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With hundreds of products in development, and blockbusters already on the market, monoclonal antibodies (mAbs) remain the single most important product group driving the biopharmaceutical industry's development today (1). The selectivity and flexibility of their mode of action provide the



potential for successful therapeutic strategies against medical conditions that, until recently had no effective treatments, let alone a cure.

mAb therapies typically require relatively high doses. Thus, the necessary product quantities are associated with high-volume production facilities in which mammalian-cell-culture processes running in multiple 10,000–20,000 L working-volume bioreactors play an important role in the design and cost of the facility.

The biopharmaceutical industry is now poised to undergo a transition influenced by trends such as market differentiation, expiring patents, an increase in biosimilars, excess capacity, and governmental initiatives to reduce the cost of healthcare (3). These trends are very real for mAbs because the product group continues to shape the biopharmaceutical industry and drive the design of production facilities that will match this transformed landscape.

As a consequence, commercializing a mAb product has gone hand-in-hand with a significant capital expense if the market strategy included a decision to build a production facility. Historically, the scale of the operation and the necessary technology have led to considerable total installed costs that often are in or above the \$100–300 million range. Although strategic decisions to go this route have resulted in bringing important products to patients and mitigating risk of capacity limitations, price tags are of such an order that the facility can represent a future burden (2).

Dramatic increases in cell-culture yields make it possible to significantly reduce bioreactor volume, thereby making single-use technology a viable alternative to stainless-steel bioreactors. Market segmentation resulting from personalized medicine and biomarkers will result in smaller product campaigns. Not only will new facilities become smaller and more flexible, but also new process technology will make these facilities more efficient, cost effective, and better able to adapt to changes in market demand. Moreover, process intensification and single-use technology will result in greener facilities with a reduced CO₂-footprint.

High-titer processes

Advances in cell-culture technology ranging from new cell lines, improved media compositions, and optimized process conditions have all contributed to a marked increase in mAb titers compared with the situation in the mid-to-late 1990s, when the first production facilities were designed. Statements from industry leaders cite titers of 3–5 g/L as the new reality for products in production, while some products in development come with titers of 8–10 g/L (4). Current state-of-the-art technologies forecast that titers in the 10–15 g/L range are

possible before process limitations come into play. The recent year's strong focus on optimizing the upstream process has resulted in 10–100-fold increases during the past 10 years, even for the traditional industry workhorse, the Chinese hamster ovary (CHO) cell line (5).



Figure 1

For next-generation cell lines such as the PER.C6 cell line from Percivia (Cambridge, MA), the perspective is further illustrated by a combination with novel process technology. Derived from the human retina, the cell line is optimized for protein production, and mAb titers of 8 g/L have been reported. In combination with Percivia's XD-process (a perfusion process with both cell and product retention over a continually flushed, hollow-fiber membrane that allows feeding of fresh nutrients to the bioreactor while waste products are being removed), the cell line has demonstrated concentrations of 27 g/L(6). Titters of this order change the current understanding of a typical mAb process design that has settled on variations of the process generalization (see Figure 1).

The future challenge will be to optimize the downstream processes in a design space confined by physical and chemical conditions (e.g., mass transport, binding rates) as opposed to optimizing output from a biological system (volume driven) in which output increases with cell viability and concentration. With high titers such as those from the XD-process, the industry enters a level of processing where some loss in the subsequent capture process can be accepted. Alternatives to the classical protein affinity capture column based on precipitation or membrane chromatography processes are thus becoming realistic (7).

Disruptive technology

Manufacturers of future high-titer mAbs will have the option of using traditional stainless-steel equipment, single-use equipment, or a hybrid combination of the two. Availability of single-use bioreactors with working volumes of 1000–2000 L makes them a compelling alternative as a production platform. In reality, the important issue is not stainless steel or single-use technology, but rather how technologies can be combined to provide the most productive and cost-effective process. Choosing one or the other technology concept depends on both strategic considerations and feasibility studies of each individual case.

Stainless steel. A stainless-steel manufacturing facility for biotechnology products is based on well-known design principles originating from the petrochemical and dairy industries, with additional considerations for cross-contamination prevention and sterility. The facility is characterized by having a fixed piping and tank layout (mobile vessels are possible below the 1000-L scale). Once the investment is made and the installation is finalized, the strategic safety of having all process equipment in-house is obtained. Only a few dependencies for consumables and spare parts remain.

Stainless-steel technology is well suited for automation applied to improve safety, ergonomics, process reproducibility, and to reduce training scope. Because instrumentation for cleaning and sterilization does not contribute directly to the production process, the technology carries some overhead and requires significant maintenance and validation. Cleaning stations for utensils and mobile tanks add to the complexity.

Single-use. Compared with stainless steel, single-use technology has obvious advantages, primarily a reduced investment cost and an inherent elimination of risk from cross-contamination because the product-contacting surface is disposed of after each batch. Piping between process steps may be eliminated with plastic tubing and manual transport to move bag containers between process stations. Working volumes as much as 3000 L for simple solution hold are available. Bioreactors with capacities as high as 2000 L have been proven suitable for running many processes.

Being highly flexible, single-use technology can be reconfigured for a new process or product in a few days. Another important feature is that installation is simplified because of a reduced need for cleaning and sterilization, which again translates into reduced capacities for clean steam, clean-in-place, and waste collection and treatment.

Still, there are a number of challenges for single-use technology. The technology is less orderly, so the arrangement of tubing must not interfere with operator activities, and process accuracy must be considered. The technology has limitations for demanding mixing and heat-transfer applications. Large-range reliable single use sensors are just starting to become available.

The complexity of single-use technology is that the core process-contacting elements are essentially built up again for each batch so instruction and training demands become more important factors. The flexible and more manual nature of processing is also reflected in increased material handling and tracking challenges. For critical components, a dual-vendor strategy is desirable but not always possible because not all single-use inserts will fit all supports or racks to hold them.

Feasibility considerations. Estimating the economic prospects of single-use technology can be done with feasibility studies, which typically can be simplified if specific cost of goods values are not required. It is important to consider the entire production scenario before simplifications are made. In many cases, not including high batch-frequency operations, single-use technology is a more favorable concept. Such is the case with respect to investment cost but also with respect to variable costs when the cost of the capital that would otherwise go into the investment of the comparable stainless-steel operation is included. Amortization and interest of stainless equipment over time must be added to variable costs, and many case studies will show that it exceeds variable cost related to increased consumables for a single-use design.

Assumptions regarding the cost of cleaning chemicals and water for injection are often included in feasibility studies but are seldom the deciding factor, because the cost is usually low compared with other consumables and cost of

capital. It is important to use cost data that reflect the scale of operation. Sometimes, estimates about reductions in operator time are introduced in to the feasibility study. Although personnel costs are important, such estimates can be difficult to realize in real life. It is a more conservative approach to state that operators may be freed up to improve process operation and monitoring instead of handling cleaning processes.

Designing the next-generation facility

A new facility design paradigm arises from the combination of high-titer processes and single-use technology. Jagschies has addressed the question of realistic estimates for future mAb product volumes (8). The viewpoint is that most products will require less than 500 kg annually capacity with few products requiring as much as 1000 kg. Assuming 5 g/L titer and typical process conditions places an annual output of 1000 kg within the reach of a facility based on six bioreactors with 2000-L working volume. Not surprisingly, the 10+ fold yield increase over the titers from earlier times is reflected in a facility housing significantly smaller bioreactors, thus paving the way for an upstream process based on single-use technology instead of traditional stainless-steel technology.



Figure 2

Figure 2 illustrates the conceptual differences between the traditional and the next-generation facility. The three-dimensional model shows typical equipment simplistically lined up to compare floor space and room height between a traditional 6 × 20,000 L bioreactor facility and a single-use 6 × 2000 L bioreactor facility. The scenario illustrates that the next-generation facility will exhibit both a

reduced footprint and reduced building complexity by being able to fit into a one production-level facility, because the bioreactors will not protrude through several levels.

This design would require in-line dilution of concentrated buffers and potentially a series of product pool bags for downstream processing of the large product volumes arising from the individual bioreactor. Depending on production strategy, the volumes involved also open up for supply of ready-made media and buffers. Therefore, the media and buffer preparation suites may be eliminated from the facility or reduced significantly.

Compared with the traditional mAb facility, next-generation single-use facilities will be more generalized with a series of process stations where utilities are presented and process equipment can be hooked up to form the required process. There will be an added emphasis on logistics and workflows, resulting from changed requirements for storage, manual transport of process liquids, and equipment, waste, and personnel flows. Life in the next-generation facility

Automating single-use technology. In changing from stainless-steel to single-use operation, manufacturers may lose aspects of the orderly process hook up and the easy tracking of when actions and process events happened, when operators intervened, and when valves (clamps in the single-use case) were opened and closed.

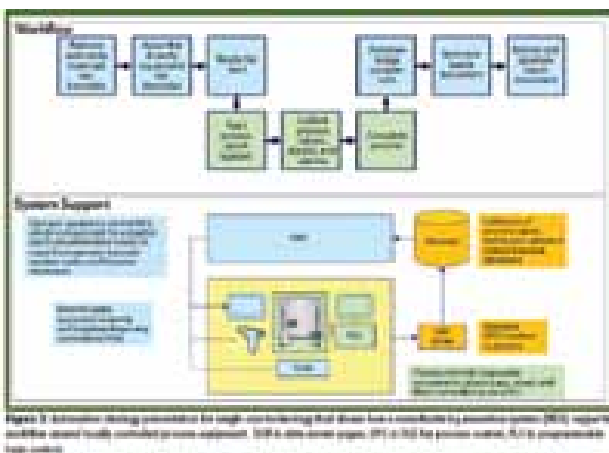


Figure 3

As it stands, the state of the art for single-use technology, written procedures and training are the cornerstones to ensuring the process remains reproducible. In this capacity, automation enables technology to create a type of comfort zone around the low-automation level process step (see Figure 3).

As facilities go from pilot plant-scale to full-production scale, the industry will see automation strategies in which the process itself is handled by the vendor-supplied local control and a central manufacturing execution system (MES) forms a process support system guiding the operator through all steps necessary for the process (see Figure 3). Tracking and material-handling technologies such as barcode systems are already available to ensure good housekeeping for materials, equipment, and new and used consumables. The most recent development is that single-use items are also available with RFID tags.

A greener facility. What will be the environmental impact of the next-generation facilities? The idea of disposing plastic bags appears as intuitively wasteful but must be compared with traditional technology that requires cleaning and sterilization between each batch.

A recent study concluded that single-use technology is approximately 50% less energy intensive than stainless steel because the consumption and heating of large volumes of water to clean and sterilize is more energy demanding than producing and inactivating plastic bags that also can be incinerated for energy recovery (9). Even though waste disposal as landfill leaves little CO₂-footprint, it does not appear as a sustainable solution in the long term. Add to these considerations the markedly increased yields and it becomes evident that a next-generation facility will have a smaller CO₂-footprint per kilogram of mAb produced compared with a traditional facility. For all facilities, it must be remembered that any single-use waste flow is only part of the solid waste flow. Mauser described in very good detail how common assumptions may be challenged through a life-cycle analysis of these technologies (10).

Conclusion and future perspectives

Although there are still some hurdles, trends will combine to bring next-generation monoclonal facilities on-line during the next two to five years. New cell lines and process technologies will result in 1000 kg mAb/year capacity in 1000-L scale becoming available in smaller, more flexible, and more cost-effective facilities with investment cost and variable cost massively improved compared with current facilities with similar output. But new cell lines and new process technologies may also seriously extend the capability of existing facilities. Provided that fundamental requirements are observed in the facility design, workflow and data-handling systems facilities can be retrofitted with next-generation technology. Development laboratories may then be able to cover pilot-plant scale, and pilot plants or sections of production plants may suddenly acquire the capacity for launch or production capacity. Thus, in the near future and with the current economic climate, the most common next-generation mAb facility may actually be the upgraded facility.

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