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Beyond the Stainless Steel — The Real Capacity Crunch...

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How do we ensure that the next generation of biotech medicines can be brought to market in a timely way, that they continue to be safe and effective, and — of growing importance — are affordable by healthcare funding agencies, and profitable to the companies developing them?

In recent years, headline messages from the manufacturing community in response to these questions have focused on capacity — measured by investment in litres of manufacturing volume. However, I contend that the issues those of us involved in biomanufacturing should be most concerned about are not related to "investment in stainless steel," even though this does strongly influence perceptions of our industry's real state of health. This is not the prime area we need to address — talent and innovation deficits are of greater long-term significance and present what I believe is our real challenge.

Despite many worries in an industry notoriously prone to mood swings, optimism for 2004 onwards has been rising. Biotech sales are climbing, approval numbers are up after a couple of flat years, the clinical trials and development pipelines are looking strong, and R&D spending and employment opportunities are also accelerating sharply. But will these positive indicators result in more biotech medicines coming to market and being successful?

The Good News...

First, there is quite a lot of good news. In 2003, FDA approved 25 new biotech drugs — a 25% improvement on 2002, when industry confidence was knocked back by failure in Phase II and Phase III trials of more than 30 new biopharmaceuticals. There are currently at least 370 biopharmaceuticals in clinical trials and a further 600 in preclinical development. Even with a modest "survival rate" through trials, these numbers suggest that there could be upwards of 50 new biopharmaceuticals on the market by the end of the decade, joining the 60 or so already with licensed status.

2003 was a far better year for biotech drugs than for traditional new chemical entities. Significantly, 50 percent of the first-in-class new products approved in 2003 were biologicals — although the grand total of eight does perhaps reinforce the need for greater innovation in the industry at large! Impressively, in 2003 the biotechnology industry managed to raise over $16 billion in financing, which is more than a 50% improvement on 2002 and one of the best years ever in biotechnology.

Biopharmaceutical sales have the potential to double within the next three years, as the healthcare industry deploys biotechnology to tackle opportunities across at least 200 diseases, creating better lives and meeting demand from senior populations with increased life expectancies.

From the perspective of ensuring the capability is in place to underpin the growth of new products, more good news is that in 2002–2003 we have seen massive investment by the pharmaceutical, biotechnology, and contract services sectors in manufacturing assets. The majority of this has been aimed at supporting, or exploiting, the industry's new-found confidence in monoclonal antibodies. And while some investment plans have certainly been slowed or put on longer hold, the best current view is that manufacturing capacity is now well aligned with need. We are therefore less likely to see a repeat of the well-publicized capacity deficit that held back the growth in sales of Enbrel in its early post-launch phase.

Of course, manufacturing capacity is bound to reflect market dynamics: following the cycle of investment in times of shortage, and retrenchment when in excess. This is a good reason why many companies are recognising the benefits to be derived from outsourcing.

The widely respected U.S. industry research consultancy HighTech Business Decisions expects 20% annual growth in the biologics contract manufacturing sector, taking the $1.4 billion contract production spending of 2003 to somewhere north of $2.5 billion within three years. In fact, the outsourcing of overall biopharmaceuticals production — including clinical trials and licensed product commercial manufacturing — is expected to pass the 50% mark by 2008.

Clouds on the Horizon...

But even with rising demand and capacity expected to remain pretty much in-phase, at least for the next few years, some production-related cost issues are beginning to cloud the horizon.

Biotech investors are waking up to the fact that the complexity of new drugs is driving higher development costs, lon-

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ger times-to-market, and greater regulatory concerns. Much of the talk in 2003, as described in the *Scrip* 2003 Annual Review, has been "price, price, price, and the concern about whether new products coming down the R&D pipeline will be worth marketing."

While I hesitate to suggest that manufacturing is the dominant factor behind the pricing of new healthcare products, there is little doubt that it is a growing issue and has the potential to constrain the commercial exploitation of the next generation of gene-derived medicines. Without any doubt, manufacturing is under pressure to get smarter and this means process development has to be more innovative — *process invention* and *creation* need to become key words.

And cost isn't just an issue for biotech and pharma stakeholders. Out in the real world, "patient affordability" is also a growing theme. Aging populations are adding to the cost pressures on already hard-pressed healthcare budget holders, companies, and insurers. Their patients want to see taxes and other funds used for "affordable" new drugs and treatments, with less perceived contribution to drug company profits.

So, among all these positive opportunities and significant marketplace challenges, how should those of us engaged in the biomanufacturing sector react?

Lessons Learned?

Before considering this question it is worth reflecting on some of the issues we in Avecia have faced in establishing a new expanded biologics manufacturing facility in the UK, which came online late in 2003, creating nearly 200 new jobs. While securing funding was, of course, its expected challenge, of more concern have been the problems of identifying and recruiting talented people. This applies not just to running the facility within operations and quality functions, but also to providing the process and analytical development skills needed to underpin processes entering the facility.

This is an issue I have discussed with both competitors and customers alike in Europe and North America and it is quite clear that this is not just a UK phenomenon — it is a factor that impacts all. Critically, it is not a challenge that can be solved by short-term investment. The solution demands long-term strategic planning and investment by companies, regions, and nations.

Changing Needs...

It is also worth crystal ball gazing as to what gene-based discovery programmes will identify as our next generation of biotech medicines. It is very easy to react to the current boom in antibodies and assume tomorrow's products will have similar demands. In fact, outside of monoclonal antibodies, many new biologics seem to be best suited to multiproduct facilities where typical manufacturing campaigns are of a few months' duration.

I suggest that in the next 20 years we will see the increased personalisation of treatments — a forecast that many industry commentators are making. This surely must be an ultimate outcome of our improving genetic knowledge. But what does this mean for manufacturers?

Quite possibly, we will see lower volumes of specific molecules (removing the benefits of scale) and far more flexibility of molecular type, which will require fast process changes and facility modifications. Almost certainly, future products will be more complex than those of today — and of course, the customers' ultimate demand for better, safer, and cheaper medicines will become ever more focused. Increasingly, therefore, addressing the unmet needs across that range of 200 disease candidates will be about smaller volumes that equate to greater product customisation, with markedly reduced dependence on conventional large-scale manufacturing efficiency.

This has implications in terms of the potential impact for outsourcing of the forecast rise in "biogenerics." In time, will biopharmaceuticals be subject to the same degree of essentially price-led market share erosion as their small molecule cousins?

We can certainly expect older established biologics to reflect more diverse sourcing in the future, thus expanding the geographical breadth of today's biomanufacturing base.

Yet labor costs are a minor element of the total production costs of biologics. The growing trend towards more personalised products is such that the close proximity and true integration of the invent/develop/make functions is becoming ever more important. This seems likely to be a key influence on the rate at which biomanufacturing spreads into lower-cost economies.

To meet changing patterns in demand, the rate of innovation in our manufacturing sector must keep pace with innovation in discovery — indeed, without such synchronization, new product inventions run the grave risk of remaining forever within the laboratory. The solution comes down to people, which brings us to the crunch: our biomanufacturing industry is short of "next generation" scientists and the problem (on both sides of the North Atlantic) is gradually getting worse.

But has this issue been fully recognized by our industry investors and stakeholders?

The Human Resources Issue

Studies by the UK's BioIndustry Association (BIA, the equivalent of BIO in the United States) and the UK Government have shown that, as biopharmaceuticals become more complex, so the importance of bioprocessing will inevitably increase. "Product" and "process" are becoming ever more closely linked. But to meet the challenge, bioprocessing has to attract more talent from a range of disciplines and increase the level of invention and innovation.

Getting the best from all that capital-intensive stainless steel demands the integration of leading-edge process technology, analytical science, and regulatory compliance. It equally calls for a specifically trained workforce and management team, committed to deliver and "incentivised" to stay with our industry.

But look beyond today's generation of key science staff and their corporate managers: the crucial reservoir of

future talent is a long way from full. In an otherwise fairly positive mid-year update on biotech, issued in November 2003, Ernst & Young noted, "A major barrier impacting manufacturing going forward is lack of trained, experienced technicians, production, and scientific staff."

Our big challenge is, therefore, to find ways to show that biomanufacturing is an exciting, rewarding, and important place to be. Perhaps inevitably, "inventing" new drugs sounds a lot more exciting and contributory than just "manufacturing" medicines and vaccines.

In part, career interest and inclinations may depend on location and perceptions of an industry where distinctions between "biotech" and "pharma" are not always clearly defined. In the UK for example, biotech still has an insecure image in the financial context, while in pharma there has been a gradual weakening in the traditional manufacturing base, with all the uncertainties associated with sector consolidation and "restructuring."

On both sides of the Atlantic, developing, attracting, and maintaining high quality scientific and managerial talent is certainly getting tougher; and it's not just that we're competing for essentially the same talent as other science-based industries. The pool of talent is also showing a year-on-year decline in real terms.

At first glance, the headline numbers don't seem especially threatening. The UK National Office of Statistics confirms that in 2003, UK universities awarded 114,000 first science degrees, alongside 159,000 in non-science subjects. But take a closer look, because student interest in chemistry (and in the wider science and engineering disciplines) is falling quite rapidly. From 1994 to 2001, place acceptances for first-degree chemistry programmes fell by 27%. In the same period, acceptances for business management rose by 55%, computer science by 98%, and media studies by 138%. The key take-home message here could be that tomorrow's graduates would prefer media careers in company analysis, information technology (IT) programme development, or corporate management rather than contributing in a cutting-edge production laboratory.

In the UK, there have been notable efforts to promote the cause of biomanufacturing, chiefly driven by the biochemical engineering community for which I must pay tribute to the sterling work of University College London.

But many of the issues faced by the industry going forward require solutions that lie at the heart of genetic and protein science, and where are the centres seeking application in these fields? The lack of recognition and awareness sits not just with the future student population, but with their teachers and mentors.

Action Imperatives

There are no simple and fast answers to this global challenge, but if biomanufacturing is to attract, reward, and sustain the science and engineering talent it needs, then the equal importance and value of manufacturing innovation to discovery innovation must be more widely broadcast and understood.

But this can only be a first step. There is a clear need for more "centres of excellence" to serve the biomanufacturing and processing sectors at national levels — and to thereby foster and enhance the total talent available to the industry as a whole. Centres focusing on innovative bioprocess research and training are fundamental to ensuring that industry can both draw new technologies, and access the talented individuals needed to implement commercial solutions to these future challenges.

Effective action is imperative if our changing industry is to fully deliver on the expectations of its various key stakeholders — be they customers, investors, or, above all, patients. And for those seeking a career in which they can "make a difference," then a role in delivering safe, effective, and affordable medicines to the maximum number of people in need, sounds to me like a pretty competitive bid and a very worthwhile objective.

Summary

We should not underestimate the good news: biopharmaceutical production demand is certainly heading north over the next few years, and a long-term place for outsource contract manufacturing seems assured.

Increasingly, though, we need innovation as much in manufacturing as in drug creation. Treatment to span a widening range of diseases means more — and more complex — drugs, but in limited volumes. So upstream process development and downstream manufacturing simply have to get smarter, to meet the challenges not only in complexity but also in ultimate drug affordability to providing regimes and patients.

Across biomanufacturing, we need to address the issues of attracting, training, rewarding, and holding the science and technical staff needed to maintain our industry's momentum.

This will require relentless commitments to ever closer links between industry and academia, to in-house training of technical and science staff, and towards wider and deeper understandings of "make" alongside the excitement of "invent."

Outsource contract manufacturers are now established members of the biopharmaceutical community, and may soon be in a majority among its producers. That underlines the sector's role — and equally our responsibility to focus on and step forward to help address the major people challenges that lie ahead.