

Delivering Affordable Biologics from Gene to Vial

Economic Challenges for Manufacturing Biologics in the New Millennium

by Andrew Sinclair and Miriam Monge

In launching this new series of articles under the theme of delivering affordable biologics, from gene to vial, we intend to examine some of the challenges the bioprocess industry faces. We will discuss the implications of key cost challenges facing the industry, develop an understanding of the economics underlying development and manufacturing, and explore options for driving out cost. We wish to encourage dialogue and debate, so in addition to the articles we will also use webcast interviews and conference sessions to define and shape this discussion.

What are these challenges? Is bioindustry really that different from other innovative industries, or should we be taking note of what happened in, for example, electronics? The biopharmaceutical industry, which is a segment of the pharmaceutical industry, has tended to regard itself as different from other industry sectors because of its complex products, long development times, and close link to human health. The past three decades have seen rapid growth in biological medicines based on recombinant DNA technology (1).

The vaccine industry, by contrast, was established in the 19th century. It was in the doldrums by the late 20th century, but in recent years it has become a driver for growth in the



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biopharm sector. There are lessons to be gained from the vaccine industry's drive to extend access to its products to the majority of the world population (2): That access has been extended by driving down costs (3). Many issues the biopharm sector faces appear to be the consequence of a maturing industry with structural impediments to its development brought about by regulation, political restrictions, and market structure.

Back to the question of whether this industry is special. As far back as 1992, the answer was probably "No" from the business perspective, at least for the pharmaceutical industry.

According to a study that year of the whole drug sector: "One of the industry's biggest problems lies not with inventing and marketing pills, but with making them," and "During the past decade their manufacturing costs have crept up to reach one-fifth of sales, double what they used to be a decade ago and more than the 15% of sales they spend on average on R&D" (4). As for biopharmaceuticals, in 1992 the industry was only just developing. Up to around 2000, the conventional wisdom was that manufacturing costs were unimportant: It was all about products and the underlying science. However, that perception was untrue for the major successful rDNA blockbuster products that were replacement proteins. They were manufactured at very large scale (tons), and manufacturing cost for them was indeed at issue.

IDENTIFYING CHALLENGES

In 1992 from an external perspective traditional pharmaceuticals were seen to have a problem in regard to both research/development and manufacturing costs. We know now that biopharmaceuticals are more capital intensive than pharmaceuticals and have relatively high operating costs (5). So why were manufacturing costs not considered to be an issue for bioprocessing? Our thesis is that manufacturing costs are increasingly

recognized as being important, indeed. This is becoming manifest in the industry and is linked to successes with monoclonal antibody (MAB) products. The situation is complicated by other structural issues relating to stagnating productivity in R&D that is increasing R&D costs (6). Our view is that process development and manufacturing are inextricably linked and must be considered as a whole. First let's consider several challenges facing the industry.

High Treatment Costs: New drugs are seen by the public and regulators to be excessively expensive. In one example, the Avastin colorectal cancer treatment is quoted at \$50,000 per treatment, with higher prices being cited for other products (7). Such costs are effectively limiting access to new drugs in many countries, whether on the basis of a patient's ability to pay or through a managed healthcare system. This situation has led to heated discussions among patients, healthcare providers, legislators, the industry, and the public at large. Many are concerned that the industry is perceived to be making excessive profits from novel treatments (8, 9), which contributes to its low esteem among patients and regulators. One way the biopharmaceutical industry can effectively tackle this negative perception is by more effective public communication and transparency around costs.

Cost/Benefit Assessments: Whether justified or not, those relatively high prices are negatively affecting the industry with cost regulators now assessing the cost benefit of new medicines. A formal methodology was developed by the United Kingdom's National Institute of Clinical Excellence (NICE) in 2000 and is being assessed and implemented by a number of other countries including the United States (10). At the same time many people are calling for more regulation and transparency in the relationships between the industry and its stakeholders, a theme we will return to in future installments of this series.

Greater Competition Between Companies: As the biotherapeutics industry develops, more players compete

Table 1: Where the money goes

	Typical*	Biogen Idec**
CoG	14%	10%
R&D	21%	26%
SG&A	19%	34%
Interest		1%
Profit sharing	9%	
Gross profit	37%	28%
Total sales	100%	100%

* Source: Reference 12 ** Source: Reference 13

for similar therapeutic areas. More competition between the major players results in multiple drugs at varying stages of development competing for the same disease targets (11).

Biosimilar Competition: Much of the debate over the cost of new drugs is being driven by spiraling healthcare costs overall, which — coupled with high drug prices — has led to a demand for mechanisms by which biosimilars (follow-on biologics) can be approved for market to reduce drug costs and increase the availability of better quality healthcare to more people. The arguments for and against are complex, but the European Union has a mechanism for biosimilar approval, with a number of biosimilars marketed to date (somatropin, epoetin alfa, and epoetin zeta, to name a few). Once the period of exclusivity comes to an end for innovators, strong price competition will come from companies supplying biosimilars.

So what does all this mean for the biotherapeutics industry? Many of the challenges we see are driven by spiraling healthcare costs that are leading to stronger calls for price regulation, increasing competition, and cost transparency. The difficult balance is doing that without stifling the innovation that brings about novel treatments in the first place.

WHAT ARE THE REAL COSTS?

Our view is that with its history of innovation the biopharm industry should be looking at significantly reducing costs in the range of 50–90% to widen patient access for high-cost MAB treatments. So here's the real question: What are the costs of developing and making a biopharmaceutical product? We've had an active interest in biopharmaceutical

development and manufacturing costs for a couple decades. Through our independent biopharmaceutical process modeling experience at Biopharm Services, we can state that the true cost structures are unclear. But there are a number of established preconceptions in relation to costs, namely that biologics are expensive to develop and manufacture and that manufacturing costs are not an important factor in their sales price.

Companies don't make freely available a breakdown of costs making up their drug prices. So there is much speculation relating to price breakdown and the role manufacturing costs play. We can glean some information from public-domain sources, and we quote two here in Table 1 for an illustration of the difficulties. The GE information is a secondary source (12), so we can't fully assess the basis of the numbers presented. The Biogen Idec numbers are taken from the company's income statement (13), and composite costs are skewed toward R&D because it has a significant number of products in development (18) compared with the number of approved products (3).

Comparing net profit margins of the top 10 companies in different industry sectors, the average net profit is 8% for aerospace, 5.2% for computer systems, and 32.2% for pharmaceuticals (14). So it would seem that the pharmaceutical sector has relatively high profit margins. Ideally, we would like to see the development and manufacturing costs associated with a particular product to gain a better insight into the product lifecycle costs. However, those numbers do illustrate the relevance of manufacturing costs. As the industry matures, we would expect to see the selling, general, and administrative (SG&A) costs reduce and the cost-of-goods (CoG) ratio increase in proportion to the R&D costs, especially as profit margins are expected to reduce when competition from biosimilars and other pharmaceutical companies increases.

Similarly, it's difficult to gain much insight into development costs. The oft-quoted Tufts figure of \$1.2 billion

dollars to develop a new biological drug is based on a 30.2% success rate and capitalizing the spend using a relatively high discount rate for today (15). This represents expenditure for an individual candidate of \geq \$360 million. The cost of bringing a biosimilar to market is estimated to be in the range of \$100–\$200 million (16).

It is difficult to know whether those numbers are directly comparable. The Tufts number is an estimate that capitalizes the costs of a development program's lifetime, whereas the biosimilar number will include most development activities except for preclinical development. Breaking down those numbers into specific activities is not simple; even Tufts does not appear to have access to that level of detail, which makes cost evaluation of clinical trials versus process development quite tricky.

Do manufacturing costs matter? If we recognize that the debate is not about just manufacturing costs, but also R&D costs and general overheads, then they certainly do. For example, take the GE numbers and restate them as the baseline case in Table 2. In scenario 1, increasing the R&D success rate to 50% would significantly reduce R&D expenditure. The same effect could be achieved by reducing discount rates and development times. In Scenario 2, we restate the SG&A so that is maintained at 19% of sales.

In this simple first-level analysis, the importance becomes apparent of reducing R&D and other cost categories in concert with manufacturing cost reductions to keep manufacturing costs from quickly dominating product pricing.

DETAILS ARE COMING

To have a meaningful debate about costs, we need greater transparency of cost structures, terminologies, and methodologies. Otherwise there is a risk that discussions, opinions, and entrenched positions and lead to accusations based on self interest. Transparency in this sense is required internally within each company to enable objective targets and effective communication among management,

Table 2: Product price cost breakdown

	Baseline	Scenario 1*	Scenario 2**
COGS	26%	31%	37%
R&D	39%	28%	34%
SG&A	35%	42%	29%
Subtotal	100%	100%	100%

* 50% R&D success

** with reduced SG&A

development, finance, and manufacturing to support cost-reduction initiatives.

As we have shown, there is much discussion over product costs and reimbursement. Clearly there is also pressure to reduce costs through more competition and the efforts of healthcare providers. This is a highly contentious area, but there is unquestionably a need for the industry to focus on reducing costs of new biologics and enable wider access both in the Western world and in developing nations.

In the past, manufacturing and development costs have been considered insignificant, but times are changing quickly, and the contribution and relative importance of both will increase as companies get their R&D costs under control. So the ability to manage biopharmaceutical development and manufacturing costs effectively will become part of a biopharmaceutical company's core competence. To deliver cost-effective medicines, the industry must recognize that development and manufacture of biotherapeutics is inextricably linked and that addressing both is important for success in driving out cost.

This leads us back to the theme of our series: delivery of affordable medicines, from gene to vial. Now we need to explore the detail that underlies issues we have outlined here through the use of case studies in the following areas:

- Learning how to measure manufacturing costs and structure decision making
- Making sustainable manufacturing = profitable manufacturing
- Determining the influence of process development decisions on manufacturing costs

- Exploring the influence of expression system choices on cost reduction
- Clarifying the economic implications of biosimilars
- Defining the role of new technologies such as simulated moving bed (SMB) chromatography, disposables, and novel unit operations.

This will help us collectively develop a dialogue on these issues and identify what is really important, what are best practices, and what is realistic and practical in terms of cost reductions.

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