Biomanufacturing capacity: Current and future requirements

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Abstract In recent years the perception has arisen that biopharmaceuticals manufacturing capacity has gone from excess to shortage. What is the cause of this change and why were the shortfalls not addressed in time? This paper looks at how the structure of the industry has influenced the current shortfall and analyses the current manufacturing sector capacity and product mix. Looking to the future, the paper discusses factors that will dictate capacity requirements over the next five to ten years.

Keywords: biopharmaceutical production, monoclonal antibodies, mammalian cell culture, manufacturing capacity

Introduction

In recent years, perceptions about the capacity to manufacture biopharmaceuticals have shifted from worries about excess capacity to fears of capacity shortage. This is exemplified by the situation with Immunex's Enbrel product.[1] Immunex has found itself in the situation where is unable to meet demand and is struggling to install new capacity; as a consequence it is forced to limit sales of its drug. How does this situation arise given that it takes in excess of 10 years to develop a new product,[2] in the latter stages of which there are strong indications relating to market and clinical promise? The complexities and uncertainties surrounding the launch of novel biological products are similar in many ways to those that surround the launch of conventional pharmaceuticals in terms of success rates, development times, etc.[2] So how has this apparent shortfall in capacity arisen and why don't we see a similar situation with new chemical entities (NCEs)?

Given the similarities in development of NCEs and biopharmaceuticals, the difference in capacity may have a lot to do with the origins of innovative new drug candidates. Historically, traditional pharmaceutical companies have developed NCEs within their own drug discovery groups. In the case of biopharmaceuticals, much of the innovation occurs outside the drug companies licensing new drugs from biotechnology. To date, the traditional pharmaceutical companies have accounted for the introduction of 70 per cent of the approved biopharmaceuticals, of which over 50 per cent originated externally.[2]

This paper considers the present structure of the manufacturing capacity for biopharmaceuticals. It assesses the implications of current arrangements and considers how they may change in the future. Cell culture capacity requirements are taken as a representative of the sector. It is assumed that much of this capacity growth is largely required for the manufacture of monoclonal antibodies.

Factors impacting on production capacity requirements

There have been many articles on the forthcoming actual and projected shortfall in capacity. These can be split in two main groups: those that focus on early phase clinical supply[3] and those that deal with shortage of large-scale capacity.[4] The issues that underlie these two areas are distinct.

Early phase clinical supply deals with both the development of a new product and linking this to the provision of clinical supplies. To support this type of function requires a development group with access to a small-scale production multi-product facility. For companies with limited product portfolios or those wholly focused on clinical supply, this function is often contracted out. There is a shortage of companies worldwide that can provide the necessary level of support. In this paper we focus on the second area: large-scale capacity.

If we look at large-scale capacity requirements, their analysis is usually presented in terms of the projected growth in product approvals and forecasting is based on contract manufacturing organisations' (CMOs) future capacity. This form of analysis presupposes first a direct relationship between product approvals and capacity requirements and second that CMOs are significant providers of capacity to the market. Whereas the first assumption is easily tested by reference to clinical trial databases, lack of published data makes the second more difficult to assess.

The definition of capacity and what influences it is complex. A few major factors that impact on capacity are:

- dosage levels varying significantly depending on product type;
- technologies used for expression;
- technologies used to manufacture;
- market projections differing for each of the main therapeutic indications.

Dosage

Dosage regimes will vary depending upon the type of product, varying from very low relative dosages for DNA vaccines (micrograms per dose) and hormone products (human growth hormone used for dwarfism is given as a one daily dose equal to 0.17 mg/kg body weight) to monoclonal antibody products whose dosage regime are several orders of magnitude higher (Rituxan® used for relapsed or refractory, low grade or follicular, B-cell non-Hodgkin's lymphoma is given an infusion 375 mg/m^2 for a total of up to eight infusions for a treatment regime). This means that for some of the DNA vaccine products the capacity required to meet demand is tens of litres whereas for a monoclonal this could amount to 10,000s of litres.

Expression

Differing dosage regimes, when coupled with the expression system, significantly impact on capacity requirements. The *Escherichia coli* organism can express the desired product to a level of about 3 g/l compared with a mammalian cell line which can express up to 1 g/l of product. Of more significance regarding productivity is that *E. coli* fermentation is usually complete within 36 hours compared with fermentation times of over 200 to 300 hours for a mammalian cell line.

Manufacturing technology

Even when considering mammalian systems, the manufacturing approach adopted has implications on cell culture capacity requirements. A good example is products made using perfusion systems where a 500 l vessel (running at 2 volumes of media exchange per day for 300 days per year) has an equivalent productivity to that of 15,000 l vessel operated in fed batch mode (processing 20 batches per year). As transgenics technologies develop, this will also impact on capacity estimations based on cell culture capacity expressed in litres.

When discussing capacity, reference is often made to the capacity in terms of installed litres of cell culture vessels or square feet of production space. Including

factors such as expression system and manufacturing technology gives rise to differing levels of manufacturing intensity (expressed as revenue per square foot). This situation will get more complex when considering transgenic-based production systems and the associated farms.

For example, compare the production capacity required to supply product for 100 patients in one year:

- For an *E. coli* derived human growth hormone type product administered at 6 mg per day per patient, the fermentation capacity required to supply the 100 patients for a year is about 1 l;
- for a mammalian type therapy where the treatment dosage is around 12 g of a monoclonal antibody, cell culture capacity required to treat 100 patients in one year is around 200 l (as a fed batch operation).

This is simplistic in that it does not take account of relative patient population sizes for the indications. But it does illustrate the point that microbial-based fermentation requirements (and associated floor areas) to meet market demands are a lot less when compared with a typical monoclonal-based product.

Defining capacity

How should we define capacity? In many articles the growth rate of capacity requirements is assumed to be equivalent to the number of product approvals and this leads to annual growth estimates of around 20 per cent per annum.[2] However, for mammalian-derived products, a better measure is the growth of cell culture media consumption. In a recent article, it was reported that the cell culture media supply companies can expect an annual growth rate of 13 per cent,[5] and that prior to January 2001 there has not been a blockbuster drug approved in the previous 18 months. When assessing capacity needs the factors listed below should be used.

- Identify capacity for which segment: clinical supply or in-market supply.
- Understand the product mix in the clinical pipeline and use it to predict capacity demands based on probable success and manufacturing technologies.
- Review the number of products in the clinic competing for the same therapeutic indication and adjust the capacity predictions accordingly.
- Distinguish between requirements for downstream facilities and upstream requirements. Upstream requirements for the larger capacities will be impacted when transgenic technologies develop.

Current capacity: Where does it reside?

For their assessment of market capacity, BioPharm Services has analysed 43 out of a total of 77 products approved at the beginning of 2000.[2] The 43 products equate to around 82 manufacturing operations, which represents around 60 per cent of the world's total operating facilities. Of the 43 products examined, 24 were produced from mammalian cell culture. From the estimate of the market size, an estimate of the amount of cell culture media was made. Based on an average expression level from this exercise, it was estimated that about 17 million litres of cell culture media was required. Having said that the analysis only covered 60 per cent of the market, this estimate for annual requirement was adjusted to 29 million litres. It is possible to cross-check our capacity estimate with an independent analysis of the cell culture media market.[5] This analysis quoted the total sales for cell culture media to be around US$83.8m. Taking an average bulk cell culture media price of around US$4/l, the estimate of media sales is around 21 million litres. This is a reasonable correlation, given the assumptions made and that the product analysis included non-US or European companies who may use suppliers not covered in the survey. Out of this analysis arise two interesting observations.

Firstly, the current estimate of worldwide cell culture capacity is about 350,000 l.[6] It is estimated that for a fed batch operation you

can process 20 batches per year, so media consumption would be 7 million litres. It is fair to conclude that there is either hidden capacity or that a proportion of that capacity is perfusion cell culture. If around 7 per cent (24, 500 l) was dedicated to perfusion then this would account for the actual media sales.

Secondly, based on media sales, contract manufacturers supply only a small part of the market manufacturing capacity requirements. Media sales to contractors amounted to US$8.3m or around 10 per cent of the market, equating to around 2.1 million litres of media which, based upon fed batch cell culture, amounts to about 110,000 l of capacity. Our estimate of the contract manufacturers' capacity is around 120,000 l. It is therefore probable that none is running perfusion-based cell culture. Note that where cell culture media are bought on behalf of the contractor, this will not be accounted for. There is one known exception, Lonza, which is running perfusion-based cell culture for a client; in this instance the client is purchasing the cell culture media.

Future capacity needs: Current pipeline

There are currently at least 77 biologically based biopharmaceuticals marketed worldwide by over 50 individual companies. This represents an almost three-fold increase since 1996 and a total market of over US$16bn in 1999.[7] The majority of these biopharmaceuticals are expressed in either mammalian cell (59 per cent) or microbial (33 per cent) systems, with other systems accounting for the balance (8 per cent) . This suggests that the dominant expression system to date has been mammalian cell manufacturing. This 'preference' for mammalian cell manufacturing, however, has not always been the case. Many of the earlier therapies used microbial systems, while most of the recent entrants use mammalian cell manufacturing. This is a trend that is likely to continue as more monoclonal antibody success stories reach the market over the next few years. Biopharmaceuticals is a rapidly growing sector of the pharmaceuticals market and makes up over 11 per cent of the products in development.[2] There are approximately 600[8] biopharmaceuticals in clinical development, of which over a hundred are in pivotal Phase III trials. Based on Figure 1, we see the number of products in Phase II or II–III clinical trials is actually only slightly less than those in Phase I trials. Also, we see that the number of Phase III trials is only about half of the Phase II or II–III trials. If we look at some historical rules of thumb, we might expect 30 per cent of Phase II drugs make it to Phase III.[9] As such, Figure 1 suggests that the number of new product introductions will be very high over the next few years, then decrease slightly as the current Phase I and Phase II therapies come through the system.

Looking at the breakdown of technologies represented by the drugs in clinical trials for biopharmaceuticals (Figure 2), the top two categories are monoclonals and recombinants (excluding synthetics). The next largest category is vaccines, which is approximately one-third the size of either recombinants or monoclonals. Given that monoclonals are almost exclusively expressed in mammalian cells, and vaccines are traditionally expressed in microbial cells, this trend supports our earlier analysis

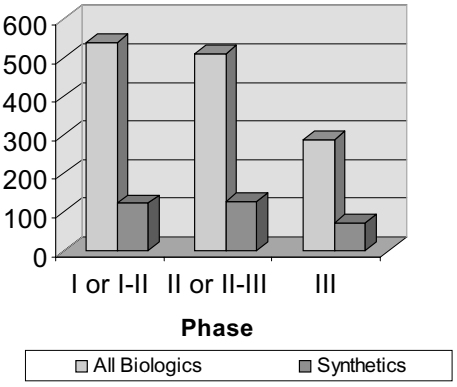

Fig. 1 Clinical trials breakdown by phase

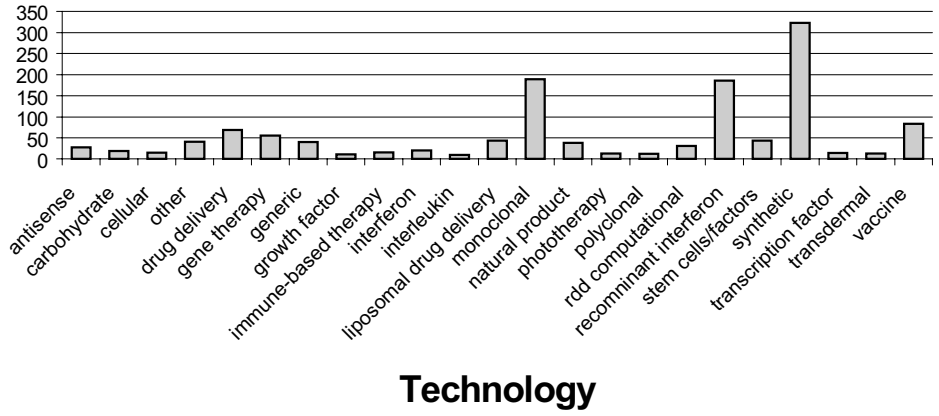

Fig. 2 Clinical trials by type (RDD = Rational Drug Design)

identifying mammalian cell as the more dominant system of choice. Based on the plethora of late stage clinical trials for biotherapeutics and the size and nature of their indications, it is highly likely that the market for biotherapeutics will exceed the projected US$20bn in sales within the next few years, with mammalian and microbial cell lines as the main technologies used for expressing these products.

Whereas an examination of ongoing clinical trials reveals the near future of biotechnology, an analysis of biopharmaceutical products in the preclinical Phase provides insight into the next decade of biotechnology. The time taken for a biopharmaceutical to go from the bench to market is steadily increasing. In the 1980s the duration was about 6 years. This has increased to around 9.8 years (1997–1999) and is now similar to the time taken for new chemical entities (10.1 years).[2] More importantly, manufacturers of products in clinical testing generally already have identified how they plan to manufacture their product in the large quantities needed. In contrast, developers of products (small biotechnology companies) still in preclinical testing are less likely to have the necessary facilities for mass production.

Of the biopharmaceutical products whose developers have announced ongoing preclinical studies, the most common technologies used are synthetics, monoclonals, recombinants and vaccines (Figure 2). A comparison of preclinical products in the biopharmaceuticals category finds that recombinants, monoclonals and vaccines constitute 44, 34 and 11 per cent respectively of this category.

In conclusion, we are currently seeing monoclonal antibodies dominate the biopharmaceuticals in development. We would expect to see the growth in capacity requirements as this is largely driven by monoclonal manufacturing requirements. But based on the preclinical portfolio, we would expect to see a proportional decline in monoclonal manufacturing capacity requirements in a 5–10 year time frame. This decline will be further accentuated (where capacity is defined as cell culture capacity) if transgenics is successful.

Future capacity issues

The questions regarding mammalian cell culture capacity are:

- Is there enough capacity in the market?
- What will the situation be in five years' time?

From the analysis of the current situation we can conclude that, as measured by installed capacity, the in-house manufacturers dominate with about 64 per

cent (Table 1) but that, as measured by activity (volume of media purchased), the in-house manufacturers actually produce 90 per cent of the products. The discrepancy is probably accounted for by significant use of perfusion systems by some companies (Centocor). If we base our future capacity requirements on the growth of media sales where growth of around 13 per cent is expected in sales to in-house manufacturers and 20 per cent increase in sales to contractors, then the capacity requirements are for 400,000 l this year, increasing to 720,000 l in 2005.

In reality, who is going to provide the future capacity? Reviewing the capacity plans shown in Table 1, one would conclude that in fact the major growth will come from the contractor sector. However, it would be incorrect to conclude that contractors are much more ready than manufacturers to share the future capacity expansion plans. Many of the manufacturers listed are investing significantly more; for example, in Ireland Wyeth Ayerst is investing up to US$1bn in manufacturing and research and Genemedix US$6m. Biogen has announced an investment in Denmark. In the USA Immunex's facility in Rhode Island will add significant capacity as will Genetech (Table 1). So the prediction is that much of the future capacity needs will be met by manufacturers.

Why can't contractors provide this requirement? Simply put, the cost of building capacity for market supply is expensive. Contractors do not have the financial resources to build a new facility without having that investment underwritten by the customer. From the pharmaceutical companies' perspective, in theory some would like to contract out development and manufacture but the need to underpin capacity with specific contracts, together with the added complexities and inflexibilities of dealing with a third party make this unattractive. The preferred strategy (Genetech, Wyeth Ayerst, Millenium, Biogen, Pfizer, Genzyme, etc.)

Table 1 Current and future mammalian cell culture capacity

Capacity (l)	Current	Planned	Total
Manufacturers			
Abgenix		?	0
Biogen	2,000	?	2,000
Centocor	10,000	?	10,000
Genetech	200,000	400,000	600,000
Genzyme	2,000	?	2,000
GI Bayer	2,000	?	2,000
Immunex	10,000	?	10,000
Medimmune	10,000	?	10,000
Millenium	12,000	?	12,000
Roche	1,000	?	1,000
Wyeth Ayerst		?	0
Subtotal	249,000	400,000	649,000
Contractors			
BASF	3,000	10,000	13,000
Boehringer Ingelheim	72,000	72,000	144,000
Akzo	1,500	?	1,500
DSM	3,925	24,000	27,925
Lonza	17,400	56,200	73,600
GlaxoSmithKline	20,000	0	20,000
Other	8,900	?	8,900
Subtotal	126,725	162,200	288,925
Total	**375,725**	**562,200**	**937,925**

? Indicates that a company is expanding capacity but the amount is not known.
Compiled from company reports, press releases and presentations.

would appear to be build large multi-product manufacturing plants that can be used to service portfolio products coming through the clinical pipeline. That way companies are able to ensure adequate capacity without necessarily committing to individual product successes.

This approach works well for the larger companies but what about the smaller players? Most small biotechnology companies are focused on discovery and their business model is to develop a biopharmaceutical to the point where they can license it out to a major player. Their concerns centre on the availability of contractors who can carry out product development and manufacture clinical supplies. Far fewer of the biotechnology companies want to develop their product portfolio and become in-house manufacturers of their own products. Where these companies do want to go down this route, contract manufacturing is an attractive option: we have seen companies such as Abgenix and Immunex use contract manufacturing as an interim measure while developing their own internal capability.

Conclusions

Trying to predict capacity requirements is not simple. On the one hand, you have the contract manufacturing sector strongly promoting the need for additional capacity, while on the other, big pharmaceutical and biotechnology companies are planning and building that capacity based on their product portfolios. There is no doubt that Immunex's experience has caused the industry to assess its manufacturing needs and, in fact, large companies are currently implementing their strategies through their large investments in new facilities.

There is a need to be realistic in the assessment of future capacity needs and a detailed assessment based on media sales linked to capacity, clinical supply, competing clinical candidates and manufacturing technology is required for any such assessment. Otherwise it is very easy to come up with a doomsday scenario that predicts a crisis for the industry. There is no doubt that in the case of monoclonals that we are seeing a significant growth in product approvals but there are a number of factors that will limit capacity requirements:

- Although growth figures of 20 per cent per annum have been used historically, these are based on approvals, not actual capacity requirements.
- The number of monoclonals coming through the clinic could peak over the next five years.
- A number of the monoclonals in development are competing for the same therapeutic indication. This has to be taken into account when assessing future capacity needs.
- There are competing technologies that could have a major impact on cell culture fermentation capacity requirements, transgenics, monoclonal antibody fragments (produced in microbial systems), etc.
- Development times for biopharmaceuticals are lengthening.

It is clear that the majority of current manufacturing requirement will be provided for in-house and that over the next five years contract manufacturers will have a minor role when it comes provision of capacity for in market supply. It also seems clear that major players are making provision for future capacity needs and that it is those biotechnology companies that want develop their own in-house capability that are at greatest risk of insufficient capacity.

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