Some Challenges Relating to the Future of Biopharmaceutical Technology

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INTRODUCTION

Although this field of technology has been expanding rapidly over the past 5 to 10 years and apparently shows a great deal of promise for the future, it seems reasonable that we should review the progress and determine if, indeed, there is a future for pharmaceutical biotechnology. After all, the enormous potential for the good of mankind and the considerable costs involved would appear to be mutually exclusive, suggesting that some serious decisions will need to be made in the near or distant future.

To provide a hypothetical example of a potential budgetary impact, let us think about the repercussions if a cure for Alzheimer’s disease were to be uncovered that required biopharmaceutical processing and separation of an active ingredient.
hypothetical cost of a single patient’s drug treatment alone might well exceed $30,000 per annum; multiply this number by the 6 million or so patients diagnosed with the disease and we begin to approach direct costs that could seriously rival or exceed the military budget! Decisions will have to be made in the future about where this money will come from, especially as it would be politically unacceptable to deny the unfortunate patients this treatment.

Although this is a hypothetical example, most biotechnology-derived drugs are used to treat relatively small patient populations, so the overall demand for money from the central authorities would also remain relatively small and more easily digestible. This may be the present (2005) situation but there can be little or no doubt that the demand for biotechnology-derived drugs will increase. We will find ourselves trying to balance the budgetary impact of the costs against all the benefits associated with an efficacious and safe treatment for a disease.

EXAMPLES OF ESSENTIAL BIOPHARMACEUTICALS

INSULIN

In the early 1970s it became evident that there was unlikely to be sufficient naturally derived insulin from slaughtered cattle and pigs available to treat the existing and expanding diabetic population by the end of the decade. A consortium of industrial scientists succeeded in genetically engineering human insulin from bacterial sources and, after 20 years of continuous development, this remains a source of human insulin guaranteed to be pure and free of microbiological contaminants.

On the other hand, bovine and porcine insulins are still produced after over 80 years of development, especially in underdeveloped countries. These materials are relatively pure but there is always a danger of contamination with prions such as bovine spongiform encephalopathy (BSE). This danger has not been demonstrated to date but it is conceivable. Nevertheless, it remains necessary to point out that the naturally derived materials are less expensive than the genetically engineered form of the drug. Health insurance companies, perhaps wisely, have never demanded generic substitution of the bioengineered form by the natural, but such are the vagaries of the healthcare system; this option remains a possibility in the future.

GROWTH HORMONE

Human growth hormone (hGH) or somatotropin has returned to the limelight recently when genetically engineered material became more readily available and more applications for the drug opened up.

The protein was originally derived from human cadaver pituitary glands and was used initially to treat dwarfism. However, it became evident that the material was contaminated with the prions that caused Creutzfeldt-Jakob syndrome and for many years this line of research was not followed up. Recently the protein has been produced by genetic engineering in significantly larger quantities and is now being explored for use in other applications (e.g., cosmetics).
In the United States alone there are approximately 50,000 adults with growth hormone deficiency, resulting in dwarfism and there may be as many as 6,000 newly diagnosed cases per annum. The cost of treating a child with growth deficiency is currently estimated at around $11,000–$18,000 per annum. An alternative way of looking at this issue is to note that it costs between $35,000 and $40,000 to increase the height of an affected child by one inch.

The legitimate medical demand for this drug is therefore at about $1 billion per year and this money presumably must be found somewhere in the system. A recent suggestion has been that the drug should be used to treat adults or children who are otherwise healthy but show signs of being a little shorter than average; this seems a questionable medical and ethical requirement for the drug (DeMonaco 2003).

Another aspect of this drug that is certainly highly questionable is its use for cosmetic and athletic purposes, but this issue is going to have to be resolved by the regulatory authorities.

INTERFERON β 1a

Das (2003) made an interesting point recently when he suggested that there were currently 371 new products currently on trial against diseases such as Alzheimer’s, AIDS, arthritis, cancer, heart disease, and multiple sclerosis (MS). For MS, Serono (Geneva, Switzerland) announced that their new drug Rebif®, a form of interferon 1a, would cost a patient $17,000 a year. Das therefore suggested that supply of many new protein therapeutics for a year was quite likely to exceed $10,000. In spite of this expense, the patient may have no alternatives and this would remain the situation where the disease had inadequate therapy or no treatment at all.

OTHER EXPENSIVE DRUG THERAPIES

Looking at the numbers of bioengineered products coming on the market and the diseases that they claim to treat, it seems that the list of diseases is getting longer and perhaps more obscure. Nevertheless, there are some diseases such as rheumatoid arthritis excruciatingly painful and have little in the way of effective treatments. The use of antitumor necrosis factors (TNF), principally as a humanized monoclonal antibody, as anti-inflammatory agents has met with some success and various forms are now entering clinical practice. However, even as this is being written (2004), reports are appearing on the side effects of this therapy. In addition, one has to wonder about the long-term effects of a therapy designed to suppress the natural antitumor substance used in nature to destroy the cancers that normally appear in the body spontaneously.

PHARMACOECONOMICS AND VALUE FOR MONEY

With concerns growing about the rising cost of drug therapies it is not surprising that a new academic discipline has arisen—pharmacoeconomics. Not entirely new, the study of therapeutic outcomes from an academic perspective has remained somewhat intuitive up to now but obviously is of considerable interest to developing
companies in the pharmaceutical biotechnological area interested in selling an expensive commodity to a limited number of purchasers.

The producer must demonstrate objectively that a new and expensive therapy represents good value for money, especially if the drug costs a great deal more than existing treatments. Breakthrough products that provide a treatment or cure where none has previously existed must also demonstrate value for money when it comes to reimbursement by the government or insurance agency. Beyond this point, the consumer must be convinced that the new drug is worthwhile, both in terms of alleviation of the condition and likely prolongation of life. Quality-of-life issues are also important and form part of the final evaluation equation.

Unfortunately, these issues are difficult or challenging to measure directly and the current situation involves a number of empirical or semiempirical numbers that seem to obscure the fact that there is no significant underlying science. This is controversial in the sense that some claim it is a practical or applied science. (However, Lord Rayleigh, the great Victorian scientist, claimed if something could not be measured it was not science.) Looking at patient outcomes following specific treatment some effects can be measured (time to death, for example), and there is usually a causal relationship between drug use and improvement in condition or cure of a disease. How exact numbers can be put to these effects has become controversial and there is a large literature on this subject.

To provide but one example of the many papers in the recent literature, Neumann et al. (2000) asked if pharmaceuticals were cost-effective and provided examples of current thinking in this field. These considerations will undoubtedly have an influence on the way in which Medicare and health insurance organizations calculate compensation.

The empiricism in this area is paramount but can hardly be avoided because there are no strong measurements for factors such as therapeutic outcome. One factor that is easily measured is the direct cost of the drug or treatment in terms of the cost of a daily dose. Strangely, this simple measurement does not always appear to be of concern, although there are situations where the cost has an outcome on the chosen therapy. Neumann et al. (2000) calculated a “quality-adjusted life year” (QALY) to demonstrate the benefits of, for example, treating a patient with a herpes zoster infection with acyclovir as opposed to providing no treatment at all in order to save money. On the other hand, they calculated that treating a 50-year-old Caucasian woman, otherwise healthy, with estrogens would cost $12,000 against no treatment. However, it is not entirely clear from this publication how this estimate was obtained although it obviously includes the direct cost of the drug. It might be worth commenting that the direct cost of a small molecular weight drug (<500 Da) does not usually cost more than about $6,000 per annum directly to the patient and most insurance companies and Medicare seem content with this, irrespective of other factors artificially built in to the estimated price.

The point of this discussion is to note that it does not appear to be feasible or, indeed, desirable to base a comparison of the cost of drug therapies as a whole on the simple cost of the drug per dose or per annum alone. A biotechnologically derived drug may cost a great deal of money per unit dose, but the actual cost/benefit ratio may be such that society can absorb the cost. This topic does not appear to have
been played out at this point in time and it is certain there will be developments in
the future.

Neumann et al. (2000) quoted an internal document dating from the Clinton
administration that stated that, for every $1 spent on drug therapy, there was a saving
of $3.50 in hospital spending. This number has been widely quoted but, as always,
there has been little or no attempt to confirm or validate this estimate. It may simply
represent the optimism of administrators dealing with a huge drug bill, aided,
perhaps, by the pharmaceutical industry. Indeed, Neumann et al. draw attention to
the skepticism associated with drug industry–supported studies of the economic
issues of drug treatment. Most reputable medical journals have now instituted strong
controls designed to ensure that the reported data is objective, thereby avoiding some
of the suspicions of earlier abuse of the system.

It could be argued that pharmacoeconomics is a serious attempt to determine if
a particular drug, no matter its origin, offers value for money. This issue will continue
to be of interest to everyone involved in treatment of disease by biotechnologically
derived drugs.

**GENERIC BIOTECHNOLOGICAL DRUG ISSUES**

The respected scientific journalist W. Wayt Gibbs, writing in *Scientific American*
(2003), has suggested that many of the issues associated with concerns about the
high costs of individual bioengineered protein drugs will go away when the patents
lapse and generic drug manufacturers become involved.

Gibbs correctly identified some of the issues when generic “copies” of estab-
lished drugs became available to the public. However, he may be in error in sug-
gesting that the cost of “biotech” or “biologics” would decrease very much for the
simple reason that these drugs are not prepared in the same way as small molecular
weight drugs. The new generation of drugs now available are typically large molec-
ular weight proteins constructed within biological systems such as yeast or *E. coli*
cells and the proteins need to be folded in certain critical ways to be biologically
active. In addition, their properties are affected by the additional attachments of
sugars and other moieties that control their solubility, stability, and availability. These
syntheses are quite different from the relatively simple small chemical entities and
will certainly be more difficult to replicate. There is also the problem of available
facilities for making these drugs, such as the fermentation plants required to grow
the biological cells. There is currently a shortage worldwide of fermentation capacity
and this will also inhibit generic competition.

There are other issues associated with the generic industry that require resolution.
The pharmaceutical industry at present consists of two main components: originators
and generic copyists. Originators discover a drug entity, patent it, develop methods
of analysis and delivery, and carry out clinical and toxicological tests before devel-
oping a marketplace. On the other hand, once the patents have expired competitors
are able to do an end-run around much of this testing and research, enabling them
to put the drug on the market more cheaply. This is in principle; in fact it is noticeable
that many of the generic prices are only slightly less than those of the originator.
It is the patent system which encourages this competition but there have been instances where the technology has been pirated before the patent(s) expire. Since originators may have to spend up to a billion dollars before a new chemical entity enters the marketplace, it is not surprising that the entry price is high since, commercially, this investment has to be recovered. Depending on the length of the remaining patent life this investment has to be recovered before competition appears on the market place, after which, in principle, market forces take over to drive the price down.

This whole issue has become a political discussion point, and in countries like Canada there is legislation to ensure that the final price is more acceptable to the consumer. This may happen in the United States but at present there is no clear answer to the problem, especially if insurance or government agencies will not carry the cost.

Returning to biologics, it seems that the technology is so specialized that any intervention by generic drug manufacturers when the patent(s) expire is unlikely to significantly reduce the cost to the consumer, and it may well be much less than that anticipated by some journalists.

**ALTERNATIVES TO PROTEIN BIOLOGICS**

It should be noted that there may be alternative drugs to those biological materials produced by gene manipulation and expression. This will be especially relevant if the high cost of bioengineered compounds becomes unacceptable to society as a whole. The point is that proteins may have unique biological activities that can be mimicked in some cases by small molecular weight compounds, in other words, conventional drugs. At present there are few examples of this type of activity but research has already been initiated—and, who knows, this may have a successful outcome.

**GENE ENGINEERING**

The recently discredited “biological dogma” held that specific proteins were synthesized by specific genes which involved unique DNA and RNA sequences. It is now evident that this is by no means a dogma although there is a broad basis in fact in many situations. The popular press keeps telling us that the genes responsible, ultimately, for such and such a disease have been isolated, implying that a cure will be available within the immediate future. Unfortunately, unless the protein responsible can be isolated, identified, and produced in sufficient quantity and quality to be clinically tested, this is simply not going to happen.

An alternative to the use of purified protein would be to insert the appropriate genes into the human cells, either generally or in the specific target cells, and allow the cells to function naturally. This approach has been tried clinically in a number of diseases but not with any conspicuous success. Part of the problem here is how to insert the gene into the appropriate cell, as discussed earlier. Some viruses capable of entering cellular structures and empty viruses, containing the gene, have been
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tested *in vitro* and *in vivo* as well as clinically. Although the possible advantages of this approach to the treatment of some diseases have been evident for over 30 years, making the approach practical and realistic has proved somewhat elusive.

As an example, at least one of the trials was criticized after a volunteer died following poor clinical practices. In another trial three patients were successfully treated for an x-linked severe combined immunodeficiency disease but 2 years after the treatment two of the patients developed T-cell acute lymphoblast leukemia. The FDA promptly placed a ban on any further similar clinical studies.

Part of this difficulty may have been caused by insertional mutagenesis at or near the cancer-promoting LMO-2 gene, resulting in an aberrant production of the LMO-2 protein. At the time the research was initiated it was considered that the chance of a viral vector inserting itself into a gene was very small but, with hindsight, it seems that the chances are actually quite high. Much of the human DNA has no known function and for a long time this so-called junk DNA was not considered to be important other than as packaging material between active centers. This viewpoint may be incorrect. Recently a retrovirus has been found to hit a gene 34% of the time, a much higher rate than would be anticipated if the process were entirely random. Since this virus had a striking preference for the initial sequences of a gene associated with turning genes on or off, the risk associated with the use of retroviruses as gene delivery systems is obviously much higher than originally thought.

Nonviral delivery systems such as positively charged liposomes are being explored but the use of viral systems requires careful consideration. There may be other viruses that could be used as safer drug delivery systems. Adenoviruses might be among this group but, in any case, they do not allow the corrective gene to be permanently incorporated into the cell and the treatment would have to be repeated at intervals.

Gene therapy using viral carriers would appear to be at a crossroad at the present time, although other options for gene delivery to cells require exploration and evaluation. The optimism of a generation ago is being replaced by cautious exploration.

**CONCLUSIONS**

Although the overall theme of this chapter may seem to be pessimistic, one would not wish to close on a negative note. On the contrary, the whole of the scientific endeavor identified as pharmaceutical biotechnology must be regarded with considerable optimism and pride, both for past achievements and for future prospects. The intention, however, is to serve as a warning that we cannot proceed too quickly and caution must always be in mind. Serious and fatal errors have been made that could affect the future of the industry as a whole. Realistically it is unlikely that failure and disappointment will be avoided in the future but these can minimized if everyone involved has a clear vision of the advantages for the future of mankind. There are so many prospects for the successful treatment of disease that we cannot give up at this stage, no matter what the issues are today.
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REFERENCES