

Institute for Alternative Futures
Foresight Seminars on Health and Innovation

SUMMARY

FORESIGHT SEMINAR ON
BIOTECHNOLOGY AND THE REGULATION OF PHARMACEUTICALS
MARCH 18, 1987

ABSTRACT

The Biotechnology Revolution has already spawned new types of pharmaceutical products that provide a host of opportunities for companies and offer major challenges to federal regulators. We are now on the threshold of even greater changes because present techniques promise to unleash new product streams.

It is difficult to predict the future on the basis of the current market. There are only seven biotechnology products on the market today, but there are hundreds of compounds, devices, and technologies already in the pipeline. By the year 2000, biotechnology products of all kinds are expected to be worth \$60 billion in the marketplace. Of these, \$9.5 billion will be pharmaceutical preparations and another \$8.5 billion will be diagnostic products.

Biotechnology will be used in a variety of ways - to produce proteins that have therapeutic applications, to understand biological processes that create diseases, and to design appropriate interventions. These techniques can lead to new approaches in disciplines such as immunology, neurochemistry and neurobiology. The recombinant techniques are dramatically increasing opportunities to develop vaccines. Biotechnology promises to increase the specificity of conventional pharmaceuticals as well as to permit us to use the body's own molecules (the so-called endogenous media) as drugs.

The ability to use the body's molecules for drugs is based on alterations at the molecular level, and regulators will require increased sophistication to evaluate the effects of products at the level of the smallest particles. This leads to the key issue: how do we evaluate safety? There are great opportunities for using biopharmaceutical products. But in many instances, we do not know about appropriate doses of material, and are forced to administer many molecules through inappropriate routes--with the risk of exposing cell types that do not generally interact with the new molecule in the body. This interaction carries the risk of toxicity. Nor do we have adequate scientific methods to know what constitutes safety and efficacy of products designed for individual patients. In the longer term, we must also consider the question of unregulated cell responses, particularly with interventions that deal with the immune system.

To address the challenges posed by biotechnology, it is imperative for the FDA to maintain state-of-the-art programs and staff with expertise for dealing with the latest discoveries and with potential problems. The agency must be flexible during the early phases of experimental work when there are no tried and true methods for dealing with

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regulatory problems. There must be a continuing commitment to building resources at all levels and support for ongoing scientific training to effectively deal with progress in molecular biology.

BACKGROUND

Dr. Samuel Ackerman, Vice President for Medical and Regulatory Affairs with the Xoma Corporation, began the seminar with a discussion of the regulatory process and the potential challenges from biotechnology. Dr. Ralph Christoffersen, Vice President for Biotechnology and Basic Research Support for the Upjohn Company, described the new product streams anticipated from biotechnology. Dr. George Poste, Vice President and Director of R&D with SmithKline and French Laboratories Corporation, discussed the future challenges facing the regulators of biotechnology.

DR. SAMUEL ACKERMAN

The FDA has a long history of evaluating the safety and effectiveness of new products. The Office of Biologics and the Office of Drugs in the FDA's Center for Drugs and Biologics regulate the new biotechnology pharmaceuticals that are intended for human use. Innovation itself is not a problem for the FDA regulators. They have developed scientific and regulatory expertise over years of assessing such traditional products as viral and bacterial vaccines and such blood products as immunoglobulins. In fact, the Biologics Office was originally a part of the National Institutes of Health, and its regulators are bench scientists. These regulators have the background and training to deal with the new bacterial-derived recombinant products, recombinants from mammalian cells, and monoclonal antibodies.

The biotechnology products are evaluated under the FDA's investigational new drug (IND) process, which is similar to the FDA's basic drug approval system. Under this approach, a new product is assigned to a specific review division. During the next 30 days, the agency reviews the pre-clinical data to determine the appropriateness of beginning clinical studies. Once studies have begun, there is ample opportunity for the sponsor and the agency to address the design of the studies and any safety issues that may develop. Products are approved after the sponsor satisfactorily demonstrates the safety and efficacy of the product--usually through statistical proofs and the recommendations of FDA advisory committees and outside experts.

After completing the IND process, the approved product must undergo clinical testing in the three major phases of the New Drug Approval (NDA) process. Phase one is devoted to basic studies of drug disposition and tolerance; phase two is for limited efficacy testing, and phase three is for more advanced safety and efficacy trials, generally based on well controlled studies. After approval, the product is available for commercial distribution.

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The FDA's experience will not entirely eliminate difficulties: there are always problems in the early phases of regulating any new product. Many of the young companies producing biotechnology products are new to the pharmaceutical industry and have little experience with federal regulation. The Office of Biologics has been able to proceed with the speed required by the new market only by relying on sound scientific principles and by employing state-of-the-art programs and staff. Biotechnology companies must be able to count on this expertise when they come to the regulatory agency with the latest round of discoveries and problems.

What are some of the specific regulatory problems associated with the newer products?

The problem of determining human specificity (of, for example, recombinant immunomodulators and monoclonal antibodies) is complicating the safety and efficacy evaluations of new products. To facilitate the evaluation at biotechnology product safety, the FOA is categorizing the potential contaminants of new products, particularly DNA contaminants in recombinant products and DNA and viral contaminants in monoclonal products.

The FDA finds it difficult to obtain evidence of pre-clinical efficacy from animal models. The agency recognizes the problem and insists on the use of relevant animal models but only to the extent that such models are likely to produce real and helpful information on human use.

Product novelty is an important issue. The FDA has used peer scientific review of product safety and emphasized the critical need for staff with adequate scientific expertise to assess the newest developments. The FDA has remained flexible in its approach to keep pace with the rapid rate of discovery in biotechnology.

DR. RALPH CHRISTOFFERSEN

It is difficult to predict future biotechnology product streams on the basis of the small number of products currently on the market. Our estimates are based upon our understanding of the future potential of products already marketed and those still in the pipeline. In the United States today, seven approved products can be traced specifically and directly to biotechnologies. These are humulin (recombinant human insulin), two human growth hormone products, two alpha interferon products, a hepatitis B vaccine, and OKT3, a monoclonal of interest for use against graft rejection.

Wall Street--if that is any measure of public expectation--has great hopes for the future in terms of new products and their market value. According to one report, by the year 2000, biotechnology products of all kinds are expected to be worth \$60 billion in the marketplace, of which \$Y.5 billion will be pharmaceutical preparations and another \$8.5 billion will be diagnostic.

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This prediction is supported by the number and variety of products already in the pipeline. There are literally hundreds of compounds, devices, and technologies that reflect the use of biotechnology. A recent bioindustry fact book listed five different classifications of drugs currently under development: in the area of human therapeutics, 114 companies worldwide are working on 53 types of immune modifiers, 20 anti-cancer agents, 40 blood proteins or enzymes, 54 hormones, 23 vaccines, nine anti-infectives, and six other types of products. The grand total: no less than 20b human therapeutic products under development. These potential new products will create major challenges for the regulatory and approval processes because, ultimately, the market will contain not seven but hundreds of new biotechnology-derived products.

To understand the future of biotechnology, we should look at the areas and therapies now being developed. Proteins constitute one of the most significant areas of exploration. Many of the new biotechnology companies are based on the relatively simple idea that genes can be cloned and expressed in some appropriate system to make proteins that will serve as therapeutic agents. One excellent example of this approach is Genentech's development of the tissue plasminogen activator molecule, tPA. TPA is an exquisite molecule that ordinarily promotes circulation in the bloodstream and has the important secondary role of dissolving blood clots. When the molecule discovers a blood clot, it binds to the fibrin in the clot and initiates a series of steps that produce dissolution. Before the advent of biotechnology, this protein was inaccessible to us--even for study. When modern science permitted us to clone and express genes and purify proteins, we (in this case Genentech) learned to clone the gene for tPA and to express it in amounts sufficient for use in clinical studies.

A significant number of proteins will be produced through genetic engineering to serve as human therapeutic agents, but this approach--despite the preoccupations of the press with protein synthesis--will represent only one of many future uses of biotechnology.

A second stream of products will help us understand and intervene in the disease process--allowing us to examine the details and the mechanisms of the biochemical interactions that produce pathology and to determine ways to alter disease processes. This group of technologies--which will be seen in small molecules as well as proteins--will have a far greater impact than the first stream, the cloning of human therapeutic agents.

One current example of this approach is the study of the molecule called human renin, which is thought to be responsible for raising blood pressure. The question under study is how to intervene against the activity of renin in humans. To answer the question, biotechnology techniques will be used to clone the gene for renin, to express it, and to have enough protein to study the ways to inhibit the action of the protein in the body. In this case, the protein is not the product, but the problem. The product will be a small molecule designed to inhibit the activities of renin that raise blood pressure.

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Another technology sure to affect the future is the sequencing of the human genome-- which should help us to detect specific genetic diseases. There are also major developments in other fields outside biotechnology that depend on the use of biotechnology. In the field of immunology, OKB, is a monoclonal antibody already on the market that is of interest for use against graft rejection. Monoclonal antibodies are also being used as diagnostic tools to help us understand the structure of antibodies, how to make them, and how to control them. This ability is leading us to new insights about ways to intervene in diseases that we know are immunologically based.

We will see similar applications in the fields of neurobiology and neurochemistry. As we begin to isolate, characterize, and control nerve growth factors and foster nerve growth receptors, we may gain control over these processes for human therapeutic use.

Vaccines are another area in which the use of recombinant techniques can dramatically increase medical opportunities, if we can work around the legal and ethical problems that accompany these new developments. A recent example is the Merck hepatitis B vaccine that offers needed protection to health and dental professionals and other people at risk and avoids many of the problems of the live vaccine. The search for an alternative to Merck's heptavax (which is an excellent product) is due to the process of extracting the product from blood, which raises concerns about AIDS.

DR. GEORGE POSTE

There are three areas in which molecular biology (or biotechnology) provides the underpinning for future pharmaceutical developments: the use of genetic engineering techniques to improve the discovery of conventional pharmaceuticals, the use of biotechnology to produce vaccines, and the recent use of the body's own molecules (the so-called endogenous media) as aru9s. The newest biotechnology companies focus primarily on the use of endogenous media, while the large established pharmaceutical companies use all three strategies.

Molecular biology is the foundation of modern drug discovery, specifically rational drug discovery, because it permits biology to be mechanistic rather than merely descriptive. The process is one of tearing apart the body's cells to identify specific molecules against which we can define drug action. That is, biotechnology permits science to tell not only what is happening in the human body, but why. With that insight comes the rational understanding that permits us to design drugs to carry out specific tasks. It permits us to predict patient response to drugs as we come to understand the different molecular lesions that give rise to symptoms that appear to be the same. These therapeutic interventions should do well in a cost-constrained marketplace where only innovative products will be the dominant factor in market penetration.

This new ability to use the body's molecules for drugs presents major economic opportunities for companies and major regulatory challenges for federal agencies. Because

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the new developments depend upon changes at the molecular level, regulatory agencies will require a more sophisticated profile of a new product. Likewise, these agencies will be forced to evaluate the effects of new products at the level of the smallest particles.

Most of the molecules under consideration are peptides and proteins. Researchers are trying to learn to use these molecules to mimic their normal functions in the body. This requires an understanding of the way molecules act and the sites in which their activities take place. Hormones are a key area of interest. These are molecules that are produced in one site in the body, are small enough to sneak into the bloodstream, and to travel through the stream to a target cell. If we can clone this type of molecule, we have a good chance of mimicking its action on the body.

Molecules that act outside the bloodstream in the body tissues are more difficult to deliver to target areas. Even though we can produce these molecules, we are still restricted to injecting these molecules to get them into circulation; we have yet to find a way to deliver the molecules to desired sites without using the bloodstream. In the meantime, the use of inappropriate routes may cause toxic reactions and other problems.

When molecules act directly (acting on a cell type by triggering a particular function of therapeutic value), we can induce a desired cellular transformation by delivering a substance to the right place with a direct-acting molecule. But many molecules of interest do not act directly; they are part of complex, multi-mediated cascades. We are left to duplicate this complexity of interactions, trying to discover how to duplicate the relationship between each mediator.

Much remains to be learned. In some cases we know how to clone a gene in sufficient quantities and even how to inoculate the gene in a desired route. But we do not know how to make certain that the gene is preceded by a desired mediator. In such a case, the gene will not achieve the desired result in the body. This lack of knowledge means that biotechnology is still highly experimental and that many innovations (even those with which fortunes have been made) have only marginal opportunities for achieving therapeutic value. In areas such as these, media hype and inaccurate reporting create misunderstandings for the public and misapprehensions for patients. We have seen the problems in the area of cancer where premature, unwarranted claims have affected the psyches of cancer patients and their families.

This leads to the key issue: how do we evaluate safety? There are great opportunities for using biopharmaceutical products. But in many instances, we do not know about appropriate doses of material, and we are trapped in present methodologies, forced to administer many molecules through inappropriate routes--with the risk of exposing cell types that do not generally interact with the new molecule in the body. This interaction may produce the risk of toxicity.

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In the longer term, we must consider the question of unregulated cell responses, particularly with interventions that deal with the immune system. Because the immune response is based on the maintenance of a balance between "off" and "on" signals, any intervention may perturb one of those signals and lead to the risk either of immune suppression (that would enable a clone to react against the body tissues) or of allowing certain abnormal cells in the body to go out of control.

There are some very significant regulatory issues that will challenge the regulatory agencies. The challenge of environmental release and how it would affect the pharmaceutical industry, primarily in relation to waste stream management is one example. We may see regulatory practices overseas being used as a substitute for trade and tariff barriers. Technologies central to the evaluation of biotechnology pharmaceuticals may be classified by the Department of Defense as critically important technology and subject to more stringent bureaucratic address.

Ultimately, biotechnology will go full circle from our present search for ways to use proteins as genetically-engineered "drugs" to a new search for conventional pharmaceutical products that will carry out new functions. An enterprise called "domain analysis" will permit us over the next decade to use molecular scissors" to cut up the domains or zones in proteins, to analyze the active sites in the domains, and then to go back and produce low- molecular-weight mimics of proteins. This search will drive us back to conventional pharmaceutical processes for the production of the synthetic molecules.

QUESTION AND ANSWER

How will regulation handle--and what will be the costs of--such products as monoclonal antibodies that will be not just human-species-specific but individual-specific?

Ackerman responded that we do not have adequate scientific evidence to know what constitutes safety and efficacy of products designed for individual patients, and we need a lot more information before we can formulate a rational regulatory policy.

Paste agreed, but added that he believes the economics of creating individual-specific products will mean the regulatory issues will not often be faced. He believes it is inconceivable that one can contemplate custom- specific therapy.

Do the regulatory agencies have adequate scientific knowledge to assess biotechnology products? What about premature and unwarranted claims; do we need further regulation?

Ackerman said the Key to adequate regulation is a continuing commitment to building resources at all levels and support for agency flexibility and on- going scientific training. Such training must permit scientists to maintain their scientific expertise.

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Paste said there is no need for new regulations, but in some cases (such as cancer where there is so much hyperbole and premature claims based on early stages of product development), there has been a flagrant violation of the principles followed in conventional pharmaceuticals: One never goes to the investment community, the press, nor to any other body short of clinical data from fairly advanced phase III clinical studies. This practice will come back to haunt the industry at large. What we need is not new regulations but more stringent analysis of claims. The regulatory agencies should be coming down harder on some of these claims.

Christoffersen noted that the federal government is not adequately dealing with the issue of retraining personnel. The extraordinary pace of advance in this field outstrips the number of people trained, and resources have not been allocated to support the needed advances in analytical instrumentation and equipment. This lack will affect regulation in five or ten years when the number of license applications increases dramatically.

Christoffersen agreed with a statement from the floor by Henry Miller of the FDA that the pharmaceutical experience of the FDA has, for many years, dealt with biotechnology types of processes. Antibiotics and vaccines have used these techniques. The mold that produces penicillin has been genetically manipulated to increase output; and other vaccines have been genetically engineered. The introduction of biotechnologies as research tools does not replace conventional approaches to developing pharmaceutical agents. It simply adds new methods for doing the work.

Where can we look for leadership to develop answers to questions about drug delivery? Will it be profitable, and what is the history so far of this technology?

Poste commented that our work in peptides and proteins in 1987 compares to our progress in antibiotics in 1948. The technologies are just emerging for the development of these molecules in terms of scale and delivery. Delivery requires a fundamental long-term research program that is costly and perhaps beyond the imagination of a country accustomed to instant solutions. Historically, the syringe and needle is a very effective form of drug delivery, and it will continue to be important for synthetic molecules and genetically-engineered molecules, assuming they are capable of working in that manner. We must, however, devise ways of rendering these molecules stable within the blood stream, and we must find a way of removing them from the blood stream after they have been introduced. Finally, we must understand the exact sequence of molecules that work as part of the complex cascades discussed earlier. In many instances, we do not understand the exact sequence of these interactions.

What approach would you take with last year's vaccine compensation legislation, and can anything be done via regulation to contribute to the problems that discourage vaccine production?

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Poste said he would not advocate changing regulatory practice or the stringency of surveillance. He believes, however, that there is a gap in current legislation because the patient could collect compensation from the government under the vaccine injury bill and then pursue civil litigation against the physician who administered the vaccine. The physician could in turn cite the manufacturer as co-defendant.

What are the barriers to vaccine production?

Poste noted that the number of diseases for which significant vaccine opportunities exist in the West is limited except for the dramatic opportunities in veterinary medicine. We have needs for vaccines for hepatitis A and hepatitis non—A/non—B; for improvements in OPT, and polio; and needs for the sexually transmitted diseases, with chlamydia at the top of the list in numerical importance and AIDS at the top of the list in terms of scientific, social, and political pressures.

Are we losing the battle against cancer?

Ackerman said that it was unreasonable to expect that we could produce a genetically engineered organism to produce a given immunomodulator. This is only a first step. Many of the newer biotechnology products mean that we have adequate products available for studying the basic mechanisms of cancer activity, and we should focus on gaining more understanding prior to launching clinical trials. These agents will be the tools in what will be a long fight against cancer.

Poste added that the extraordinary understanding of the AIDS virus in the last 5 years derives from the fundamental support of basic research in this country since the war--and the power of molecular biology.

To date, we have deciphered less than 1 percent of the human genome. How are we going to obtain information about the rest of the sequence?

Christoffersen said that characterization of the human genome is prima facia an important project. However, it can be argued that the technologies available for sequencing the genome may be too slow and error prone. It might be better to wait some time and allow the technology to develop and research specific areas of the genome--not attack the entire genome problem because it is there.

Poste noted the joint venture between Hitachi and Fuji in Japan that combines automated DNA sequencing with thin film methodologies and robotics. They have indicated that they will be able to sequence a million base pairs a day by late 1997. They are already sequencing several hundreds of thousands of base pairs a day. Whoever cracks the design code is going to have a significant competitive advantage not only in understanding the disease but also the ability to produce drugs whether they be classical drugs or recombinant products. We will also have to deal with the very complex ethical area of

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mapping genetic predisposition to disease. Although we will be able to recommend life style changes based on a genetic profile to prevent major health problems e.g., heart attacks, we will also have to deal with some very profound issues that are going to come up faster than both the scientific and legislative communities are going to be able to handle. For example, insurance companies might use information about an individual's genetic profile to determine their predisposition to diabetes, cancer, or impending dementia