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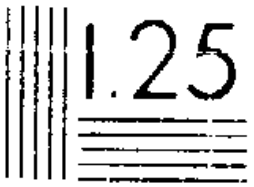
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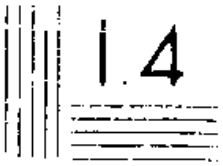
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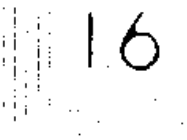
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COMMERCIALIZATION OF GENETIC ENGINEERING TECHNOLOGY*

prepared by

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Introduction

Since gene-splicing techniques were first elucidated in the early 1970's, there has been much talk of the infinity of ways in which the practical applications of the findings of the research laboratory would revolutionize human society. Perhaps because the ability to mix genes in ways new to evolution had created worries over genetic accidents, the promises of the wondrous things to come were made with a fervor that reflected the desire of much of the scientific community to gain public acceptance of the use of its new tools. Genetic engineering was to provide an abundance of scarce biological materials needed in medicine, such as human insulin and hormones. The rare protrein interferon, touted in the late 1970's as a possible wonder drug for the cure of cancer, could be made in abundance. Safe vaccines would be made easily by simply producing large quantities of the viral or bacterial antigens necessary to produce an immune response. Crop plants were to be engineered to fix their own nitrogen from the atmosphere. And genetically engineered bacteria or the enzymes they produced would transform the chemical industry, providing cheap fuels by fermentation of bulk plant material, and by replacing many energy intensive, polluting processes with simple, cheap biological steps. It all sounded wonderful -- and deceptively simple.

Now, ten years into what some have termed the biological revolution, how accurate were these predictions? How many have come true?

And how many new and even more spectacular developments have come along since recombinant DNA which could have immediate practical applications? When the prophets first gazed into the crystal ball of biotechnology, did they forsee how long the road was to be from the laboratory cloning of the gene for a desired protein, and the operation of an efficient, economical process for making large quantities of a highly purified substance, one which met all of the regulatory requirements for safety and efficacy? And did they have any idea of what it would cost? What, then, is the current status of the biotechnology industry today? Has it lived up to its expectations?

The Commercialization of Biotechnology

Nothing is ever as easy as it looks. Establishing an effective industry based on biotechnology contained very many hidden traps and unanticipated difficulties. The learning process is, in fact, still taking place, as the biotechnology industry, far from mature, struggles through its adolescence.

First of all, even though most of the world's basic research is supported by national governments, the world of industry and technology is largely a private affair. That is, international commerce, overall, is dominated by private investment and development. Industries are created to fill a demonstrated or anticipated demand for a product or services which, in most cases, is expected to bring a profit to its backers. Of course, many industries and many countries are state owned. Nevertheless, they must still play according to the

rules of international commerce; they must be efficient, they must meet the demand effectively and, if possible, they must show a profit. Governments do attempt to regulate commerce in a number of ways: taxation or relief form taxation, trade tariffs and duties, subsidies and loans to the industries they wish to promote, and the regulation of the quality of the products themselves. However, whatever particular form commercialization takes, it is still governed by basic economic principles.

Unlike many nascent industries, the biotechnology industry was begun by a number of scientists turned entrepreneurs. They shared the dream of the potential that could be realized by the judicious application of genetic manipulation techniques to produce products which people needed and would pay for. But, most really didn't have the faintest idea of how to set up an industry. They knew it would take money, but didn't really have any idea how much. In the early days, they couldn't expect much from governments, so it was a matter of convincing investors that there was money to be made in biology. Even by 1975, this was not a particularly easy package to sell.

But some investors could be found. The San Francisco area, with several of the leading universities in molecular biology, was one of the first where capital was raised to pursue the new biology. Boston was another. Then it began to catch on and spread around the world. The first companies in their early days were, however, a far cry from what could be called an industry. The scientist-entrepreneurs bought old warehouses and converted them into laboratories. They then hired some scientists, who generally continued doing what they had been doing in the university laboratories from whence they came. But they

were to focus their minds on practical applications.

In the beginning, there was not much attention paid to what commercial development really meant, nor did those in the fledgling industry really understand what it meant to manufacture something, where the yield of product, its purity, the efficiency and costs of the process, and quality control must be taken into account. It is curious that the companies one expected to be the leaders in biotechnology -- the pharmaceutical and chemical companies, all with plenty of experience in large scale fermentation, manufacturing, cost engineering and regulatory affairs -- were slow to exploit the potential of genetic engineering. Perhaps this illustrates a principle in commerce, that the mature, more stable industries are not the innovators. It seems to require new investors and new entrepreneurs to launch a new branch of technology, even though the larger and wealthier companies may eventually enter and dominate the industry.

Eventually, the scientists of the new companies had achieved the expression of some useful proteins in their bacterial cloning vehicles. Then it was necessary to pay attention to the problems of increasing the scale of production from a few liters to several thousand liters. It was here that the transition from science to engineering was most abrupt. Bioengineers were nearly nonexistent in the late 1970's. The current demand has resulted in a number of new training programs initiated in universities in the past two years.

At this stage, it was necessary to face a fact that had been ignored in the earlier years. It was largely a myth that the new biotechnology would be much less capital intensive than the industries it would compete with and replace. The fact is that to build a large

scale fermentation and production facility requires a great deal of money. By 1980, there were already more than a hundred independent biotechnology companies, most of them quite small, and most of them in the United States. In order to survive, most sought cooperative research and development arrangements with large companies. It was largely the funding provided by the larger corporate partners that enabled the small biotechnology companies to begin the transition from institutes of applied research to something resembling a complete industrial establishment. But that was not enough.

Contrary to the expectations of many of the early and some of the present dreamers, biotechnology means far more than scientists in a research laboratory able to isolate the gene for a desired human protein, and clone and express it in a suitable host bacteria. It also means being able to produce that product economically and in quantity. When these problems were finally confronted, it soon became clear that the large scale production of a genetically engineereed product was not necessarily easier or cheaper to produce than getting it the old way. In some cases it was more expensive.

Thus an important aspect of commercialization is to select very carefully all of the elements in the production scheme and then engineer them for the highest efficiency. That is, one's ideal biotechnology enterprise must commit a major part of its resources to such matters as yield and the ease of purification of the desired products. This may entail not only the cloning and expressing of the desired gene, but additional genetic manipulations of the cloning vehicle to enhance production of the desired protein while suppressing the synthesis of unneeded ones. That is, one must engineer the

control of gene expression as well as the synthesis of the gene product itself. Most of the existing biotechnology companies are now struggling through this stage with the few substances deemed worthy of production. But this is still not all. Even if you are now able to manufacture a novel, and presumably much wanted product of genetic engineering, you are still faced with many tasks before it becomes available to the potential consumers.

Thus we now come to the real driving force underlying the commercial biotechnology industry: profit. There is no doubt that the scientists who first sought to create practical benefits from the novel findings of molecular biology were diriven by a great deal of idealism. But for those investing the millions to make the enterprise possible at all, and this includes most of those who sit on the boards of directors of the independent biotechnology companies, the over-riding motive is to make money. Thus, before proceeding to even develop a process for making a product, a number of very important questions must be answered.

First of all, who are the consumers? And what are they willing to pay for your product? Who else is trying to make and sell competitive products? How do you know the product will work as you hope it will, especially before you have subjected it to years of trials? In the case of human pharmaceuticals, the testing for safety and efficacy, a process requiring many years, can only take place after the investment has been made to actually produce the substance. Both the development of the manufacturing process and the animal and human trials are far more costly than the research which identified the product in the first place. This principle is as true for

genetically engineered substances as it is for the products of organic chemistry.

If, like most of the new pharmaceutical agents coming out of the biotechnology industry, they have never been available before, then there will be little or no market data upon which to base your decisions of how much to produce or, indeed, whether it is worth producing at all. At present, for example, several companies are devoting much attention to the development of possible cancer therapeutics (immunotoxins, interferon, interleukein-2). The decision has been made to go ahead and develop such products long before it has been shown whether or not they will really be useful therapeutic agents purely on the assumption that the market for cancer therapeutics will increase enormously over its current size. On what is this assumption based? Actually, very little. This, then is an example of the kinds of risks being taken by some of the existing companies and their investors in the hope of striking it rich. In this case, the risk reflects somewhat the size of the expected gains.

More often, the risks are less; the product is more likely to be of known value and the market much more certain. It can never, however, be known with precision, especially in a highly competitive industry. Therefore, one must expend some effort to increase the demand for the product and the willingness to pay for it. The science of marketing, then, has as important a place in biotechnology as it does in any other industry. Potential markets must be assessed. The potential consumers must be identified and told about your product. All details are important, including the type of advertizing used, the way the product is packaged, perhaps, and above all, your success in

demonstrating why people should use it.

Obviously, in some cases, it may be a well known substance, such as motor fuel. In that case, all products on the market may be more or less equivalent. The edge will go to the company which can produce it at the lowest cost and sell it for the least. This is true for most commodity chemicals. In another case, the product may be a vaccine against a serious disease. If you can show that your vaccine is completely safe and effective, you will have a market advantage over your competitor who may not have done as thorough testing. Timing is also important. If there is a race on to develop an effective genetically engineered human hormone, the developer who first secures the best patent protection will have the advantage.

There can be other problems as well. All governments regulate commerce in some ways. In the United States, for example, the food and drug laws can impose major obstacles in the development of new products, particularly those for human use. For new pharmaceuticals, the testing period required to establish the efficacy and safety of a product averages about seven years. While a "fast track" has been instituted for certain genetically engineered products deemed to be identical to previously tested natural products, there always remains a question of whether or not they are indeed identical. A bacterially produced protein is likely to contain different impurities than one extracted from the pancreas of cows. The presence of sugars in the natural product and possible conformational differences must also be taken into account. Chemicals used in agriculture are also regulated, including pesticides, animal feed additives and animal medicines. These tend to be less stringent than for products for human internal

consumption but can, nevertheless, require years in some cases to answer questions of safety to the consumers.

There are two other types of regulations which the developers of genetically engineered products must accept. First, almost every country has a set of safety rules to be followed by those engaging in recombinant DNA activities. While these have generally been greatly relaxed over the years, as most genetically engineered bacteria and virus were deemed to be relatively harmless as human disease agents, there is now increasing concern over the deliberate release of genetically modified organisms into the environment, especially those with agricultural applications. Here, survival, at least for a limited time, is necessary. In the United States, the Environmental Protection Agency has announced plans to promulgate regulations governing such activity. At present, a voluntary system of approval for field tests is administered by the National Institutes of Health. Most countries have not yet had to face the matter of the deliberate release of genetically engineered organisms into the environment, but, at the rate which biotechnology is advancing world wide, they soon will.

A second area concerns regulations governing the import and export of goods. It is here where problems already exist with regard to drugs and pesticides. Substances banned for use in some countries, such as the United States, may still be manufactured there and exported to countries with less stringent environmental and health regulations. Moreover, human tests of new drugs in certain nations, especially some of the developing countries, are not required to meet the stringent ethical criteria for experiments on human subjects

imposed by most advanced countries. Thus, there are pharmaceutical companies in the United States that test drugs outside of the country in order to gain data as quickly as possible and possibly a market position in other countries, even before approval is granted at home. These issues have raised a number of far-reaching ethical questions.

To summarize, then, commercialization of genetically engineered products resembles, overall, the commercialization of conventionally produced competitive products. There are some important differences, however. The greatest is probably novelty, in that not only have many of the potential products never existed before, but the commercial potential is very difficult to assess. In an industry which is not nearly as well capitalized at the more mature industries, and thus can less well afford to take major risks, commercialization of many types of novel products is inherently risky. A second important difference is that the manufacturing processes for many biological substances must be individually tailored, case by case. This is certainly true to a large extent in some aspects of the chemical and pharmaceutical industries, but in biotechnology, where complex living organisms are the actual means of production, it is rare to be able to use the same process in more than a few specific cases.

The following elements must be taken into account in the commercialization of any new product or process in the biotechnology industry, more or less in the order listed. A decision should be made at each step to go on to the next. The more a commercial strategy deviates from this scheme, or less able one is to resolve each step definitively, the greater the risk of commercialization:

* The basic research to demonstrate feasibility.

* Filing of patents.

* An assessment of the market potential of the product.

* A cost analysis of producing the product.

* The development of a laboratory scale process of optimum efficiency.

* The filing of more patents.

* The scale-up of the process for manufacturing.

* The actual manufacturing of the product.

* Testing for efficacy and safety.

In-vitro tests Animal tests Trials in humans	OR	In-vitro tests greenhouse tests field trials

* Approval for use by appropriate regulatory agencies.

* Promotion and advertizing.

* Distribution and sales.

Most discussions of proposals for establishing biotechnology programs, especially those coming from scientists in basic research with little industrial experience, have focused on the first and to some extent, the second of the above list. This was the perspective from which the first companies were founded. But it is the remainder of the list which takes by far the most expense and the most time. It is no wonder, then, that biotechnology, <u>as an industry</u>, has progressed somewhat slower than its investors' original expectations. The importance of each of the additional steps had to be learned, one by one, the hard way, just as a child first learns to sit, then to crawl and finally to walk. Yet the same errors are being committed by many

even now, particularly in developing countries with little first-hand knowledge of what establishing an effective biotechnology industry really entails. So the myth that biotechnology is far less capital intensive than conventional industry still prevails in some quarters, as does the notion that one can go from lab to consumer in short time.

Biotechnology is based upon novel techniques which allow for the invention of solutions to many practical problems through the judicious application of biological knowledge. But the principals according to which an industry must operate in the world of international commerce are not novel. The length of time it has apparently taken to build a successful biotechnology industry only reflects the time it takes to consumate the marriage betweeen science and business. Each has had to learn the language and the ways of the other before they could begin to understand how to make it work. They are, in fact still learning.

The Current Biotechnology Industry

A successful biotechnology industry would have to be considered one which can competently carry out each of the elements necessary for commericalization listed above. If we look at the status of present day industry, we see a rather mixed picture. In general, it is still a struggling industry learning how to cope with each of the requirements for successful commercialization and trying to find organizational structures in which both creative science and commercial activities can flourish. The newer, independent companies began with their focus on science and have had a much more difficult time

learning how to make and sell products. The mature pharmaceutical and chemical industry, on the other hand, was at ease with most of the latter stages of commercialization, but the new kind of science, involving the manipulation of genes, was foreign territory. What has been happening over the past eight or so years has been a gradual convergence. The independents, more by muddling through than by careful planning, are learning how to commercialize their products. The big, conservative corporations are learning the value of creative new science.

There are now, throughout the world, more than two hundred independent companies devoted exclusively to some aspect of biotechnology and many more of the larger and older enterprises that have begun their own programs or have invested in the independents. One could not say, however, that there has been successful commercialization of biotechnology in very many instances. There has not been enough time; the industry is simply too young. That is, it is still eating up capital far faster than it is producing it. There are very few products that have reached the marketplace -- human insulin, some animal vaccines, a number of tests based on monoclonal antibodies. But these are few in number in comparison to the level of activity. A great many more products are under development, but many of these are of unproven value. Because of the pressure to make money for the investors, there has been a rush to produce and test a number of products (in the traditional fashion of the pharmaceutical industry) before their mode of action or their biological function was understood. The interferon bandwagon is a case in point. No one is sure if interferon administered as a therapaeutic agent will be of any

value in treating cancer. At best, it may be useful only in conjunction with other chemotheraputics. But because of limited capital and pressure from investors, it is now an industry where risks are being taken.

To be sure, some companies will succeed better than others. The attrition has, in fact already begun. Several companies have declared bankruptcy; others have curtailed the scope of their activities in order to concentrate more effectively on only a few areas. Many believe that the number of companies in existence now is much higher than that which can survive. It terms of the total markets sought and the competition for them, it is a matter of simple arithmetic. As companies get into trouble, they become prone to acquisition by larger companies. That is what is expected to happen to many of the smaller, late entries into biotechnology. In order to survive to become a successful commercial entity, an organization must have all of the following attributes:

* Access to truly novel new ideas with commercial potential.
* Strong patent positions.
* Sufficient capitalization and assets to survive a lengthy development and testing period before income from sales is realized.
* Effective management.
* Sound judgment in assessing market potential of products.
* Good luck.

A company which is weak in any one of the above areas probably will not survive. The last item is included because it is impossible to know with certainty which choices to make in formulating a business strategy.

The World Biotechnology Industry, Present and Future

The foregoing discussion should not be construed as negative or pessimistic. It is only realistic. The establishment of biotechnology as a thriving enterprise has been or is being no more painful or difficult than the development of other areas of technology. It is only that biotechnology, and genetic engineering in particular, have been presented in their most glamorous, optimistic terms. This was partly a defensive reaction in order to gain acceptance by the public and and their representatives in government, who weren't sure what it was all about, and to attract investors. Now the glint has faded, but only to put biotechnology in a more realistic perspective than it had been. Overall, it is a healthy industry and will succeed, although its growing pains are far from over.

The single most difficult obstacle in the industry overall has been and will probably continue to be the availability of capital, especially for new ventures in areas of biotechnology for which the market return is uncertain, no matrar how exciting the science may This is also the major difficulty in countries, developed or developing, which are trying to enter the biotechnology industry.

Most of the early investment in the biotechnology entrepreneurs was in the United States. There still seems to be risk capital for new business ventures provided a profitable outcome can be identified in the forseeable future. Even in America, however, it is not that easy. The established companies have a definite advantage over any starting out. But even these companies have problems. One of the most serious is perhaps that it is viewed as somewhat sinful for a

company to lose money, even during the period of intense capital investment when new products are still in the research and development stage. This does not always allow the breathing space to the scientists and engineers that is necessary to develop the process or product to their satisfaction.

While independent entrepreneurism has been the model followed in the United States, this was much less the case in Europe and Japan, both of which now are building thriving biotechnology industries. Probably more for cultural than any other reasons, an independent biotechnology industry did not arise spontaneously in Europe, outside of a handful of companies, such as Biogen in Switzerland. When the industry began to attract world wide attention around 1980, there was definitely a biotechnology gap between the United States and Western Europe. This distrurbed the governments of a number of countries, who then decided that in order to ensure their country's competitive position in this new area, a national biotechnology policy was in order and that the government would have to provide initial financial support. This, then, is how the industry arose in Great Britain, France and in Japan, among others. In most of the industrialized world outside of the United States, most activity in biotechnology has come from existing large corporations, rather than from new independents.

At present, the commercial industry is truly international. Many cooperative agreements, partnerships and contracts have been concluded among companies in all countries, without regard to national competition. To the industry, business is business, and that far outweighs any consideration of whether one's partner is in the same or a

different country. In the United States, for example, One hears much of the Japanese threat to the American biotechnology industry, as it was in automobiles and electronics. But this is heard far more among politicians than in the biotechnology industry itself, which has numerous business arrangements with the Japanese.

Biotechnology in Developing Countries

The chief problems of many developing countries -- hunger, poverty, tropical diseases -- are ideal targets for the tools of biotechnology. Ironically, again for purely financial reasons, the attention of the world industry is being focused on the markets and demands of advanced countries. That is where the money is. There is little interest among commercial concerns to address the problems unique to developing countries. They simply can't pay enough.

What, then, can the developing countries do to build capabilities in biotechnology? What can concerned parties in the industrialized nations do to assist them? Clearly, in a world commerce governed by investment and profit, the initiative will not come from the investment of private capital. A number of possible mechanisms are now being explored.

The UNIDO effort to establish the International Centre for Genetic Engineering and Biotechnology has been underway now for nearly three years. This is an attempt to build a world class research, development and training center to foster the establishment of a biotechnology industry in devoping countries. However, In dealing through national governments, this exercise has become entangled in

third-world politics, and some fear that the criteria of excellence which must be satisfied in order to best serve the needs of the developing countries may be overshadowed by competing national prides. Mr. Kamel will discuss this effort in more detail later in this conference.

Other models are also being explored. In September of this year, a biotechnology network, led by France and Great Britain, was organized to promote biotechnology activities in both developing and developed countries, including training students and scientists from developing countries. A proposed U.S.- Latin American Biotechnology Center, involving cooperative programs among universities and industry, is currently being explored at the University of California. The possibility of forming privately funded non-profit international research and development institutions, which could enter into bilateral agrements with developing countries is also being discussed in several quarters.

Whatever model is chosen, the successful establishment of a self-sustaining biotechnology industry in developing countries is absolutely dependent upon a serious commitment by the governments of those countries. Ample funding must be provided, not only to the new industries themselves, but to the universities which provide the essential resources for basic research and the training of scientists and engineers. There are no quick and easy solutions. Developing countries must not be misled into believing that the fairy godmother of an international centre, or the foreign aid program of a wealthy country will solve their pressing problems through biotechnology overnight. It will take a lot of money and years of hard work.

Future Directions in Biotechnology

Up to this point, I have dealt with the practical matters of commercializing biotechnology and the status of the world industry. I would like to close this presentation by discussing briefly the technology itself and where it is heading.

Most of the industry to date has be engaged in what now may be viewed as the most primitive applications of biotechnology. That is, the first applications of gene splicing were to clone and express the gene for a known protein of known utility in a bacterial host, in order to simplify the production of that product. Insulin, for example, obtained from animal sources, is quite adequate for the treatment of most diabetics. But the process is expensive and requires the processing of large quanties of material from slaughter-houses. To synthesize human insulin in bacterial factories was an appealing idea, and it has been done, although not at the economic gains originally imagined.

But when it comes to very rare biological materials, there is a considerable advantage to genetic engineering. Peptide hormones and immune modulators are very difficult to obtain in quantity by other means. Even if all of the substances isolated do not have commercial potential, the techniques have enabled investigations which could not have taken place otherwise.

These applications are, however, barely utilizing the vast potential of the techniques now available. One area of exploration which is now beginning to receive attention is the construction of substances which never existed as such in nature, by piecing together

parts of useful molecules to obtain a product with a novel function. For example, immunotoxins, in which a monoclonal antibody is linked to a portion of a biological toxin molecule, are being investigated as anti-cancer agents which seek out and destroy only cancer cells, leaving normal cells untouched.

The creation of genetically modified organisms with unique properties is definitely one of the ways of the future. In agriculture, it is the living organism itself which is the product. Genetically engineering pest resistance, stress tolerance, higher nutritional value and higher yields of the edible portions can be expected to receive much attention, although the success of such applications will require a number of years. But genetically modified bacteria, added to agricultural soils to stimulate the growth of existing crop varieties, can be expected much sooner.

Perhaps the ultimate expression of the new techniques in genetic manipulation and molecular systhesis might be termed molecular engineering. We now have the means to synthesize the gene coding for any desired amino acid sequence. Cloning methods make it possible to make any quantity of that protein. The difficulty is that we don't know what to make.

There is growing interest in research to develop computer modeling methods to predict the conformation and biological or enzymatic function of given polypeptides. Conversely, one would also need to know what polypeptide sequence would yield a particular conformation or biological function. When these techniques are perfected, it will be possible to design and build proteins with virtually any desired set of properties such as new enzymatic functions or binding proper-

ties. The potential for application of molecular engineering methods are endless. This is clearly the way of the future.

So you see, we are just beginning.