The clinical pharmacology of biotechnology products
M M Reidenberg, editor

COSTS OF DISCOVERING, DEVELOPING, MANUFACTURING AND MARKETING BIOTECHNOLOGY PRODUCTS

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INTRODUCTION

The costs of biotechnology products are important to both the producer and the patient. From the producer's viewpoint, development costs are a major determinant of return on investment, which is an important factor in deciding whether a pharmaceutical company will attempt to translate a biological discovery into a therapeutic drug.

Costs also have a direct bearing on the pharmaceutical industry: rising R&D costs are one of the main reasons for the growing trend of mergers and consolidations. Costs influence patterns of international resource allocation, and hence international competitiveness, and have become an issue in their own right in the seemingly continuous policy debates on the pharmaceutical industry.

In the case of biotechnology, costs are of special importance for several reasons:

- The nature of the industry (in particular the predominant role of small startup companies),

- The inverse relationship between specificity of therapy and size of the population eligible for treatment: as therapy becomes more specific, the potential number of patients may diminish,

- The need for special production facilities and quality control,

- The relatively high ingredient cost of the final product,

- The attitude of payers--either the patient or third parties.

There has been no comprehensive study of the costs of developing biotechnology drugs, although the literature gives us references to certain parts of the process and one overall example (IL-2). Furthermore, the question is becoming somewhat blurred as the numerous facets of biotechnology are increasingly integrated into the entire discovery and development process of the "conventional" drug companies.

Nevertheless, there are a number of new discovery strategies that have only become possible with the advent of biotechnology and related tools, and there are a growing number of biotechnology-derived products being developed as therapeutic drugs, by either startup biotechnology companies or by conventional pharmaceutical companies. These are the endeavors that can be legitimately identified as biotechnology drug development.

The approach I have taken is to review the information that has been published about the costs of discovering and developing conventional drugs; then to decide how we might expect biotechnology drug development to differ; and finally to examine whether these ideas are supported by the information that can be found.

COSTS OF DEVELOPING CONVENTIONAL DRUGS

A new study of costs, by DiMasi, Hansen, Grabowski and Lasagna (1990), has provided up-to-date estimates of the average pre-tax cost of developing a New Chemical Entity (NCE). These authors obtained project-level data on the cost and timing of development from a confidential survey of 12 U.S.-owned pharmaceutical firms for a stratified random sample of 93 self-originated NCEs first tested in humans during the period 1970-82. (The sample was drawn from a comprehensive database of all compounds studied by all pharmaceutical companies in the U.S. since 1962, updated triennially.) R&D expenditure data were collected through 1987 from each firm for each of the phases of clinical drug development, and the preclinical costs for self-originated NCEs were derived by the investigators from a knowledge of each firm's total annual R&D expenditures.

For every NCE that is approved, several others are abandoned at some point. Therefore, the cost of failed projects was allowed for, along with successful ones.

R&D was treated as an investment with returns delayed until marketing approval. To account for the time cost of R&D, the authors capitalized expenditures to the point of NDA approval at a discount rate relevant to the pharmaceutical industry (9% being the preferred value).

Results:

The authors first calculated out-of-pocket costs, namely the total internal plus external costs incurred before adding the cost of capital.

The average out-of-pocket clinical period cost per NCE tested in humans was found to be $11 million (all figures in 1987 dollars). Using an estimated clinical period success rate of 23% (the average value found in the survey) gave an average out-of-pocket clinical period cost per approved NCE of $48 million. Adding estimated preclinical costs of $66M raised the average out-of-pocket cost per approved NCE to $114M.

Development time was estimated for the various phases of development. On average, the time from synthesis to approval was approximately 12 years. Accounting for time costs by capitalizing R&D expenditures at 9% interest rate doubled the total cost per approved NCE to $231M.

Comparing the results to those of a previous study with similar methodology (Hansen, 1979), total development time had increased by two years, and total cost per approved new drug had increased 2.3 times after adjusting for price inflation.

BIOTECHNOLOGY DRUG DEVELOPMENT: SIMILARITIES AND DIFFERENCES

For biotechnology drugs, one could start with the assumption that (very broadly) discovery, preclinical and clinical development might cost about the same as for conventional drugs, while production and quality assurance would cost more.

Let us examine these factors in more detail, identifying in particular the stages where the costs are likely to differ from those of conventional drugs.

From Discovery Through Preclinical Development to Proof of Concept

Production of Preclinical and Clinical Supplies

Production of active ingredient and formulation into a pharmaceutical dosage form is an area where biotechnology drug development costs more than conventional drug development, since these supplies must be produced in a manner that meets all applicable standards for toxicology testing and for the IND (or its equivalent), and in addition must satisfy all the manufacturing conditions for a sterile substance. Furthermore, this must be done before the learning curve and the economies of manufacturing scale have allowed reduction of costs. Therefore, preclinical and clinical supplies may be considerably more expensive than for conventional drugs (e.g., several million dollars up through the first set of clinical studies).

One consequence of such high cost at an early stage of development is that it will tend to reduce the number of analogs in a series that can be brought into clinical testing.

Delivery Systems

Biotechnology products pose special challenges in delivery for therapeutic purposes. Unless the native compound has acceptable pharmacokinetics or is active by one of the usual parenteral routes, then special dose forms may have to be developed -- in particular to prolong actions, protect from degradation, or otherwise improve the pharmacokinetics.

"Reduplication" of the discovery phase under certain discovery strategies.

Today's biotechnology lead compounds are generally proteins or peptides such as receptors and their ligands, enzymes, modifications of all these, and monoclonal antibodies. (They may in the future be oligosaccharides, as we come to understand the biological role of sugars, or oligonucleotides, as we develop methods of antisense gene modulation. Here I shall only consider protein-related products.)

Biotechnology-derived proteins can lead to drugs in two ways: by yielding medically useful proteins or peptides directly, or by providing tools for discovering the smaller molecules that we know as conventional drugs.

When biotechnology is used to produce protein or polypeptide drugs, we could expect the cost to be in the same general range as for conventional drugs, since the potential savings in a possibly shorter clinical period and higher success rate will tend to be offset by the higher costs incurred much earlier in the process for producing the ingredient and manufacturing suitable pharmaceutical dosage form.

However, pharmaceutical companies prefer small-molecule drugs that are absorbed by mouth and able to be given for long periods for chronic diseases. The costs may be different when biotechnology is used as a tool to discover such molecules. Depending on which strategy is used to exploit the protein-intermediate tools, the costs could be lower or higher than with conventional drugs.

If biotechnology-derived enzymes or receptors are used in vitro to predict (e.g., through the powerful new x-ray crystallography and computational techniques) the structure of synthetic ligands and antagonists and then to screen such compounds for activity, then the cost-effectiveness of an overall discovery facility (which could serve several different therapeutic areas from a single physical installation) might be greatly improved over the older screening techniques.

But another equally valid discovery strategy requires the clinical evaluation of the protein product. Once we look beyond the "replacement" era of biotechnology compounds (e.g., insulin, growth hormone, EPO, and a few others), we have access, through biotechnology, to a large number of potentially interesting natural proteins, plus antagonists in the form of monoclonal antibodies to them, whose therapeutic potentials are unknown and therefore require testing in animal models and eventually man. Before (or while) one embarks on the effort to create the appropriate small-molecule mimic or antagonist of the target protein, it is advisable to determine whether the protein itself is therapeutically useful. So we have to take the large molecule into animal pharmacology and toxicology testing (which is required to be performed but may or may not yield relevant information) and then human trials up through phase 2a, in order to ascertain its therapeutic properties.

Thus for a pharmaceutical company to make full use of biotechnology in a strategic sense, it may have to start by discovering and producing a protein with anticipated activity, then develop that protein through animal pharmacology and toxicology right through the stage of phase 2 clinical trials in order to prove the possibility of therapeutic utility in man. The development process is then

started again by treating this protein as a discovery lead for the development of a conventional drug molecule.

Compared with conventional drug development, this strategy involves an additional discovery step which, requiring substantial investment so early in the drug development process, will increase the overall costs of drug development, perhaps substantially.

On the other hand there are in this strategy factors that would offset this higher cost. They include:

- Bringing the intermediate protein itself to the market and generating enough profit to recover the costs of the additional discovery step.

- Generating more discoveries, potential leads, and development compounds from the same discovery program.

- Increasing the final success rate of the development compounds that result from this discovery strategy.

It is too early to tell whether these cost offsets will indeed occur.

Clinical Development and Regulatory Approval

Assuming that the standards of regulatory approval are unchanged for biotechnology drugs, it is possible that because of their parenteral nature (which leads the compound into acute or short-term treatment indications), the length of the clinical period from the start of phase 1 testing to submission of the PLA (Product License Application) at the end of phase 3 could be less, and hence the costs for the clinical program (excluding supplies) could be less than for

conventional drugs. However there is not enough experience to date with biotechnology PLA submissions and approvals to determine whether this is so.

Manufacturing

Manufacturing costs are a major issue in biotechnology and the process has been described as the industry's Achilles heel (Boss, 1990). By contrast with conventional drugs in an established pharmaceutical company, choice of a manufacturing strategy--particularly for a biotechnology startup company--is relatively complex and could be critical to the success or survival of the company.

For a conventional drug, an amortized plant is likely to exist or capacity can be hired, since there is a worldwide surplus. By contrast in the case of a biotechnology product, the facilities do not exist and probably have to be built from scratch at a cost of, say, $50M.

In the case of a fairly simple biological, such as a monoclonal antibody, Boss (1990) estimated that the fixed cost would be $20 million, while the manufacturing cost per gram would be $2,200 before depreciating the capital costs. The price of the final product to the patient was estimated to be $4,300 gram assuming a 30% cost of goods. It was further noted that a course of therapy for an anti-cancer monoclonal could require several doses of up to 10 grams each, with a marginal manufacturing cost of active ingredient of up to $60,000. These costs and prices are much greater than the price of therapy with conventional drugs. It should also be noted that some experts familiar with the area have estimated that the above costs per gram are a substantial underestimate, or could be achieved only after a long learning curve of production.

Costs of Marketing

There are few estimates of the costs of marketing biotechnology products specifically. However, marketing costs are not affected by the origin of the product, but depend on the therapeutic area, the exact properties and indications the new drug has, and the nature of the company (e.g. established or startup).

We shall therefore take a typical biotechnology product, namely a recombinant protein and make the following key product assumptions:

- Hospital use
- IM/IV administration
- Relatively narrow physician audience (e.g., infectious disease or surgeons)
- No samples are distributed
- Enters an already established therapeutic category, eliminating the need for broadly-based educational efforts.

For a product with these characteristics, the initial marketing costs were estimated to be $7 to 8 million per year, with a total of $23 million for the first three years.

Other Factors

Protection of Intellectual Property

While the costs of patenting biotechnology products may be a relatively modest direct cost of drug development, a more important question is the amount of protection thus obtained, because this is a powerful determinant of whether biotechnology investments can be protected, and hence of the attractiveness of this investment area.

There are no patent laws specifically for biotechnology products, and new issues and interpretations have arisen with the types of discoveries made in biotechnology. In conventional drug development by the established pharmaceutical companies, there is now enough history and knowledge of the issues for disputes to be settled without litigation, usually by cross-licensing agreements. By contrast in the biotechnology area, the merits are less well defined and disputes tend to involve litigation. This is because of the very high stakes involved for the individual companies (particularly in the case of the biotechnology startup companies), their extreme dependence on one or two initial products, and the independent personalities of the leaders attracted to startup companies in this frontier of science and business (Mertz, 1990).

Examples of issues in biotechnology that have gone to litigation include the action by Genentech against Burroughs Welcome and Genetics Institute over three patents for TPA; Xoma's suit against Centocor over antibodies to endotoxins, and between Amgen and Genetics Institute over recombinant erythropoietin.

Until the results of the various disputes are settled by litigation or agreements and we have a general knowledge of the rules that result, there will continue to be less certainty about the extent of intellectual property protection in the biotechnology area than in conventional drug development.

EXAMPLES OF OVERALL COSTS IN BIOTECHNOLOGY

Interleukin-2

One detailed example is available in the literature, and this suggests that the costs of developing a biotechnology protein drug are indeed fairly comparable to those of developing conventional drugs. For the development of Interleukin-2, M. Ostrach of the Cetus Corporation stated in December 1989 that Cetus' RD&C costs had been $75M before including the cost of capital. In addition, the pilot plus full-scale manufacturing facilities cost $45M, and marketing $15M.

The $75M figure is the one that should be compared with the DiMasi et al estimate of $114M, before interest, for conventional drugs. As IL-2 has not yet been approved for the U.S. or other major markets, and since Ostrach estimated that a one-year delay in introduction would add $35M to the development cost, the total would reach $110M by the end of 1990. Thus, the additional development time and costs needed to reach the major markets, plus the cost of capital, will bring the total time and cost of developing IL-2 well into the range of the average conventional NCE.

An alternate calculation was to take Cetus' total costs over the 10-year development period, to that date, of IL-2. This method shares the advantage of DiMasi et al of including "dry wells", but since the outcomes are not yet known it is probably an overestimate if attributed solely to IL-2. By this method, $370M had been incurred (by December 1989, before any product had been approved for the U.S. market.)

DISCUSSION AND CONCLUSIONS

The Problem:

While biotechnology has transformed the discovery phase, it will not necessarily reduce the cost of drug development. Based on the very limited information available to date, it appears that the cost of developing individual biotechnology protein drugs will be fairly similar to that of conventional drugs, namely over $200M per NCE on average, including the cost of capital which is half the total. There are several factors that could move this estimate up or down, and a more precise value will have to await a larger sample of approved biotechnology drugs and a special study of the type done by DiMasi et al.

Although the regulatory environment for biotechnology drug development began with less encumbrances than today's conventional drug development, it is now tending to show some of the characteristics of the mature regulatory environment that surrounds conventional drug development, and this tendency may increase in the future. Furthermore, the progressive increase of regulatory standards and requirements means that costs are likely to rise also.

It should be noted that because we are still in the "startup" phase of biotechnology drug development, the true average costs of biotechnology drugs will not be assessable until a more steady state is reached, in particular until the fate (success or failure) of the first generation of development candidates has become known. This will not occur before the mid 1990s at the earliest. Until then, the development time, costs and success rates of those biotechnology drugs actually approved will tend to be more optimistic than the real average, although by steadily diminishing amounts. This is due to several factors: the

first generation of biotechnology products consisted of the most obvious and logical targets, (e.g., replacements for hormones or other substances already available from natural sources, such as insulin, growth hormone and alpha interferon); the examples approved first necessarily include those with shorter development times; and the regulatory requirements for this new technology were least at its inception. It is only after the mid 1990s, when this startup phase is complete, that we will be able to measure the true mean times and costs.

The more precise mechanistic targeting of biotechnology products should logically lead to drugs that are more precise than their predecessors, with more specific efficacy, less toxicity and a sharper focus of drug effects. At the same time, however, this very specificity could narrow the patient population for whom the drug is approved and indicated and hence the size of the market--perhaps even to "orphan" indications--while the costs of these products could raise questions of reimbursement, including what indications are reimbursable under the various cost-constraint strategies that are being developed and tightened.

While this may be an inevitable cost of the increasing depth of the discoveries we can now make with biotechnology, it does mean that all who are concerned with the drug discovery process (not only the companies involved, but also academic researchers and regulators) will need to keep at least an open mind to prevent the utilization of these new discoveries from becoming even more costly and time-consuming. Today's constraints could lead to an impasse in the development of drugs from biotechnology, or at least retard the transfer of the discoveries of biotechnology into available therapies.

Possible Solutions:

The necessarily high relative cost of biotechnology products, and the small target patient populations for some of them, suggest that in this era of cost constraints, some new thinking is needed to optimize the conditions for commercialization of new potential therapeutic discoveries from the biotechnology sector.

From the biological and industrial perspectives, much remains to be learned about the most efficient discovery and development strategies. (We may even have pleasant surprises as the wealth of biotechnology options makes discovery easier; but realistically, on past trends, it is more likely that costs will increase.) To be successful a pharmaceutical company must ascertain the most cost-effective strategies and ensure they are followed, but it will be some time before the optimal courses become clear.

The regulatory environment is a major area that is under society's control, since it is the height of the regulatory hurdles to clinical investigation and marketing approval, plus the length of the regulatory review time, that play a large role in determining both the time and the costs of drug development.

There have been numerous studies of how to optimize the regulation of pharmaceutical products (Hutt 1984), and another high-level study on the Food and Drug Administration, has been set up in the U.S. (the Health & Human Services Advisory Committe on FDA) before the previous one (the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS) had even completed its report. By now the measures that could be taken are well known (PMA, 1990). Some of the key points I

believe are most relevant to biotechnology products can be summarized as follows:

- Rationalize regulatory requirements medically. There is little point in perpetuating regulatory requirements that are not strictly necessary medically. A large simplification could be achieved if all regulatory requirements were reassessed by this criterion to prevent the accretion and perpetuation of unnecessary requirements. This is one of the few areas where progress is possible, and one with a large effect. Di Masi et al showed that a year's reduction in the duration of phase 3 would reduce the capitalized development cost by $18M, while Ostrach showed that a year's delay with IL-2 would cost $35M.

  An example of rationalization would be simplifying the regulatory requirements for certain classes of products, such as mouse monoclonal antibodies. There is now considerable experience with these compounds in man, and they appear to be relatively non-toxic. Can ways be found of simplifying the quality assurance standards, and even deleting the toxicology requirements needed, before certain types of human trials are permitted?

- Harmonize rational requirements: EC-US-Japan. There are three major world regions for drug development and marketing: the EC, the USA and Japan. This is a critical moment in history as the EC seeks to harmonize the regulatory system for its internal pharmaceutical market. To avoid further increasing the costs, it is essential that such regulatory requirements, while being rationalized are also harmonized internationally. If these two

steps do not occur, precious drug development resources will continue to be wasted and drug development costs will be unnecessarily high.

- Good Regulatory Practices. A considerable improvement in efficiency might be achieved if regulatory agencies were required to adhere to generally recognized management standards, such as meeting deadlines, answering correspondence promptly, respecting agreements, and holding managers accountable for the performance of their groups.

- Substituting phase 4 studies for part of phase 3. In view of the real difficulties in finding ways to shorten or truncate the increasingly-burdened system of drug development and approval, it has now become more respectable to think of an idea that was previously considered too radical: truncation or elimination of phase 3 studies in favor of phase 4. This, along with shortening the approval process is the only place where really substantial time, and hence resources, can be saved (e.g., a total of five years). The arguments are contained in the above references and are too long to consider in detail here. However, devising an acceptable method of achieving this may be one of the constructive and rewarding challenges of the 1990s.

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Discussion - COSTS OF DISCOVERING, DEVELOPING, MANUFACTURING AND MARKETING BIOTECHNOLOGY PRODUCTS

L. Gauci

One should not forget that the very rapid development of interferon alpha for the treatment of hairy cell leukemia indicates the willingness of regulatory agencies involved, to assist in the registration throughout the world.

W.M. Wardell

But that was one of the first compounds of the new era, and new questions will be asked of subsequent ones that were not asked of the first. I think it is inevitable that there will be an accretion of requirements. That is what has happened with conventional drugs, and my impression is that it is happening with biologics as well.

P. Juul

I am not very happy with a registration after phase II, as it has been suggested in Europe concerning certain anti-cancer drugs, and I am not in favor of letting the expanded access program, which we also have problems with, lead to an earlier registration. I think there is another solution. If one accepts compassionate IND usage then it is acceptable that the drug is only used by specialists but we can accept that hospitals or the patients pay for the drug, meaning that you will have an interim phase when the product is not registered but the company is not loosing these enormous sums of money which you mentioned. One of my reasons for not accepting or liking an early registration is that it is our experience that it is very difficult to get rid of a drug once it is on the market: The regulatory authorities have as much difficulty in getting rid of it as the company originally had in getting it into the market. So these patients even with serious diseases should not be treated more badly than other patients. With regard to good regulatory practice I would say that U.S. and Japan could just follow the rules of the EEC where NDA should be definitely answered within less than a year and if we don't do it and we don't answer, it means that we have to accept the drug on the market.

M.M. Reidenberg

It has been shown that virtually all of the drugs that get well into phase III end up getting marketed. There is also data showing that phase III has too few patients in it to pick up adverse events that occur as frequently as one in a thousand. So, I think that

a really thoughtful consideration of what information is learned during phase III that is essential for early marketing would probably show that most of the time very little is learned. I think that as a society we make a fundamental mistake in thinking that a drug is experimental on day minus one; on day zero it is approved as safe and effective, and on day plus one it become standard practice and it is a safe and effective drug. Our perceptions as a society, our de facto regulatory requirements, are totally out of congruence with the reality of therapeutics. I feel that it would be far preferable to have drugs made generally available much earlier in the development process with the understanding that they really are experimental. I think with this we would need to have an agreement for more substantive scientific research after marketing. And I think it would be necessary for the regulatory agencies to be able to reasonably reevaluate decisions for marketing and labelling, and have the ability to go all the way to removal of an approved drug. I think that the issue then for the company is how much risk to take that rescinding approval may occur. I suspect most company's managements would oppose it, but I think such a process would bring regulatory and developmental activities far closer to the reality of therapeutics.

L. Gauci

If there was a mechanism whereby the drug could be sold to patients suffering from conditions for which it is not properly developed, this would allow the company to finish the work properly and may help on improving dosaging schedules.

D. Maruhn

I would like to take issue with the notion that on an average clinical development costs of biotechnology products might be lower than those of conventional drugs. That could be true for drugs which are used for short term treatments but in the case of substitution therapy the costs of clinical development are similar to those of conventional drugs. However, one should take into account that reduplication of clinical studies certainly adds a substantial burden to the costs of development. We are trying to optimize our international efforts and what we use is an instrument what we call the International Clinical Development Plan thus trying to avoid that too large number of patients are exposed to the drug and to ensure that we get the minimum of requirements for all important countries where we are going to apply for a registration of the drug.