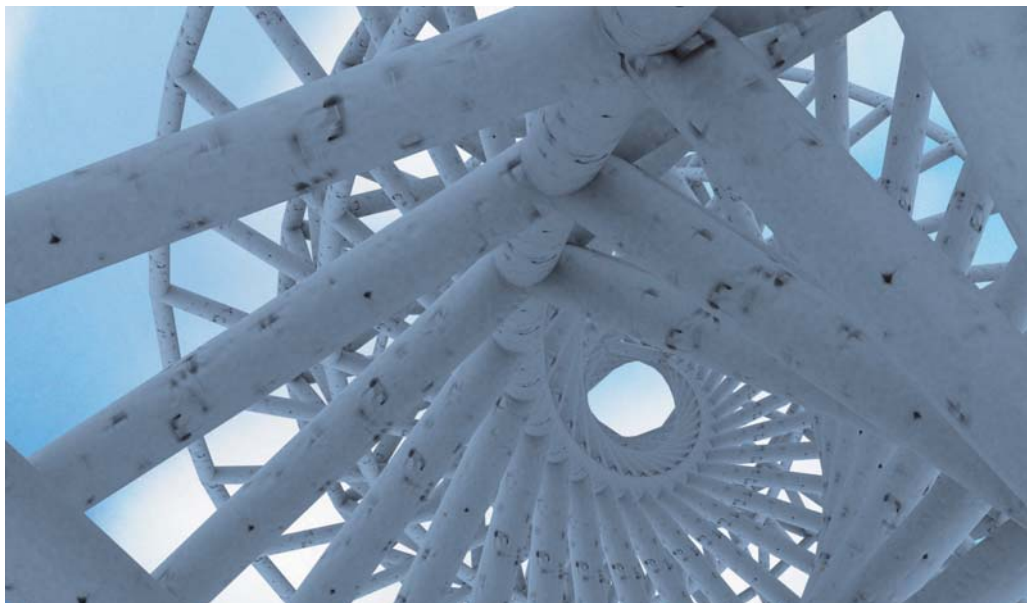


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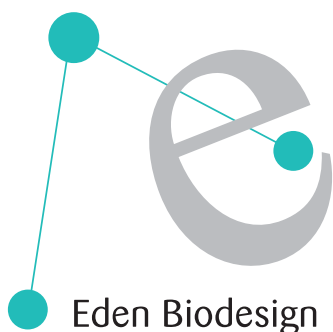
Curbing the Rising Costs of Drug Development: Solutions from Global Biopharmaceutical Manufacturers

Biopharmaceuticals – Medicines Today

Although the road hasn't been entirely free of potholes, biopharmaceuticals are finally completing the journey from 'bright promise for tomorrow' to 'medicines today'. Thirteen of the 67 block buster drugs currently with annual sales over \$1 billion are biopharmaceuticals (1). The growth in biopharmaceutical revenues has been significantly ahead of those for traditional pharmaceuticals running at over 20% compound annual growth between 1998 and 2003 (2). And a recent list of '100 great new investigational drugs' contained about

30 molecules that can be considered as biotech (3).

It's not all blockbusters and backslapping however. Investors are increasingly wary, particularly in Europe, having seen too little too late in terms of return on investment. Money is hard to come by for small biotechs which lack short term revenue prospects and the expected surge in new biotech medicines as a result of mapping the Human Genome has not yet materialised. In 2003 only 19 of the top 100 biopharmaceutical companies world wide turned a profit. In short, biotech companies are under pressure from investors to deliver on the bottom line, and sooner rather than later.



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BEGIN WITH THE END IN MIND

Opportunities remain however, and there are reasons for optimism. Not least of these is the concept of 'personalised medicine', or more properly, the benefits arising out of pharmacogenetics (the genetics of drug metabolism and action) and pharmacogenomics / pharmacoproteomics (gene / protein expression and drug action). The opportunity is to match treatments to the specific needs of patients, giving greater clinical success, reducing unnecessary or ineffective treatments and thereby even reducing treatment costs. Probably the best example of this principle in action is Herceptin, Genentech's breast cancer monoclonal antibody, and its linked HER-2 receptor diagnostic test. For life threatening conditions such as breast cancer the ability to get the appropriate treatment quickly optimised and 'right first time' has obvious benefits.

Personalised medicines; we have the technology, but have we the will?

Introducing tests that significantly reduce the target patient population for a block buster medicine obviously implies a smaller patient market, and therefore either smaller revenues for pharmaceutical companies or major drug price increases for patients. If the current market for a treatment, for example asthma, was split into ten component parts – each addressed by a different new drug - industry would have to develop ten new medicines instead of one for the same number of asthma sufferers. In the age of the block buster, when massive sales are required to cover the costs of the R&D failures, how will this happen?

To put this into perspective; a current estimate of the average cost of bringing a new molecular entity to the pharmaceutical market is \$802 million (4) and growing year on year at more than 7% above inflation. These controversial findings triggered an independent follow up study in 2004 by the US Federal Trade Commission (5). In December this reported back an even higher average cost of \$839-868 million.

Admittedly, the cost varied from indication to indication (HIV/aids drug \$470 million, rheumatoid arthritis \$936 million) and from company to company (from \$521 million per drug for one major pharmaceutical company to \$2119 million for another) but which ever way the figures are examined, the numbers are large. If costs keep rising the possibilities for better targeted medicines at smaller patient groups seem lower and lower, excepting perhaps a few niche indications.

Lower costs – better medicines

So what can be done to control or better yet actually bring down the costs of development so that the full potential of biotechnology is realised into new medicines? Does the solution lie in reducing the regulatory burden on developers? Recent high profile product withdrawals and safety concerns seem to suggest not. Perhaps more use of strategic alternatives such as outsourcing and off shoring? However biomanufacturing and the understanding of the product it confers is increasingly being seen as a key value driver for drug developers, particularly at a time when biogeneric medicines could be just around the corner. Is the answer to perform less rigorous

therefore less expensive clinical trials? In 1994 adverse drug reactions were cited as the fourth biggest killer (after strokes and before lung disease) in the USA (6). It seems more likely that the future will bring more stringent trials, not less.

Global Survey: A little context

It is clear that there is no simple answer to deliver safe, effective but cheap new medicines, but whilst articles on drug development costs are not uncommon, it is rare to find an opinion on this issue from the scientists and managers who are actually responsible for developing these new medicines. With this in mind Eden Biodesign commissioned a survey of just under 700 Biopharm International subscribers, all biopharmaceutical development professionals. Of these 57% were based in the USA, 28% in Europe and 7% from Asia. Of all respondents, 40% worked in companies employing more than 1000 people, whilst 30% worked in companies employing less than 50. The survey also included scientists working for contract manufacturing organisations (15%).

Is development expensive?

Although only 4% of respondents disagreed with the basic premise that development costs for biopharmaceuticals were high, it is perhaps not surprising that the majority (53%) thought that biopharmaceutical companies charge a fair price considering the investments made and risks taken to develop new medicines. Still it seems worth considering the finding that a sizeable minority (28%) thought that the companies they worked for should consider reducing the level of profits they expect to make

(Figure 1). For US based respondents, this was even more pronounced with over a third (35%) appearing to disagree with the industries focus on margins.

Why so expensive?

When asked to name the most important factor contributing to the high cost of biopharmaceutical development from a list of options, or suggest an alternative, there was a big difference of opinion (Figure 2). Whilst the narrow favourite was 'overcoming the technical challenges in product development' there was a fairly even split between this and the next two: the costs of running the clinical trials and general regulatory requirements. Biopharmaceutical development is not surprisingly viewed as challenging by the people who are experts in it.

How can we tackle costs?

Each of the survey respondents was asked to rank a selection of possible strategies as a means of reducing development costs whilst maintaining safety, quality and efficacy of new biopharmaceutical medicines, or to suggest their own alternatives (Table 1). The results revealed two strategies clearly standing out from the others in popularity. 'Developing new high yield process technologies to increase productivity' came in second, but the top answer was 'using best practice biopharmaceutical development skills to streamline product development, thereby reducing time and costs'. Outsourcing options and reducing the regulatory burden were far away in terms of preference.

The importance with which 'developing high yield technologies' was viewed was no surprise as bioprocessing

technology has been cited many times recently (for example; 7) as critical to the future of biopharmaceutical production. In the UK, the government has recently committed over £3 million to a National Bioprocessing Knowledge Transfer Initiative, aimed at, among other things, promoting the flow of ideas and technologies from academia to industry. This serves to emphasise the importance with which new production technology development is viewed outside, as well as within, the industry.

In an earlier question only 9% of respondents thought that biomanufacturing was a key factor in high development costs (Figure 2) and similarly outsourcing to contract manufacturers either in the West or in lower cost economies did not score highly as viable strategies, at least in terms of reducing costs (Table 1). Of further interest was that the survey findings for only those respondents who worked for a contract manufacturing organisation exactly mirrored those for biopharmaceutical developers on these points. In other words contract manufacturers themselves don't have any stronger a belief than drug developers that greater outsourcing represents the solution to lowering biopharmaceutical development costs.

The fact that the number one response was 'using best practice biopharmaceutical development skills to streamline product development' must be significant. 'Best practice' and 'streamlining product development' sound like fine phrases, but what do they actually mean? Surely they refer to 'know how', genuine expertise honed by the experiences of actually

developing process after process for product after product, learning from setbacks and successes and applying the accumulated knowledge to overcome those technical challenges cited earlier as the main factor for high costs. The problem in the biopharmaceutical industry is that such development know how rests in the minds of a very few while innovations with potential to make a real impact on healthcare rest with the many. For the 4,471 biotech companies in the world (8) there are just over 100 licensed recombinant protein drugs. These belong to just 46 companies of which only 19 have more than one product approved.

The key to the future

The final question asked on development costs was "what is the one issue that the biopharmaceutical industry needs to tackle to make sure the potential of biotechnology is fully realised in new medicines over the next decade?" This is a tough question and one only half of the survey respondents felt able to answer. It is impossible to list every response however they have been grouped, in as far as is possible, by category (Figure 3).

The four top categories were: introduction of new technology, development expertise, controlling drug pricing, and regulatory issues.

Developing and utilising new process and product technologies to provide better medicines was a broad category and responses varied from the narrow, for example 'more cell therapies' to the wide, for example 'increase the productivity of production processes by using novel technologies to develop more potent medicines more quickly

and more cheaply'. The common theme is best summed up by another response: 'innovate, innovate, innovate'.

Common themes from the wide range of responses provided under the loose heading 'development expertise' were streamlining development operations and sharing know how through training. There were several responses specifically relating to overcoming the challenges of biomanufacturing.

From the responses grouped under drug pricing and costs, it is clear that many feel that the pharmaceutical industry's spending on drug marketing is inappropriate. In other words patients are paying for too much product promotion. The money might be better spent on actually developing more effective medicines or reducing prices. The common theme was best summed up by the response 'make drugs affordable'.

Virtually all the responses in the regulatory grouping were on the two themes of better harmonisation of regulations between territories and greater co-operation between regulators and industry. True or not, plenty of respondents appeared to believe that regulatory agencies are stifling innovation and unreasonably restricting development of new medicines.

From the responses in the social, political and ethical category and also the communication responses, it is apparent that a lot of people have concerns over how well the biotechnology industry represents itself and the opinion with which it is viewed by society in general. Many perceive there to be risks that threaten future innovation if this is not addressed.

The fairly low response for greater financing of biotech companies was interesting. Perhaps people working within the industry believe there is enough money about; it's a question of spending it more wisely.

Conclusions

Earlier in this article there was a reference to a seemingly large difference between the average costs of pharmaceutical development, per new molecule, between different pharmaceutical companies (4). Whilst the report authors provide clear a health warning about reading too much into selective data, it seems reasonable to assume that some organisations are better at developing medicines to a budget than others. Orders of magnitude better, if the data is taken at face value. There is obviously no simple, straightforward answer to the question of how to control the costs of biopharmaceutical development. These survey findings however suggest that the majority of development professionals surveyed believe that the starting point to reach such a solution lies in the experience and expertise of product development and in the promise of new bioprocessing technologies.

The questions remain: how can expertise in product development be shared better? And how can biotech companies with little real development experience hope to evaluate the best bioprocessing technologies and utilise them to best effect?

Elsewhere in the survey (data not shown) when respondents were asked to select from a list of major European contract manufacturers those who had genuine experience and understanding

of product development, the consensus response was 'none'. Whilst this data is in no way authoritative and only included seven companies, when taken together with the other survey findings, the indications are that most development scientists don't believe that access to development expertise and innovative bioprocessing technology is through the existing model of a contract manufacturing partner. This could be because the majority of biological manufacturing organisations have their roots in fine chemicals and NCE drug substances and therefore lack biopharmaceutical development expertise or that many of the smaller companies have an offering based only around a piece of novel technology rather than actual product development experience. To make contract manufacturing profitable there is a strong driver for manufacturers to reduce the complex task of biopharmaceutical production to as simple a unit operation as possible, which is not always to the benefit of the product or the client.

There would seem to be a need for innovative initiatives to promote best practice in product development as well as in bioprocessing. This latter seems to be well acknowledged with the recent Canadian proposal for a national training network to increase the supply of personnel highly qualified in biomanufacturing (HQP), North Carolina's ambitious biomanufacturing training programme and the introduction of a UK National Vocational Qualification in biomanufacturing based around The Partnership for Learning initiative in Liverpool.

Promotion of best practice in product development is not as well addressed,

although there are some signs that this is changing. One of the founding principles of the UK National Biomanufacturing Centre for instance is to provide access to genuine product development expertise in addition to funding for small companies and state of the art biomanufacturing facilities. This public/private partnership is a unique model that has received much interest from other national governments and regional bodies and this, together with follow on initiatives like the proposed Canadian Centre for Biopharmaceutical Manufacturing, perhaps could be part of the answer.



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Table 1

In your opinion, which of the following represent the most viable strategy to reduce the cost of product development and manufacturing whilst still maintaining quality, safety and efficacy: Please rank these in order of importance, with 1 being the most important.

Rank	Strategy	Response average
1	Using best practice biopharmaceutical development skills to streamline product development and reduce timelines and costs	2.16
2	Development of new high yield process technologies to increase productivity	2.27
3	Outsourcing manufacturing or other development activities within the US and Western Europe	3.59
4	Reducing the regulatory requirements for orphan drugs and personalised medicines still further	3.72
5	Outsourcing manufacturing or other development activities to lower cost economies such as Eastern Europe, India and the Far East	3.99
6	Something else entirely	4.83

Figure 1

As someone who works in the biopharmaceutical industry, what is your opinion of the industry's pricing strategies in general?

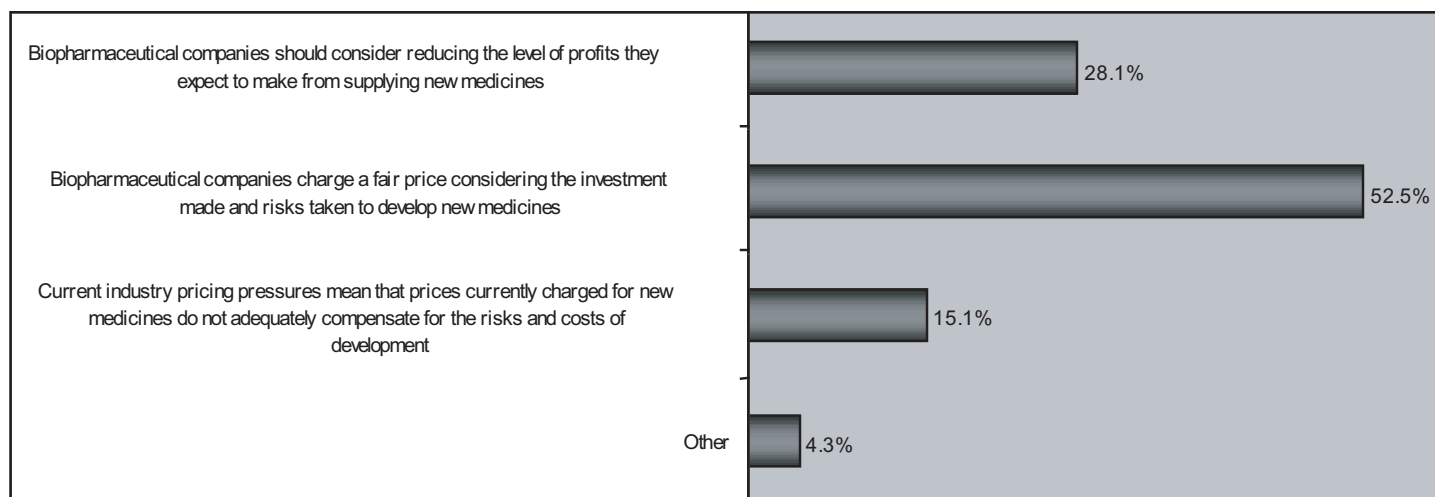


Figure 2

Do you think the high cost of biopharmaceutical development is mainly due to:

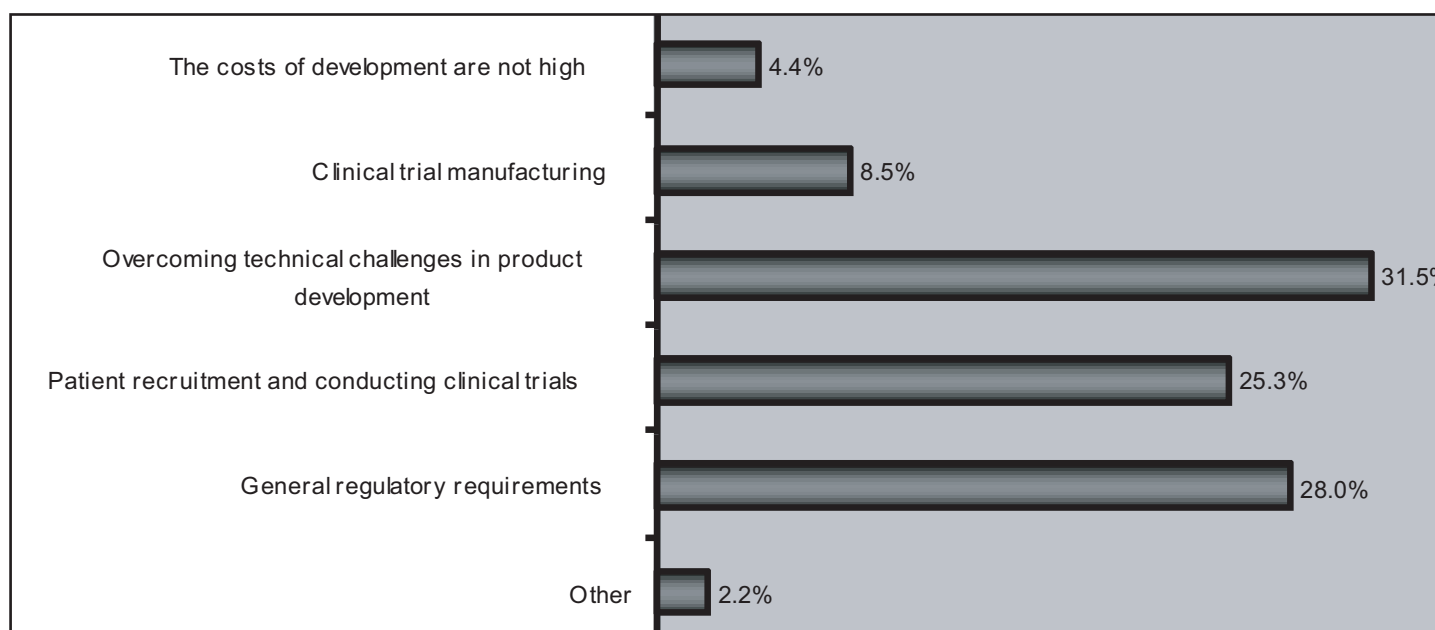


Figure 3

If there is one issue that the biopharmaceutical industry needs to tackle to make sure the potential of biotechnology is fully realised into new medicines over the next decade, what is it?

Responses grouped by category.

