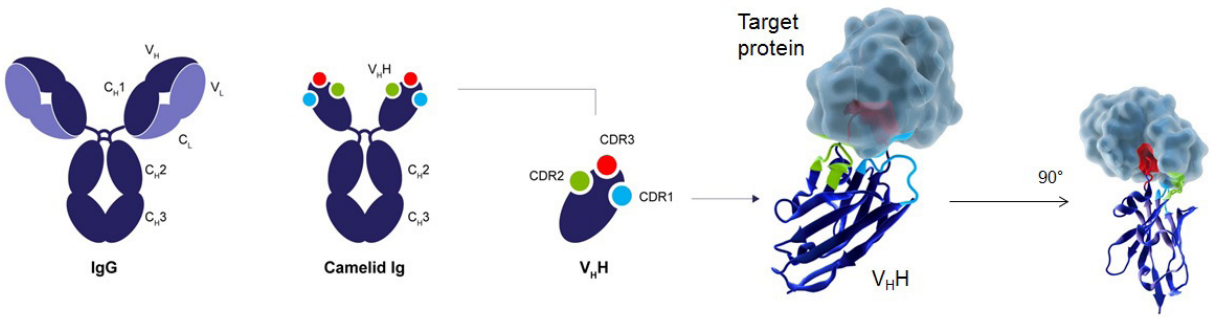

Figure 2: Regular IgG antibody compared to a Camelid heavy-chain antibody. The VHH antibody fragments offer high specificity, affinity and stability.

amount of clean room space, column hardware, buffer required, labour, and time needed for each batch. It also reduces the quality control burden, the amount of single-use consumables and volume of water required for cleaning and sterilization. All of these contribute substantially to a reduction in final cost of goods.

Being able to increase a batch yield from 15% to 90% means that the product is effectively five times cheaper to produce since one batch, using the improved process, achieves the same amount of final product as five batches using the original method. By reducing process complexity and increasing yield, there are clear resource and financial savings to be recognised.

Establishing locally-based manufacturing capabilities for biologics, such as high-quality hormone biosimilars, offers the APAC region the ability to produce these vital therapeutics for their own use. Creating new capacity locally gives the opportunity to incorporate the latest biomanufacturing developments and refine the product manufacturing processes accordingly, thereby maximising the efficiency of the processes and essentially 'leapfrogging' the methodologies commonly employed in existing facilities. Deployment of these 'next-generation' manufacturing processes will enhance both productivity and cost-effectiveness and enable sustainable production of these vital biotherapeutics to help achieve regional self-sufficiency and meet growing global demand. APBN

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About the Author

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Dr Frank Detmers is currently director of ligand application for CaptureSelect at Thermo Fisher Scientific. His role is focused on the immobilization of affinity ligands on solid supports to enable the creation of novel CaptureSelect ligands and encompasses the development of new applications for these purification solutions.

He was part of the BAC BV team that joined Thermo Fisher Scientific following its acquisition in 2013. Frank has a PhD from the department of Molecular Microbiology of the University of Groningen (The Netherlands) and worked as a post-doctoral researcher at the Department of Cell Physiology at the Nijmegen Center of Molecular Life Sciences (NCMLS, Nijmegen, The Netherlands).