Pharmaceutical BIOPROCESSING

Biosimilars stimulate quality and innovation

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The multibillion dollar market for biopharmaceuticals is expanding at a significant pace the last few decades. This market is dominated by monoclonal antibodies (MAbs), and quite a few of these mAbs have reached block buster status. Patent expiries of especially the block busters stimulated the biopharmaceutical industry to develop and market biosimilars products. The European Medicines Agency (EMA) was the first to approve biosimilars. The last few years the US Food and Drug Administration (FDA) started to approve biosimilars as well.

In contrast to small molecule drugs and its generics, biopharmaceuticals including mAbs are much larger and much more heterogeneous due to the complex post-translational modifications dependent on the cell type and process conditions used. Chinese hamster Ovary (CHO) cells are the preferred expression system for recombinant proteins. Methods for transfection, gene amplification and clone selection are well established. CHO cells also perform human-compatible post-translational modifications thereby improving safety and efficacy of the product. However, CHO cells as well as other eukaryotic cells can still be regarded as a black box. For example, the CHO-K1 contains more than 24,000 predicted genes [1] of which most of its functions are unknown, although progress is made especially in the area of proteomics and metabolomics.

One of the most important post-translational modifications is the glycosylation of proteins. Glycosylation is determined by the expression system and can be important for the half-life of recombinant proteins in the body. Also, an increased level of fucose in the glycan backbone lowers the antibody-dependent cell cytotoxicity of an antibody, thus directly affecting its efficacy. Some CHO cell lines also express N-glycolyl neuraminic acid and/or gal-α(1-3)-gal epitopes [2] which may induce unwanted immune responses in humans. Other post-translational modifications like changes in the amino acid backbone due to oxidation or deamidation, especially those in the variable domains, may pose safety and efficacy issues. Product aggregation or truncation also may pose safety issues that need careful control during its manufacturing.

The regulatory authorities recognize that a biopharmaceutical consists of a mixture of compounds with a significant degree of heterogeneity, and as such a (licensed) originator can be regarded as a mixture of biosimilar compounds. To make a biosimilar of a licensed product as such is generally more complex than to manufacture the originator product, since the biosimilar needs to be highly similar to the reference biological product (FDA: "notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product"). Thus, the development of biosimilars necessitates an extensive and careful characterization of originator batches by a broad range of different state of the art orthogonal techniques. New techniques together with improved conventional techniques like mass spectrometry may reveal quite some originator batch to batch variations in specific critical quality attributes, not unexpected since these products were

developed in general many years ago. Biosimilar development significantly boosts efforts to modify the biosimilar product to make it highly comparable to the originator product. For this extensive process and product understanding is crucial. This has led to an increased number of (proprietary) tools to modulate specific critical quality attributes in the bioreactor like the level of sialylation or fucosylation, either genetically or by changes in culture/bioreactor conditions. Furthermore, tools are available to remove unwanted product charge variants by e.g. ion exchange chromatography. This enhanced product and process understanding will lead to a manufacturing process with less variability and an increase in product quality. This also drives development of new originator products that are more difficult to mimic.

To capture market share, approved biosimilars are also marketed at a much lower price than originator product. The price erosion can be 30% or (much) more. During development the biosimilar process will be heavily scrutinized to decrease the cost of goods as much as possible. A significant part of the cost of goods will be the amortization of the manufacturing facility. For green field facilities a modular construction will decrease the investments. To decrease the facility size, processes can be intensified to decrease the size of the unit operations. Product titers are still increasing from about 0.1 g/L in 1990, 1 g/L in 2000 to >4 g/L in 2010 and may be further increased by using e.g. SPOT™ technology [3], allowing the economic use of disposable bioreactors for high market volume products within a manufacturing facility. Together with the introduction of disposable unit operations in the purification part, this leads to a reduction or even elimination of expensive clean and steam in place systems needed for the classical stainless-steel plants. Intensification by perfusion is gaining acceptance since it allows high cell density cultures while maintaining cell specific productivity and product quality. Continuous manufacturing technology is being developed that will significantly decrease the size of the manufacturing unit operations. Together with enhanced automation of unit operations, ,continuous manufacturing is expected to be increasingly used within manufacturing facilities. Although some way to go, process analytical technology (PAT) will allow the real time release of drug substance and drug product [4].

Overall, the introduction of biosimilars stimulates innovation, lowers the cost of goods and increases quality, not only for the manufacturers of these biosimilars, but also forces originator companies to innovate. The decrease in costs for medicines will be embraced by the health care insurers and consumers. A lower price will make it more affordable for lower income countries, and as such will improve overall living standards. There are still some barriers, like acceptability of biosimilars by the public and health care practitioners, but organizations like Medicines for Europe are actively working on solutions to eliminate these barriers.

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3. SPOT™ is proprietary technology from Bioceros B.V.
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