mAbs 1:5, 443-452; September/October 2009; © 2009 Landes Bioscience

Industrialization of mAb production technology
The bioprocessing industry at a crossroads

Brian Kelley

Bioprocess Development; Genentech; South San Francisco, CA USA

Key words: bioprocessing, cell culture, purification, economics, capacity, manufacturing, production, facility, biopharmaceutical

Manufacturing processes for therapeutic monoclonal antibodies (mAbs) have evolved tremendously since the first licensed mAb product in 1986. The rapid growth in product demand for mAbs triggered parallel efforts to increase production capacity through construction of large bulk manufacturing plants as well as improvements in cell culture processes to raise product titers. This combination has led to an excess of manufacturing capacity, and together with improvements in conventional purification technologies, promises nearly unlimited production capacity in the foreseeable future. The increase in titers has also led to a marked reduction in production costs, which could then become a relatively small fraction of sales price for future products which are sold at prices at or near current levels. The reduction of capacity and cost pressures for current state-of-the-art bulk production processes may shift the focus of process development efforts and have important implications for both plant design and product development strategies for both biopharmaceutical and contract manufacturing companies.

Background

Bioprocessing technology for production of therapeutic monoclonal antibodies (mAbs) has advanced greatly since their introduction into the market in 1986. Early murine mAbs were derived from hybridoma cell lines, using diverse production technology; the first licensed mAb therapeutic, OKT3, was produced in the ascites of mice.[1] The development of recombinant technology based on cloning and expression of the heavy and light chain antibody genes in CHO cells enabled mAb production to take advantage of the common technologies already used for recombinant products like tissue plasminogen activator, erythropoietin, Factor VIII, etc. These recombinant cell culture processes for antibody production initially had low expression levels, with titers typically well below 1 g/L.[2]

The combination of low titers and large market demands for some of the first recombinant mAbs like rituximab (Rituxan), trastuzumab (Herceptin), infliximab (Remicade) and others drove many companies and contract manufacturing organizations (CMOs) to build large production plants containing multiple bioreactors with volumes of 10,000 L or larger. Other products derived from mammalian cell culture in the mid-90s also required large production capacity (Enbrel, while not a mAb, is an Fc-fusion protein which is produced using a similar manufacturing process), driving further expansion. In parallel with the increase in bioreactor production capacity throughout the bioprocessing industry, improvements in the production processes resulted in increased expression levels and higher cell densities, which combined to provide much higher product titers.

Today, the potential of combining high titer process technology with the large installed bioreactor base has resulted in a great excess of production capacity for mAbs, far outstripping the increase in market demands over recent years. This has stimulated discussions of the controversial issues of the best use of current production capacity, the impact of manufacturing cost of goods (COGs), and the choice of the appropriate mAb production technology for emerging product candidates. Should companies choose conventional bioprocessing technologies, or invest in novel technologies which may lead to superior expression levels or lower production costs? Have process development strategies adjusted to this paradigm shift where nearly unlimited capacity and very low COGs are enabled by the current state-of-the-art? If not, how should process development groups respond?

This article will analyze the current mAb production technology, review production capacity and demand estimates, and consider the position of these conventional technologies in the future of commercial mAb production for therapeutic use.

Current State-of-the-Art: Potential for mAb Process Industrialization

The processes for manufacturing recombinant therapeutic mAbs have several common features, and efforts to benchmark the current state-of-the-art draw upon information that is shared at conferences, but often not published. For production of purified bulk drug substance, i.e., the intermediate that is used to produce the final drug product sold to healthcare providers and patients, a consensus process has emerged from the major biopharmaceutical process development groups (**Fig. 1**).

Mammalian cells are used for expression of all commercial therapeutic mAbs, and grown in suspension culture in large bioreactors. The majority of commercial mAbs are derived from just a few cell lines[3] (Chinese Hamster Ovary (CHO), NS0, Sp2/0), with CHO being the dominant choice because of its long history of use since the licensure of tissue plasminogen activator in 1987.

Correspondence to: Brian Kelley; Email: Kelley.brian@gene.com
Submitted: 06/18/09; Accepted: 07/16/09
Previously published online:
www.landesbioscience.com/journals/mabs/9448

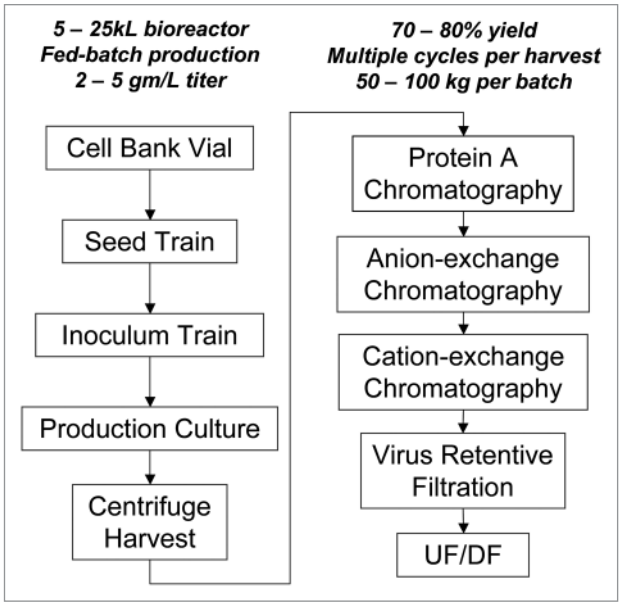

Figure 1. Consensus process flowsheet for mAb Bulk Drug Substance. A consensus process flowsheet has emerged for production of recombinant therapeutic mAbs. Suspension mammalian cell cultures bioreactors operating in fed-batch mode provide high product titers in 10–14 days. Following harvest by centrifugation and depth filtration, Protein A chromatography captures the product, and two additional chromatographic polishing steps complete the purification. Two membrane steps are used to assure viral safety of the product, and concentrate and formulate the drug substance.

CHO cells have attractive process performance attributes such as rapid growth, high expression, and the ability to be adapted for growth in chemically-defined media. Typical production processes will run for 7–14 days with periodic feeds when nutrients are added to the bioreactor. These fed-batch processes will accumulate mAb titers of 1–5 g/L, with some companies reporting 10–13 g/L for extended culture durations. Production bioreactor volumes range from 5,000 L (5 kL) to 25,000 L (25 kL).

The antibody purification process is initiated by harvesting the bioreactor using industrial continuous disc stack centrifuges followed by clarification using depth and membrane filters. The mAb is captured and purified by Protein A chromatography, which includes a low pH elution step that also serves as a viral inactivation step. Two additional chromatographic polishing steps are typically required to meet purity specifications, most commonly anion- and cation-exchange chromatography.[4] A virus retentive filtration step provides additional assurance of viral safety, and a final ultrafiltration step formulates and concentrates the product (the step order of the virus filter and two polishing steps is somewhat flexible, and may vary among company platforms).[5] Overall purification yields from cell cultured fluid range from 70–80%, and the concentrated bulk drug substance is stored frozen or as a liquid, and then shipped to the drug product manufacturing site. While the purification processes developed in the 1990s using the separations media (chromatographic resins and membranes) available at the time were not capable of purifying 2–5 g/L feedstreams, improvements in separations media make it possible today for many facilities to purify up to 5 g/L, which would generate batches of 15–100 kg from 10 kL–25 kL bioreactors.

Large manufacturing plants are designed with multiple bioreactors supplying one (or sometimes two) purification train(s). The individual purification unit operations can be completed in under two days, and often in just one day, and therefore several bioreactors can be matched to the output of a single purification train. The increased capacity of these plants arising from the elevated titers will decrease the drug substance COGs, by virtue of the economies of scale afforded by the large bioreactors. As will be described in more detail below, these plants are capable of producing enormous quantities of mAbs with very attractive costs.

Further, this consensus manufacturing process is amenable to standardization that establishes a common processing platform for many mAbs. Each company is likely to use a slightly different platform process, but the similarities outweigh the differences when it comes to the process flowsheet (**Fig. 1**) and the typical manufacturing plant design. The use of a platform approach reduces the investment per mAb product candidate, streamlines development efforts, simplifies raw material procurement and warehousing, and reduces scale-up and technology transfer complexities. Several companies have revealed that they have very similar development timelines from the start of cell line development through first-in-human clinical trials, and many are using common tools such as high throughput systems for cell line and purification process development.

This state-of-the-art has the hallmarks of a highly industrialized family of manufacturing processes. Many companies have converged on the use of very similar processes, this common production technology is mature and robust, and the outcomes of product quality, production capacity and costs are predictable. This standardization and maturation of the mAb process technology has emerged relatively recently, since the early years of the 21st century.

Why would companies need to stray from this mature and convergent platform? In some process development groups, continued advances in cell culture technology have driven mAb titers up steadily, putting pressure on purification technology that would eventually limit or bottleneck the plant's production capacity. Concerns have also been raised about the need for increased production capacity, and pressures to reduce COGs further. These factors could drive the development and implementation of novel bioprocess technologies, such as perfusion technology for cell culture, or non-conventional purification methods like precipitation, crystallization, continuous processing or the use of membrane adsorbers.[6]

Assessment of the process fit into a production facility now enables purification bottlenecks to be identified, and process designs can be adapted to enable larger batches to be purified. Often, new technology is not required, but instead simple adjustments of the consensus process will avoid the typical plant limits of product pool tank volume, unit operation cycle time or supply of process solutions. Overall purification yield, if allowed to drop a few percentage points, can often be a key degree of freedom for debottlenecking a plant as well. The use of current separations media combined with a focus on facility has shown that many plants can be debottlenecked to support titers of up to 5 g/L.[7] If

these conventional platform technologies can generate 50–100 kg batches from existing facilities, is there a driver for larger batch sizes? This question can be put in context of product demand in the subsequent sections.

It is valuable to conduct a critical assessment of these drivers for higher production capacity or reduced COGs and determine the validity of the arguments that the bioprocessing status quo is not sufficient. This has fundamental implications for important aspects of process development, facility management, capital investment and broad future trends in mAb production technology. This analysis will focus on commercial operations, as the clinical stages of the product lifecycle have different objectives that could benefit from flexible and lean operations, capital avoidance strategies and minimal upfront investment. The optimization of clinical process development strategies is a separate topic, but the design of clinical processes should reflect the key elements of the eventual commercial process.

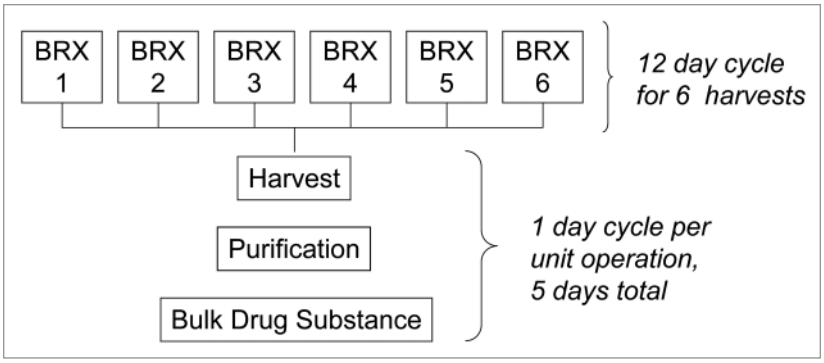

Figure 2. Model mAb production plant design and capabilities. A model large scale mAb production plant employs multiple bioreactors configured to supply a single purification train. A plant having six individual 15 kL bioreactors is potentially capable of supplying 10 tons of purified mAb per year using conventional technologies, or 4–5 products with 1 ton demands. This enormous capacity per plant would result in a marked decrease in drug substance production costs, and results in significant excess capacity throughout the biopharmaceutical industry.

Analysis of Drug Substance Production Capacity for mAb Products

An analysis of the production capacity for mAb drug substance is relatively straightforward, as much of the information on plant capabilities is available to the public. Both internal and external databases[8] were used to develop estimates of mammalian cell capacity and demand. While the number of bioreactors and their volumes are known, details of the purification train capacities are generally not. It has been reported that some facilities can purify up to 5 g/L titers and potentially generate a 100 kg batch from a 25 kL bioreactor, yet it should not be assumed that all facilities could purify such large batches. It would be safe to assume that a 2 g/L titer should be easily supported, however, and that a 5 g/L titer would fit in some, but possibly not all, facilities.

It is useful to examine the production capacity of a single plant, which could be described as a model plant for the purposes of this article. The model plant would have six 15 kL bioreactors, for an installed base of 90 kL capacity (the largest plant in operation today has 200 kL of capacity), and be supported by a single purification train (**Fig. 2**). If this plant ran a cell culture process with a titer of 5 g/L and had no purification limitations, it would offer a capacity of 10 tons of mAb drug substance per year. The design basis for this model plant has been described in the literature,[9] and would use conventional purification technologies that are available today.

In 2007, the installed capacity for mammalian cell processes was 2.3 million liters, and is projected to rise to 4 million liters in 2013 based on current plans for capacity expansion for both CMOs and biopharmaceutical companies (**Table 1**). There will be at least 25 plants with the same or greater capacity of the model plant described above by 2013, with many other smaller plants in operation as well. A conservative estimate can be taken, such that each bioreactor generates 20–24 batches per year, which is consistent with a 12–14 day production culture cycle and a short plant shutdown. When combined with a purification yield of 75%, this equates to 300 tons/yr if the process titer averaged 5 g/L, or 120 tons/yr for a titer of just 2 g/L (**Table 1**). These theoretical capacities need to be compared to current and projected market demands to provide the appropriate context for implications to facility utilization.

Table 1. Production capacity estimates for mammalian cell-derived mAbs[a]

Year	CMO	Product company	Total	Capacity at 2 g/L	Capacity at 5 g/L
2007	500 kL	1,800 kL	2,300 kL	70 tons/yr	170 tons/yr
2010	700 kL	2,700 kL	3,400 kL	100 tons/yr	255 tons/yr
2013	1,000 kL	3,000 kL	4,000 kL	120 tons/yr	300 tons/yr

[a]Capacity estimates from ref. 8.

While the estimates for drug substance production capacity should be corrected for overage required for drug product manufacturing, the losses in mixing vessels, filling lines, filters and ancillary equipment decrease with filling volumes, and diminish at very large production scales that require large filling volumes. Stability and testing requirements will also impact overall yields. Because these losses are a function of scale, facility and configuration, they are not accounted for in this analysis, but typical losses could be 10–30%, and are not large enough to change the primary conclusions of the capacity analysis.

Analysis of Drug Substance Demand for mAb and Fc-Fusion Products

The estimates of the drug substance market demand rely on a combination of several publically disclosed factors, and cannot be considered a precise value. By using the annual product revenue

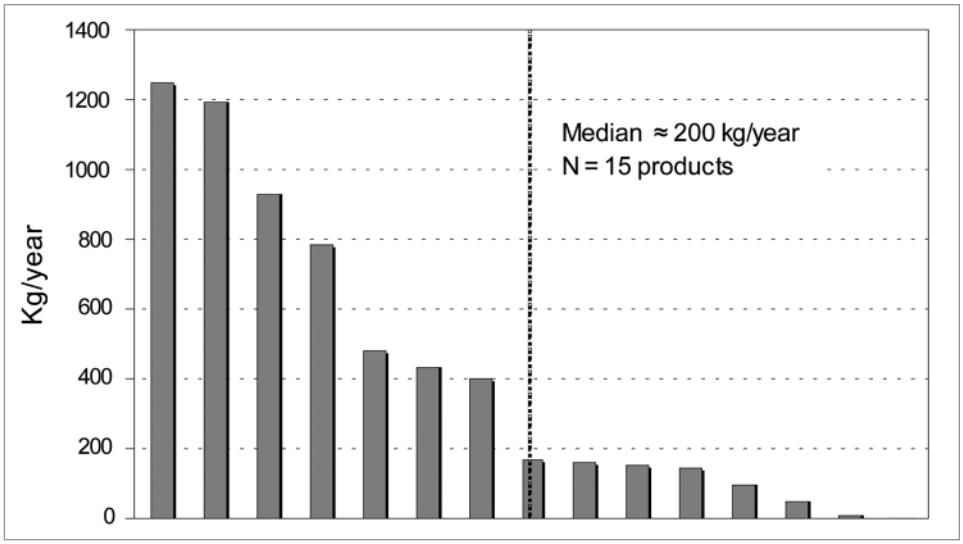

Figure 3. Estimated demand for therapeutic mAbs and Fc-fusion products in 2009. The total demand for the top 15 mAbs and Fc-fusions in 2009 is estimated to be approximately 7 tons, with the four largest volume products requiring approximately one ton per year. More than half of the products were estimated to require less than 200 kg per year (reviewed in ref. 8).

provided in annual reports, and an average wholesale price from public and private databases,[8,10] combined with a modest process yield loss and fill overage upon drug product manufacturing, a rough estimate of the annual drug substance demand can be generated. Both mAb and Fc-fusion proteins such as Enbrel are included in this analysis, as they would share the production capacity given their use of similar production technology. Some Fc-fusion proteins do not accumulate to titers as high as mAbs, and therefore would require proportionately more production capacity. In addition, other recombinant proteins not included in this analysis will also require mammalian cell culture production capacity. A survey of these products is beyond the scope of this review, and their total mass and volumetric demands are much lower than mAbs.

Again, both internal and external databases[8] were used as sources of information. The total estimated demand for therapeutic mAbs and Fc-fusion proteins in 2009 will be 7 tons. The median demand for the 15 licensed products in the database was approximately 200 kg/yr (**Fig. 3**). It is useful to note that this median product demand would be satisfied by just four batches from the model plant described above if the titer was 5 g/L, and only nine batches if the titer was just 2 g/L. It is not uncommon for some companies to have Phase III mAb processes today with titers as high as 4–5 g/L. Even titers of 2 g/L for very late stage products that reflect older cell culture processes will provide sufficient supply for nearly all pipeline products, given access to the large excess capacity in the industry.

Future demand estimates are even less certain, and are a complex combination of the factors that drive mAb clinical development: the probability of clinical success, competition from other pipeline or commercial products, development and regulatory review timelines. Several consultants provide estimates of the demands, which could increase to as much as 25 tons per year in 2013 (data not shown). This value would correspond to an annualized growth rate of 37%, which seems an aggressive value for growth of this sector, which has shown a revenue growth rate of 11%.[11] This demand is still small compared to the production capacity of the industry as a whole, even at modest titers of 2 g/L.

These analyses of production capacity and demand strongly suggest that there will be a significant amount of excess mAb production capacity throughout the biopharmaceutical industry in the foreseeable future. Even if several blockbuster products are licensed which far exceed the current maximum demands of approximately 1 ton per year, they will not give rise to a production challenge if multiple plants can be accessed for production, which has been the pattern of the production lifecycles for bevacizumab (Avastin), etanercept (Enbrel), rituximab and trastuzumab, or if their titers are sufficiently high (2–5 g/L). Access to large production facilities can be assured through the contracts with CMOs, or by partnering with the biopharmaceutical companies that hold the majority of mammalian cell production capacity.

Often, arguments which state that a new technology is required to meet growing therapeutic mAb demands assume that many products will reach blockbuster status and the highest peak product demands in industry are likely to grow in future years. Still, the forces of competition from other biologics or small molecules for common indications, and improved mAb characteristics such as selection for extended pharmacokinetic profiles or lower dose will likely combine to cap demands below 2–4 tons per year for all but the most unusual products. It is important to note that even in the case where a landmark product commands 10 tons per year, a single one of the model plants could cover this demand. Further, as cell culture titers increase in concert with movement of today's molecules through the pipeline and on to becoming commercial products, a smaller number of batches will be required to satisfy the demand.

Thus, it seems that production capacity and cell culture titer will not be drivers for process design targets for almost all pipeline mAb products. Arguments that improved process technologies are needed to debottleneck today's mAb production to satisfy market demand appear to be largely unfounded, but for very exceptional circumstances.

mAb Drug Substance COGs Evaluation and Sales Prices

Data on the production COGs for pharmaceutical products are not typically available in the public domain, but there are

indications that mAb drug substance costs have dropped significantly in the last decade as larger plants came on line and process improvements increased titers. Published estimates for COGs have shifted from approximately $300/gm[12,13] to $100/gm[14,15] with a potential minimum as low as $20/gm for the model plant producing 10 tons per year.[9] Note that these are only projections, not actual costs, and may reflect the ideal situation where a plant is operated at full capacity. The cell culture titers increased from <1 g/L, to 1–2 g/L, and then 5 g/L for these estimates. Several other COGs estimates from conference presentations and publications range from $50–100/gm for current processes with titers ≥2 g/L, as economies of scale serve to reduce costs.

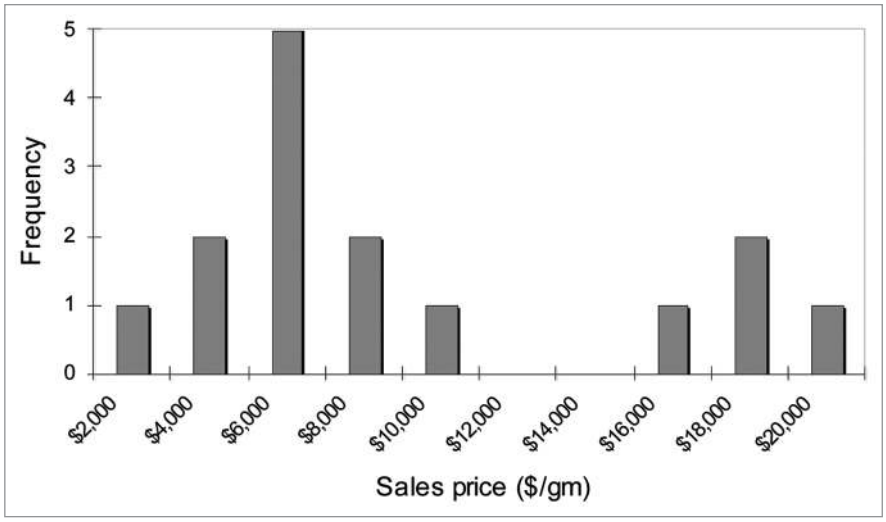

Figure 4. Distribution of average wholesale prices for mAb and Fc-fusions in 2008. The average U.S. wholesale prices per gram for 15 commercial mAbs and Fc-fusions are shown. The minimum is approximately $2,000 per gram, and the median is approximately $8,000 per gram. Note that a significant price erosion (50% of the minimum shown here) for a product with modest demand (100 kg/yr) could result in an unprofitable market, as revenues for the therapeutic product ($100 million/yr) may never provide a positive return on investment.

Raw material costs are estimated to be less than $8/L for cell culture media (with an 75% purification yield, this becomes a small cost element for high titer processes, as it may be only $2/gm for a process with a 5 g/L titer) and approximately $4/gm for the purification process. It appears that COGs reduction provided by reducing raw material costs further will only be a significant benefit for very large products with very large production scales. For the median mAb, a savings of 25% of raw material costs (25% of $6/gm x 200 kg/yr) would only result in a $0.3 M savings per year, and likely not recover the investment necessary to develop the improved process using cheaper raw materials, considering the fully burdened labor cost for development staff of $0.3–0.5 M per year.

The 2008 average sales prices for the top 15 mAbs and Fc fusions range from $2,000–20,000/gm, and the median sales price is $8,000 (**Fig. 4**). The fraction of the sales price associated with the drug substance COGs for a process with a titer of 2 or 5 g/L would be very small (approximately 1–5% at most). It may not be widely recognized or reported that because of these increase in titers and economies of scale, mAbs will be a class of biological products with relatively low production costs, although this calculation does not account for many other expenses, such as royalties incurred for accessing either the necessary process technology, or for the antibody sequence or target, in addition to the burdens of the cost of research, sales and failed projects in the research pipeline. This will have critical implications for process development, manufacturing and product lifecycle strategies.

Thus, it appears that drug substance COGs will not be a significant driver for process technology decisions for pipeline products as long as reasonable titers (>2 g/L) can be achieved; titers greater than 5 g/L are very unlikely to have a meaningful impact on either capacity or COGs, and even higher titers could have no impact on costs as the bioreactor output would exceed the purification process capacity. For nearly all mAb products, with the exception of blockbusters with a very low sales price, there will be no direct link between mAb drug substance production costs and sales prices in the future, as companies are able to take advantage of the economies of scale provided by large production capacities and increasing titers. However, the current slate of mAb products may have very different cost bases given that their process titers are likely to be much lower, as a consequence of earlier technologies used to establish their cell lines, media formulations and bioreactor management strategies.

A summary of COGs components for the final product vial is shown in **Table 2**. Cell culture titer is a strong influence on COGs, but the difference between 0.5 and 2 g/L is much larger than between 2 and 5 g/L. The rough cost of the upstream process is inversely proportional to titer, while the downstream costs are in direct proportion to the product mass purified. As the titer increases from 0.5 to 5 g/L, the majority of the drug substance COGs shifts from upstream to downstream unit operations, as has been described by other models.[16] The clear benefit in increasing product titers for these large-scale production facilities is evident, as the 10-fold increase in titer decreases the drug substance COGs by over 85% ($124/gm to $16/gm). The cost of manufacturing the drug product is estimated at $10 per vial, which represents a reasonable average for a parenteral product, but will depend upon many factors including configuration, batch volume and testing requirements. The fill-finish costs could become a larger component of final product costs than drug substance COGs in some cases, although this is largely dose and product titer dependent. When drug product device or delivery technologies are employed, the proportion of costs associated with drug substance production will be reduced even further, sometimes dramatically. Recognizing that drug product manufacturing costs may exceed drug substance costs for some high titer mAb processes emphasizes the diminishing returns of increasing titer further.

Table 2. Sensitivity analysis of mAb drug substance COGs for the model plant (six 15kL bioreactors)

Titer (g/L)	Plant capacity (tons/yr)	Raw materials ($/gm)		Depreciation & labor ($/gm)[b]	Fill/Finish costs per vial ($)	Total Drug Product Cost ($/vial)	
		Cell culture[a]	Purification			100 mg	1 gm
0.5	1	20	4	100	10	22	134
2	4	4		25		13	43
5	10	2		10		12	26

[a]Assumes medium cost of $8/L. [b]Based on the model plant ($500 M capital investment + 250 staff = $100 M per year).

Although not indicated in **Table 2**, the largest potential cost driver is the drug substance plant occupancy or utilization. A single product plant running a 5 g/L titer process that is capable of producing 10 ton/yr, but which only needs to produce 1 ton/yr to satisfy demand, will have a cost structure that cannot take advantage of the high titer process. This is the major driver for the design and licensure of facilities for multiple products, which will benefit from standardized processes. While this impact of excess capacity can dwarf the drug substance manufacturing costs, there is little influence that the process design could have on managing this cost. It is interesting to observe that the original motivation for a proposal to establish a consortium model with shared mAb production capacity[17] was the ability to satisfy peak demands for blockbuster products when production capacity was limiting. Today, as a result of excess capacity, the new driver would be to distribute plant overhead among several products and bring new molecules to existing facilities.

Future pricing trends are difficult to predict, and certainly there will be cost containment pressures on biopharmaceutical products. The development of personalized medicines to satisfy smaller markets could become a larger sector of the mAb market, but these products will only require a reduced product demand and will likely command prices per gram that are at least as high as current mAbs, but almost certainly not lower. Consider a small market with only a 50 kg per year demand. A sales price of just $2,000/gm would result in revenue of $100 M per year, which is unlikely to recoup the company's investment, which averages $1.2 B by some estimates.[18] For innovator companies, the main cost driver of product development and subsequent commercial production is the clinical development costs of the many failed products that never generate revenues, and not the manufacturing cost of the successful mAb products. Even price erosion that may arise from competition from follow-on biologics or biosimilars in the mAb sector, which many would estimate as only amounting to 10–30% reduction in sales price, would not markedly shift the production cost as a percentage of sales for a high-titer mAb process.

Critical Evaluation of Very High Titer Processes and Alternate Production Technologies

Much attention has been focused in recent years on improving mAb production technologies. This has enabled the current state-of-the-art, with debottlenecked processes capable of handling up to 5 g/L titers. What could happen if this current technology were in competition with an even more efficient technology of the future? The potential for high titer cell culture processes operating in existing facilities has identified what appears to be a futile cycle: In the drive for higher titers which generate ever larger batches in the large-scale production facilities, one will eventually exceed the plant's purification capacity (even with new separations media, bottlenecks will be reached), potentially requiring the development of new technologies. Implementation of these new technologies would require more capital investment and retrofitting of the facility to accommodate the non-standard unit operations, which then generates a challenge to managing a multiproduct facility and product changeover. Why spend additional capital, and complicate plant operations, including a potentially expensive shut-down phase to conduct the retrofit? An increase in titer above the purification capacity of a large production plant that then drives development of new purification technology could be counterproductive.

This has led to the proposal for future production facilities to be designed for lean and flexible operation, but at relatively small production scale. Disposable bioreactors have been used at up to 2 kL scale, and a plant with disposable cell culture technology would require less capital to build.[19] It has been proposed that these plants could still enable production at high capacities, which isn't trivial with 2 kL bioreactors because the capacity equivalent to the model plant would require 45 bioreactors operating in parallel, and could potentially be operated with reduced labor, although a high degree of automation would be required, hence reducing the COGs further. While the production cost would be reduced, this is unlikely to be a competitive advantage, given the low production costs for mAbs as described above. A reduction of a product's COGs that ranges from 1–5% of the sales price using current technology and existing facilities is hardly a strong competitive advantage.

A downside of this smaller plant operation would be the high cost of quality control. Even with small, lean facilities, the QC and QA costs will scale with the number of batches produced. The 7.5-fold scale difference between the largest disposable bioreactor available today and the model facility would require many more batches to satisfy demand. This would beg comparison to the economies of scale offered by manufacturing facilities using current large-scale production plants.

Consider a less-risky alternative to developing very high titer processes or employing new production technology: take advantage of the existing production capacity, and avoid retrofitting or building a new plant. The most capital efficient plan is to make no capital investment at all. The costs of three manufacturing scenarios (a new large-scale factory based on the model shown above, a new small-scale factory using disposable bioreactors, and

Table 3. Estimated cost breakdown for three production scenarios

		Model large-scale plant	Small-scale plant using disposables	CMO	
Basis: 5 g/L		6 x 15 kL	n x 2 kL	15 kL	
Capital Investment[a]		$500 M	$125 M	-	Difference in annual cost for two best alternatives ($M/yr)
Depreciation[b] ($/yr)		$50 M	$12.5 M	-	
Raw Materials[c]		$10/gm	$20/gm	$10/gm	
Labor ($/yr)[d]		$50 M	$20 M	-	
CMO		-	-	$3 M/batch[e]	
COGs $/gm	10 ton/yr	20	23	60	$30 M
	1 ton/yr	110	53	60	$7 M
	0.1 ton/yr	1,010	345	60	$29 M

[a]The new facility based on disposables is assumed to cost just one-quarter of model plant to build, and uses only the number of bioreactors ('n') needed to satisfy the demand. [b]A 10-year straight line depreciation is used to estimate the depreciation costs. [c]Raw material costs per gram are assumed to be slightly higher for the disposable facility. [d]Labor costs for the new facility are assumed to be just 40% of the model plant (100 vs 250 staff, respectively). [e]A constant cost per batch is assumed for the CMO, all-inclusive of production, testing and release.

the use of a CMO with a fixed per batch cost) are provided in **Table 3**, for various production scales ranging from 0.1 to 10 tons per year. Simple assumptions for capital depreciation, labor, and raw material costs are included, to provide a first-order estimate of COGs. While there will certainly be capital expenditures associated with keeping an existing facility operating, these are small compared to the initial investment to design, construct, start-up and validate a new facility. At the largest scales of production, the model plant is least expensive, but very close to the small-scale plant, although the labor costs to manage a fleet of 45 x 2 kL bioreactors might not be supported by the generous staffing discount applied to the new factory using disposable technology, which would widen the gap to the smaller factory considerably. At the intermediate and smallest production scales, use of a CMO is a very attractive alternative to either single-product facility. The final column shows the annual difference in production cost between the two least expensive options for each scenario; it is the difference in the two lowest COGs per gm multiplied by the gm produced per year. Even the largest difference, approximately $30 M, would potentially be small compared to the revenue for the blockbuster 10 ton/yr product (just 1% of a $3 billion product). For the smallest demand, 0.1 ton/yr, the $29 M differential is likely to be a significant cost for this small market, and would be a strong driver to use a CMO or existing multiproduct large-scale facility.

Many companies have chosen to contract out drug product manufacturing, and retain control over the drug substance production. Because many of the critical quality attributes of mAbs are set by the drug substance manufacturing process, there is a natural desire to have control over this critical step in the supply chain. Yet, today manufacturing of mAb drug substances using platform technology at established plants is much more predictable with regard to process robustness and product quality, and access to production capacity is more secure than a decade ago. If many companies were to build new plants employing new disposable technology for commercial production of their pipeline products, thereby minimizing capital investment, then this could lead to another generation of mAb manufacturing plants that would likely be run at partial capacity, and incur higher production costs due to low production rates and the higher cost of quality control and quality assurance. Until a new plant supports multiple products, it is difficult to argue for a cost advantage for this manufacturing strategy.

A likely future scenario is a slate of mAb products with smaller demands. These would arise from a combination of forces including market fragmentation, increased competition among biologics, engineering or selection of molecules with higher specific activity, and smaller indications arising from personalized healthcare enabled by biomarkers and patient genotyping. These smaller volume products could be produced at either small-scale dedicated plants or large-scale multiproduct facilities. The latter offers advantages of economies of scale and reduced cost of quality that would seem to be an attractive production strategy.

The market competition for future mAb products will more likely be driven by real or perceived differences in product safety, efficacy, and possibly pricing, than by the impact of drug substance production technology and costs.

Implications for Bioprocessing Strategies

The integration of production capacity and cost analyses will have significant implications for the bioprocess design basis and process performance targets for future mAb products. Provided a reasonable standard can be achieved, the process design targets for mAbs should not be driven by capacity or COGs concerns for all but the largest blockbuster products. Titers at product launch of 2–5 g/L should be sufficient for the next generation of mAbs, and will not need to drive new cell culture production or purification technologies based on processes with higher titers.

It is worth noting that drug substance COGs will be much higher for difficult-to-express mAbs whose titers are much lower than the current standard; this would hold for other recombinant proteins, which are unlikely to express as well as mAbs, as well as for antibody-toxin drug conjugates where the additional

processing and toxin costs will be significant. Product titer is still a key element of COGs for recombinant proteins that require relatively large doses like mAbs.

A focus on product quality and process consistency should be the first consideration for process development groups, and would reinforce the use of established and well-characterized production technologies. The confidence in delivering product with an acceptable set of critical quality attributes that will meet the target product profile are likely maximized when conventional unit operations are employed. This type of focus is even more important for non-mAb recombinant proteins, where variation in product quality attributes is typically less well-understood or controlled.

Novel purification technologies may need to be uniquely enabling in order to make inroads into mAb processes. Modest cost reduction or perceptions of debottlenecking may have little practical value, and never recover the significant investment in development, scale-up and validation. The benefits may not sufficiently reward the acceptance of potential risks involved with being the first to adopt new technologies, and reliance on single source vendors who are also producing new separations media for the first time.

In considering adoption of new process technologies that would include royalty payments based on use for production of commercial products, the royalty costs could easily dominate the total COGs given the process economics described above (a 1% royalty on sales for the median mAb would be $80/gm, potentially more than the fully loaded drug substance COGs). Conventional technologies in the public domain are likely to remain the more attractive option, unless new technologies are uniquely enabling.

Production costs can be influenced by dual-sourcing strategies, where multiple vendors could be used to source raw materials such as chromatographic resins or membranes, and a competitive bidding process used to manage costs. The dual-sourcing approach is also amenable to a platform technology approach, where the product license application would include process characterization and validation data for processes using both separations media suppliers, and potentially develop a design space for both raw materials.

Post-licensure process improvements would still be used for products commanding a large commercial demand, to ensure supply for patients and reduce COGs where possible and appropriate. This strategy differs from a concerted effort to reduce COGs for all pipeline products by customizing each manufacturing process, which would entail significantly more investment for process development, could result in many non-platform processes, and would not be a profitable investment for non-blockbuster products. There is usually sufficient time during the build-up of a newly-launched product's demand peak levels to initially transfer production to a second plant, and then introduce an improved manufacturing process with higher titers, if needed.

Pressures to adopt a corporate (or even industrial) processing platform continue to mount.[20] Quality by Design will reward future processes that build on well-established processing technology, forming knowledge space that can be leveraged for reduced efforts on process characterization and validation for each new product candidate.[21] Adherence to a common industry processing flowsheet, as in **Figure 1**, will ensure that the process can be transferred to other manufacturing facilities with minimal cost, risk or delay could arise from use of novel technology; this approach has been used successfully for several approved mAbs and Fc-fusion products in the last decade. The recognition that current performance is 'good enough' to satisfy market demands and profitability can reduce the desires to take on undue risk or incurring significant new investments during the development phase. Alternate expression hosts, while still touted by some[22] would seem to hold little attraction, unless they enable unique product characteristics with clinical or patient advantage. The large database of product safety and quality established by production in CHO and other well-accepted cell lines would suggest the investment to establish production capabilities and even a platform for expression using transgenic animals or plants, microbial hosts or even human cell lines would not be cost-effective. Finally, the speed to clinic is maximized when using platform technologies, and if major process changes are adopted during subsequent development phases, these would require comparability assessments and potentially incur risks to matching product quality or meeting aggressive timelines.

The great majority of currently licensed mAbs use the platform process shown in **Figure 1**. Most products licensed over the next several years will also use these technologies, giving rise to a vast complex of commercial plants which are manufacturing a product using this common, industrialized platform. Multiproduct plant changeover is a key factor to consider, as new higher titer processes can be scheduled in the production plan gaps between the low-titer legacy mAb production slots, allowing several blockbusters to be supported by one plant. This would make it even more challenging for new technologies to make inroads, as they will be sharing a multiproduct facility with a legacy mAb process. This inertia may at first seem to be a constraint, but could also be viewed as an advantage for mAbs to enable portable, low cost production with minimal risk of scale-up or process transfer.

Conclusions and Recommendations

The field of bioprocess development for mAb production finds itself at a crossroads resulting from significant changes in multiple factors impinging on process design targets. The combination of excess production capacity and increasing cell culture titers enables simple strategies and platform processes to meet market demand for nearly all mAbs in the development pipeline, and enjoy sufficiently low production costs resulting in drug substance COGs not being a key process design driver. This could lead to a frameshift in process development strategies, and a slowing of the relentless march to develop processes with higher and higher titers. The new paradigm would suggest that if acceptable standards of productivity and COGs are met, then one should not make process design decisions based on perceptions of capacity limits, purification bottlenecks, or COGs pressures for anything but the most unusual situations (noting that clinical production drivers could be different).

In this case, the objectives of process development groups would shift from a focus on invention and innovation for new technologies to optimization and maturation of current production technology. The maturation phase should allow for continued refinement and improvements in manufacturing technology and COGs reductions, but will be more evolutionary than revolutionary. This may reflect a natural progression for process technologies driven by the introduction of new classes of products. In one theory of the link between product and process innovation, process innovation lags behind product innovation, but eventually peaks and declines as the product class becomes a well-established market.[23] The decreasing rate or need for process innovation could reflect maturing production technology, maximization of returns on the capital sunk into existing facilities, diminishing returns of new technology, and other factors.

This situation would allow companies to avoid risky process development designs that could have challenges in scale-up, technology transfer or reliance on a single raw material suppler. Novel production technology should be carefully evaluated, and implemented only if it is clearly enabling and concrete drivers are identified. Novelty for novelty's sake is no reason to stray from an acceptable processing platform that enables portability among the many facilities that share a common design basis, and offers attractive economies of scale. A focus on controlling product quality and process consistency at all production scales and facilities would trump minor improvements in titer improvements or COGs reduction.

Development objectives should shift to a focus on understanding the process fundamentals of the current platform. There are many areas of research relevant to bioprocess technologies associated with antibody expression and purification that should continue to drive investment in areas of cell biology, biochemical engineering, protein chemistry and stability. Even today's state-of-the-art processes offer ample opportunities to make cell line development even more predictable through control of certain critical quality attributes, such as stability and levels of mAb expression, minimization of sequence variants,[24] etc. For production cultures, modeling and manipulation of cellular metabolism to control accumulation of waste products such as lactate, understanding recent observations of disulfide bond reduction in high-titer mAb processes, and refining scale-down process models would all be valuable areas of research. Considering purification processes, the complexities of cell harvest and depth filtration should be studied, measurement of product binding isotherms and binding kinetics would enable chromatographic modeling of product and impurity separations, virus retaining filter fouling behavior should be better understood, and characterization and control of both soluble and insoluble product aggregates offer fertile grounds for investigation. For all unit operations in the current platform, these investments in fundamental understanding will expand the knowledge space for the manufacturing process, and enable the benefits of Quality by Design to be realized more quickly and broadly.

For companies with little or no installed commercial production capacity, commercialization strategies that would access the significant excess capacity currently available at CMOs and innovator companies by using conventional technologies could be a wise approach. This avoids any capital investment at all, while still providing a path to unlimited demand and acceptable costs. The implications for clinical production processes are that they should be developed to take advantage of the eventual commercial processing benefits enabled by using current platform technology, driving similar process definition for Phase III and even Phase I processes, to avoid issues of product comparability during the final process scale-up to large manufacturing facilities.

The mAb bioprocessing world is becoming flatter, meaning that access, understanding and implementation of the consensus technology should be assumed for those skilled in the art, and the majority of biopharmaceutical companies in all countries will have access to knowledge of common mAb drug substance production technology. While there may be financial incentive to foreign production in a tax-advantaged location, the low cost and high capacity enabled by use of existing facilities blunts the argument that this is driven by reduced labor costs, or that these foreign plants would benefit from new, more efficient production technologies. Note that a common process for global production would necessitate similar technologies in both domestic and foreign plants, further constraining the opportunities of using novel technologies to new plants built in foreign locations if they represent a very different processing philosophy.

Could our industry be at the cusp of defining a processing platform that has matured sufficiently to last several decades? Consider the plasma processing industry as an example of a current good manufacturing practice (cGMP) processing platform adopted by many manufacturers, which has stood largely unchanged since the 1960s. Few major changes were made to the basic manufacturing process until the introduction of chromatography in the 1980s and 1990s.

mAbs are becoming a unique class of therapeutic products. They are parenteral biologics with unlimited production capacity and low production costs, whose pricing will have no direct link to drug substance production. The pricing will instead reflect the innovator companies' clinical investment in addition to costs incurred from failed pipeline products. This represents an unusual combination of aspects of traditional recombinant protein therapeutics and small molecules, and our development and commercial production strategies will need to evolve in response to this shift.

These distinctive features of therapeutic mAbs produced by current platform processes should even be considered as key factors in drug discovery efforts, as non-mAb modalities or novel scaffolds may not all benefit from the advantages enjoyed by mAb production (e.g., much lower titers from Fc-fusions, or higher aggregate levels for non-native engineered proteins). The class of mAb products has many unique and valuable features derived from industrialized bioprocess technologies, which in themselves can become key factors in a unified and fully integrated drug development strategy.

Acknowledgements

The author wishes to thank Dana Andersen, Ann Lee, Brad Wolk, Rob van Reis, Robert Kiss, Greg Blank, Phil Lester, John Joly, Fabrice Beretta, David Chang, Bill Bennett, Chris Horan, Tim Moore and Markus Gemuend at Genentech. Additional thanks are due to Guenter Jagschies, Tom Ransohoff and Robert Steininger.

References

1. Becker H. Muronomab-CD3 (Orthoclone OKT3). In: Dubel S. Handbook of Therapeutic Antibodies Volume III: Approved Therapeutics. Weinheim, Wiley-VCH 2007; 905-40.
2. Birch JR, Onakunle Y. Biopharmaceutical Proteins: Opportunities and Challenges. In: Smales CM, James DC. Methods in Molecular Biology, vol. 308: Therapeutic Proteins: Methods and Protocols. Totowa, NJ: Humana Press Inc., 2005; 1-16.
3. Wurm FM. Production of recombinant protein therapeutics in cultivated mammalian cells. Nature 2004; 22:1393-8.
4. Fahrner RL, Knudsen HL, Basey CD, Galan W, Feuerhelm D, Vanderlaan M, et al. Industrial purification of pharmaceutical antibodies: development, operation and validation of chromatography processes. Biotechnol Genet Eng Rev 2001; 18:301-27.
5. Shukla AA, Hubbard B, Tressel T, Gunhan S, Low D. Downstream processing of monoclonal antibodies-application of platform approaches. J Chromatogr B 2007; 848:29-39.
6. Low D, O'Leary R, Pujar NS. Future of antibody purification. J Chromatogr B 2007; 848:48-63.
7. Trexler-Schmidt M, Sze-Khoo S, Cothran AR, Thai BQ, Sargis S, Lebreton B, et al. Purification strategies to process 5 g/L titers of monoclonal antibodies. BioPharm Intl Supplement March 2009; 8-15.
8. Ransohoff TC, Ecker DM, Levine HL, Miller J. Cell culture manufacturing capacity: trends and outlook through 2013. PharmSource 2008.
9. Kelley B. Very large scale monoclonal antibody purification: The case for conventional unit operations. Biotechnol Prog 2007; 23:995-1008.
10. Red Book. Thomson Reuters 2009.
11. DataMonitor. Monoclonal Antibodies: Update 2008. www.datamonitor.com
12. Chadd HE, Chamow SM. Therapeutic antibody expression technology. Curr Opin Biotechnol 2001; 12:188-94.
13. Werner RG. Economic aspects of commercial manufacture of biopharmaceuticals. J Biotechnol 2004; 113:171-82.
14. Jagschies G. Where is biopharmaceutical manufacturing heading?. BioPharm Intl Supplement 2008; 72-88.
15. Sinclair A. Design and optimization of manufacturing. In: Gottschalk U, ed. Process Scale Purification of Antibodies, Hoboken, NJ: J Wiley & Sons 2009; 263-91.
16. Farid SS. Process economics of industrial monoclonal antibody manufacture. J Chromatogr B 2007; 848:8-18.
17. Kamarck ME. Building biomanufacturing capacity-the chapter and verse. Nat Biotechnol 2006; 24:503-5.
18. DiMasi JA, Grabowski HG. The cost of biopharmaceutical R&D; is biotech different? Manag Decis Econ 2007; 28:469-79.
19. Barnoon BI, Bader R. Lifecycle cost analysis for single-use systems. BioPharm Intl Suppl 2008; 30-43.
20. Kelley B, Blank G, Lee A. Downstream processing of monoclonal antibodies: current practices and future opportunities. In: Gottschalk U, ed. Process Scale Purification of Antibodies, Hoboken, NJ: J Wiley & Sons 2009; 1-23.
21. Rathore AS, Winkle H. Quality by design for biopharmaceuticals. Nature 2006; 27:26-34.
22. Langer ES. New expression systems create opportunities for innovators, CMOs, and Product Developers. BioPharm Intl Suppl March 2009; 20-2.
23. Pisano GP. Development Factory: unlocking the potential of process innovation. Harvard Business School Press 1996.
24. Harris RJ, Murnane AA, Utter SL, Wagner KL, Cox ET, Polastri GD, et al. Assessing genetic heterogeneity in production cell lines: Detection by peptide mapping of a low level Tyr to Gln sequence variant in a recombinant antibody. Nat Biotechnol 1993; 11:1293-7.