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Recombinant protein and mAb biopharmaceuticals to become a commodity?

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Keywords: biosimilars • commodity • disposables • GMP • health care costs • mAbs • manufacturing • QbD • recombinant proteins

In the last 100 years, quite a few serious adverse events have occurred in the western world with drugs. For example, nearly 300 people were killed or injured by sulfathiazole tablets tainted with phenobarbital in the 1940s, which led to the initiation of what was later called good manufacturing practice (GMP) by the US FDA [1,2]. More events occurred with polio vaccines in the 1950s, leading to ~150 cases of polio [2], and thalidomide in the early 1960s, leading to ~10,000 cases of serious birth defects [1,2]. These events compelled the introduction of strict rules by the regulatory authorities in the USA and Europe to minimize re-occurrence. In 1963 GMPs for drugs were first published by the FDA (28 FR 6385 [3]). Drug manufacturers were required to test that their products were safe and efficacious for their intended uses.

These GMP requirements, which expanded and became stricter in the years to follow, were quite effective. The downside is that it also increased the costs, since drugs needed to be manufactured in expensive facilities containing validated production clean rooms. A large scale GMP manufacturing plant easily costs hundreds of millions of dollars to build and validate. Bristol-Myers Squibb recently built a facility for US\$750 million [4]. The mere depreciation of these plants has a large impact on the manufacturing costs. This was not a big issue for the monoclonal antibodies (mAb) and other recombinant protein drugs that hit the market since the early 1980s, for example for the treatment of diabetes, blood and vascular diseases, autoimmune diseases

and cancer. These products have a very good safety record. Due to patent protection, thus market exclusivity, the manufacturing costs of quite a few of these products were a minor fraction of the revenue. Some of these products had or still have blockbuster status.

Due to expiration of patents, competitors are bringing biosimilars to the market. Reduction in selling prices of 30% or more are not uncommon. This reduction will put pressure on the manufacturing costs. Commercial-scale manufacturing costs of mAbs have already decreased several-fold to \$50–100 per g of drug substance. It has even been argued that this could go down to a few US\$ per g mAb or less by optimizing the current manufacturing processes in large-scale facilities [5].

In order to reduce costs, there is a clear trend towards intensification of manufacturing processes. Higher product titers might reduce the size of bioreactors to less than 2000 l, allowing the use of disposable bioreactors. In addition, in the downstream purification, disposable alternatives for classical process steps are becoming available, such as charged membranes to replace chromatography columns, and disposable centrifuges for example harvest clarification. Some of these disposable systems have already been on the market for a decade or more. Disposables offer clear advantages such as no need for cleaning and cleaning validation, thus no or less need for expensive clean and steam in place systems, more flexibility in manufacturing, and a smaller facility [6]. Pre-assembled sterile disposable systems will also allow the introduction of completely



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closed manufacturing processes. Downgrading the clean rooms/areas might be possible, which will have a significant effect on the costs of a clean room and thus decrease the costs of a manufacturing facility.

Nonetheless, some hurdles remain. Overall, to date, disposables are not that robust. Issues of concern are leakage of bags, generation of (plastic) particles, and leachables that might end up in the product. There are also issues with standardization, including standardization of testing for leachables [7]. The whole supply chain will also become more complex. Not only because the number of raw materials is increasing, but also because manufacturers need to ensure that their disposable suppliers consistently deliver the high quality needed. Moreover, the risk of being dependent upon one manufacturer site and/or supplier of disposables needs to be mitigated. However, it is envisioned that the quality and standardization issues can and will be solved in the near future. Ongoing efforts by suppliers will increase the quality of the disposable materials and improve the design of the disposable systems.

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Besides process intensification and disposables, the QbD concept was introduced by FDA approximately a decade ago and is described in the ICH Q8(R2) guideline [8]. This states that quality should be built into the product by a thorough understanding of the product and the manufacturing process, along with the risks involved in manufacturing the product and how best to mitigate those risks. Ongoing significant enhancements in methods to characterize the product and control the manufacturing process, together with an increased understanding of the cells that produce the drugs and how the drugs actually work in the human body, will help to apply QbD to its full extent. The benefits for the manufacturer are less rejection of batches, and significant reduction of the quality control and quality assurance costs.

References

- US FDA. Milestones of drug regulation in the United States. www.fda.gov/aboutfda/whatwedo/history/forgshistory/cder/ centerfordrugevaluationandresearchbrochureandchronology/ ucm114463.htm
- 2 Immel B. A Brief History of the GMPs for pharmaceuticals. *Pharmaceutical Technology* (2001).
- 3 A GMP Timeline. www.immelresources.com/LR_GMPTimeline.html

To come back to the posed question: will recombinant protein biopharmaceuticals and mAbs become a (low cost) commodity? This can be expected for off-patent products because of competition with biosimilars. Especially in Europe, insurance companies are pushing physicians to prescribe generic medicines when available. The increasing costs of healthcare, mainly due to a growing elderly population, increases the pressure on pharmaceutical companies by many insurance companies and/or governmental bodies to lower the price of (expensive) medicines [9]. Technically it should become possible to manufacture recombinant proteins/mAbs at much lower costs whilst retaining a substantial profit margin.

Many vaccines can be considered a (low cost) commodity. Several manufacturers are producing comparable quality material, at a low price. Childhood vaccines in particular were so successful that many countries in the Western world wanted to guarantee vaccine supply by direct control of vaccine manufacturing in state-owned facilities. Governments also kept prices for vaccines down since they were the main or only buyer [10]. The downside was that the number of private companies developing and manufacturing vaccines drastically decreased since the 1970s. Issues with the influenza vaccine supply for the USA in 2004 resulted in a major increase in incentives by the US government to boost the vaccine industry (as requested by the FDA [11]).

To conclude, a careful balance is needed. It is likely that quite a few recombinant protein and mAb biopharmaceuticals will become a commodity. However, the pricing should be such to fuel innovation and boost competition.

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- 4 Moesta P. Biologics manufacturing in a rapidly changing environment. BioProcess International Conference. Boston, MA, USA, 16 September 2013.
- 5 Kelley B. Industrialization of mAb production technology The bioprocessing industry at a crossroads. *MAbs* 1(5), 443–452 (2009).
- 6 Shukla AA, Gottschalk U. Single-use disposable technologies for biopharmaceutical manufacturing. *Trends Biotechnol.* 31(3), 147–154 (2013).

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- 7 Industry Report: Disposable Techologies and Single Use Systems for Biomanufacturing (2014). www.disposablebiomanufacturing.com
- 8 ICH Q8 (R2) guideline: pharmaceutical development. www.ich.org/fileadmin/Public_Web_Site/ICH_Products/ Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf
- 9 Bioplan Associates. 10th annual report and survey of biopharmaceutical manufacturing capacity and production (2013). www.bioplanassociates.com
- 10 What are the prospects of a new golden era for vaccines? (2008).
 www.abpi.org.uk/our-work/library/medical-disease/Pages/ default.aspx
- Influenza vaccine supply (2005). www.fda.gov/NewsEvents/Testimony/ucm161669.htm