Operational Excellence – the Future of Biopharmaceutical Manufacturing

In response to mounting challenges, biopharmaceutical manufacturers are looking into ways of achieving Operational Excellence; Lean-enabling technologies play an important role in lowering costs and reducing waste, helping to make a process as efficient as it can be.

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Many industries, such as food producers or car manufacturers, have embraced the concepts of high volume/low profit operations for many decades (1,2); but why have such methodologies recently become so important to the biopharmaceutical industry?

Over the last five years, the industry has witnessed a number of new challenges. While companies face the usual requirement to grow revenues and profits, we see developing pressure on drug prices as the large healthcare providers (both public and private) re-evaluate many of the therapies they use. Biopharm manufacturers are also facing rising operational costs (labour, energy and materials), as well as having to manage substantial financial risks – for example, deciding whether to build new facilities or use existing plants. Finally, there remains the competitive threat of biogenerics, particularly from the emerging economies of Asia. We now have a situation where manufacturers must (in line with the process of industrial maturation) implement operational improvements across the entire value chain (see Figure 1).

In response to these challenges, the industry is consolidating and embracing the concepts of ‘Lean’ and ‘Operational Excellence’. Approaches include the use of process analytical technology, platform-based processes and disposable production components, all of which can reduce time-to-market and the costs of development and manufacture, through increasing product and process quality, and reducing waste – keys to achieving so-called ‘Operational Excellence’.

WHERE ARE WE HEADING?

There is no doubt that the product portfolio of the biopharmaceutical industry is being driven by monoclonal antibodies (MAbs) (see Figure 2). At the same time, however, the industry is debating the exact scale of MAb manufacturing required – is multi-ton manufacturing on the horizon? In a case study of very large-scale monoclonal antibody production (3), Kelley looked at a single-branded product need of up to 10,000kg/year; he concluded that such production is possible with current technology and sees little or no need to turn to unproven alternatives simply for cost reasons. In our own study, looking at the production scale of currently marketed biopharmaceuticals, we see at least four recognisable trends that will reduce average production scales for novel protein drugs (4), concluding that the future of antibody manufacturing will need to offer solutions for a small group of therapeutics at the ton-scale, and much more economical production of proteins at 50-500kg volumes – something that can be achieved through Operational Excellence.

Figure 1: Biopharmaceutical trends – pressures and opportunities

Figure 2: How the industry is being driven by monoclonal antibodies (5,6)
EFFICIENT PRODUCTION

Operational Excellence describes the goal of achieving superior yields, lead-time and throughput whilst eliminating waste. It is a systematic approach to attaining world-class performance in productivity, quality and delivery of services and/or goods. Two effective tools for achieving this are Lean and Six Sigma. Along with GE Healthcare Life Sciences, one large biotech company anticipated some of the industry pressures a few years ago and implemented a programme of Lean initiatives – recognising that rapid pace of growth created many process improvement opportunities. Other companies have also been heavily investing in Operational Excellence tools.

Lean can be broadly described through five principles:

- Define value – from the end-user’s point-of-view
- Identify the value stream – develop an understanding of how value flows to the product/service/person/object that is moving through the process
- Establish flow – create a situation where the product/service/person/object moving through the process does so with no interruptions or issues
- Examine ‘pull’ from the end-user – until something needs doing from that perspective, don’t do it
- Describe perfection – it’s the aim that can never be achieved, but processes will be improved by trying

The main focus of Lean-enabling technologies is to reduce waste. Below is a list of the most common causes of waste, while Figure 3 shows where time and money can be saved when implementing Operational Excellence tools:

- Overproduction
- Transportation
- Motion
- Waiting
- Over-processing
- Inventory
- Defects
- Under-utilisation

MANUFACTURING FLEXIBILITY AND CHROMATOGRAPHY

The industry has many tough decisions to make in the short term to ensure its long-term viability. As cell culture processes improve, the marketplace becomes more competitive, and we rapidly move towards multi-product/multi-scale manufacturing at multiple sites; there is then much speculation as to whether we need to invest in new technology to meet manufacturing demands, or just look at continuous improvement of current techniques and technology. Whilst we always have to be aware of possibilities through both of these routes, the consensus in the industry suggests that much can be done by focusing on the latter (3,8).

Over the last ten years, innovations from chromatography suppliers such as GE Healthcare have helped biomanufacturers overcome many issues, providing dedicated tools for difficult challenges like media screening and column packing, and resins that can cope with high titres and specific purification issues – resulting in higher productivity. Looking to the future, we envisage that in the coming decade:

- There will be an increasing need for MAbs as therapeutics
- Certain diseases, such as influenza, will necessitate speed in development and production of vaccines
- Product titres for MAbs will reach levels of 5g/L or greater

Figure 4 highlights our research into current industry best performances, summarising our findings and providing an indication of where the industry stands today and the improvements that may be achievable.

Lean can be used to find ways to create better process flow, reduce downtime and stoppages, and reduce non-productive activities such as changeover time between production campaigns, cleaning procedures, or preparation of equipment and process buffers. However, Lean and Lean-enabling tools can also be used in process development and optimisation. One example is High Throughput Process Development (HTPD) on filter plates (for example, PreDictor™ plates), which allow identification of the most appropriate chromatography conditions for a process by running a series of experiments in a very short period of time, helping to define the design space and limits of operation. This approach is also used to select the most appropriate chromatography resins for each step.

Figure 5 highlights how Lean concepts can be applied to a chromatographic process step to improve on first-generation tools. In our Lean interpretation, we assume that only the loading of material to be purified, the removal of impurities from the bound product in several wash and strip steps, and the elution of the purified intermediate product are essential value-adding activities.
The preparation of resin slurry and column packing, as well as cleaning (CIP) and equilibration, are not.

**USING MODERN RESINS**

Historically, most downstream processing stems from the success of first-generation chromatography products and process designs. In more recent years, however, a number of improvements in resins have become available that significantly impact chromatography capabilities. One such example is Protein A resins where the introduction of higher capacity and more stable resins offers simplified CIP regimes and longer working lives. Another is novel ion exchangers with higher capacities, increased volume throughput and multimodal selectivities that can shorten a process from three to two steps.

Figure 6 (page 60) illustrates how utilizing updated resins changes the performance of the whole downstream process. The assumptions and calculations used for this graph are from a model study performed at GE Healthcare (4). Costs relating to the facility, equipment and upstream processes are excluded from the calculations, but all downstream-related labour, resins, membranes, filters and buffer costs are included. The absolute dollar numbers are not directly applicable to all situations, but the relative effects of the changes are relevant for most cases.

When replacing the capture step (Protein A resin) in a classic process using first-generation Sepharose™ Fast Flow resin with a modern Protein A resin (MabSelect™), process time is reduced and specific costs ($/g) are lowered by ~50%. Completely changing to recently developed resin technology reduces the process time to two days and the costs to just above 30% of the original level (‘model process’). This translates into a two- to three-fold productivity increase for the corresponding original downstream process, in part by enabling many more batches per year.

In short, Lean analysis can help manufacturers uncover many of the real issues behind their costs and bottlenecks, such as using early generations of tools and poorly optimised unit operations.

**TWO STEPS RATHER THAN THREE**

One of the main features of Lean is to look critically at process steps; for example, if the same quality result can be achieved with one less step, process engineers can implement Lean to remove unnecessary operations. For example, applying at least three chromatography steps to purify protein pharmaceuticals such as antibodies is still considered dogma by many. However, there are at least two published variations of a two-step chromatography process with the promise to meet quality objectives in many of the cases where they have been applied (9,10).

The use of a two-step purification scheme may not reduce the direct costs by much relative to other improvements, but smaller buffer volumes will be required and consequently buffer preparation and storage requirements will be reduced. This increases manufacturing flexibility, for example, by enabling a process to be located within the floor space of a small existing facility.

**DISPOSABLE TECHNOLOGY**

One of the key issues observed by those who have started to promote disposable chromatography (for example, using membrane adsorbers instead of packed bed columns with beaded matrices) is the time consumed before and after the purification – that is, for column packing, cleaning and eventually storage.

Prepacked columns for fairly large-scale operation have become available (ReadyToProcess™, GE Healthcare). With these pre-tested and pre-sanitised devices, resin slurry preparation and column packing is not necessary and the corresponding waste is removed. The columns are made of construction materials that can be disposed of by incineration, and are ready for use in single or campaign mode. However, since the devices are also stable in typical CIP regimes, it is up to the user to decide whether multiple-use is the preferred, more economical option.

**CONTINUOUS VERSUS BATCH MODE**

The idea of operating chromatography in continuous mode is not new but, in contrast to continuous processing of bioreactors, it has never become widely established in large-
scale biopharmaceutical protein manufacturing.

From the processing of small molecules, it is known that this mode can increase productivity and reduce the consumption of buffers, as well as enabling high-resolution separations in isocratic mode. At GE Healthcare, we have tested a specific variant of continuous processing referred to as 3-Column Periodic Countercurrent Chromatography (3C-PCC). We have used the capture step with a Protein A resin to establish the usefulness of this method, and have developed a small-scale fully automated custom ÄKTATM system to support those who wish to test the approach.

In our experience, the 3C-PCC system is a very simple hardware set-up that allows almost complete utilisation of the packed resin; since all product that breaks through during loading is caught by the next column in the system, less waste is generated throughout the operation and buffer consumption is reduced. In our labs, we have found up to a 30 per cent improvement in productivity (g L resin /hour), and a reduction in buffer consumption by up to 30 per cent.

CONCLUSIONS

Manufacturers must carefully consider their processes and ascertain whether they are running optimally. As the industry swings to mass production of monoclonal antibodies, it is now more important than ever to ensure that development and manufacture is as efficient as it can be.

We can see a few trends worth watching over the coming decade; the market can be expected to develop in two areas:

- Large-scale, efficient manufacturing for blockbusters
- Small-scale, flexible technologies for rapid experimentation and efficient production of small volumes used in testing, clinical trials and small patient populations

Disposables solutions are in vogue, although ‘ready-to-use’ is the relevant feature, offering the required manufacturing agility. Upstream and downstream processes are becoming more integrated and more industry-friendly, instead of remaining as separate unit operations with awkward interfaces. Continued improvements in chromatography (capacity, throughput and quality) and membranes will be complemented by numerous approaches to improve ease-of-use and increase efficiency.

Suppliers to the biopharmaceutical industry will need to take these developments into account, and GE Healthcare plans to work closely with the industry to provide the necessary tools for Operational Excellence. But we are not just looking at the short-term issues. It is important to recognise the challenges facing biopharmaceutical production during the course of the next decade – including flexible development and manufacturing, multi-product facilities and tackling the issue of biosimilars. Regardless of whether a company is a contract manufacturer or produces its own biopharmaceuticals, there are huge pressures on the industry to develop Operational Excellence. On top of this, we must never lose sight of the over-riding need to provide innovative vaccines, MABs and therapeutics that can improve health on a global scale.

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Note

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References

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