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Biotechnology Regulatory Framework for Biomedical Products: The United States Perspective*

I will discuss the biotechnology regulatory framework for biomedical products concentrating on the United States perspective. A framework for the regulation of biotechnology products is important for both the public and the industry. The United States Food and Drug Administration or the FDA has the legislative authority and regulatory responsibility for assessing the safety and effectiveness of products developed through different technology, including biotechnology. As such, the FDA plays a very important role in the regulatory framework for such products and provides a critical function as the "gatekeeper" for product commercialization.

In order to approach this topic in a manner that I believe would be the most helpful for the goals of this article, I would like to: (1) provide a brief background and historical development of the U.S. biotechnology regulatory framework; (2) discuss the role of the FDA and its regulatory policy for products of the new biotechnology; (3) describe the frontiers in biotechnology, that is, the new developments in the field and the regulatory challenges that they create; and finally (4) discuss future perspectives and the importance of international cooperation not only in research and development and technology transfer but also in development of standards and regulations building towards an international biotechnology regulatory framework. We must work toward this goal since biotechnology has produced a global industry with a global marketplace. But, whether a product is developed for use within a country or for export, certain common regulations certainly aid the industries development of future marketing options and strategies.

The pathway for U.S. regulation of the new biotechnology began at the Asilomar Conference in February of 1975 when guidelines for recombinant DNA experiments were first developed. I remember that conference vividly and the anticipation, anxiety, concern, and responsibility expressed by the organizers and participants. This was a historic conference, whose potential impact was little recognized by the organizers. Three fundamental principles emerged which shaped the U.S. federal policy in biotechnology. First, that the integrity of the scientific process must be ensured so that objective risk assessment can form the foundation of sound public policy, regulations, and scientific exploration. Second, that public participation is critical to the development of governmental policies. Third, that the analysis of safety considerations for health and the environment should be approached by consensus both in the government and in the private sector.

These principles were translated into the Asilomar guidelines and the 1976 National Institutes of Health or the NIH guidelines which had the tacit force of regulations and ushered in the contemporary regulatory era. The NIH guidelines were risk based with exemption of classes of ex-

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periments and organisms on a case-by-case basis. As new knowledge became available and the concerns about safety of this technology diminished, progressive exemptions were developed particularly with regard to laboratory research and to developments in pharmaceuticals and diagnostics.

The FDA developed a balanced approach to regulation, beginning with the conclusion reached early on, that the new biotechnology did not require new laws or regulations. New biotechnology was considered a refinement or extension of older techniques used for developing new products. The FDA concluded that while there were no statutory provisions or regulations that affected biotechnology directly, the U.S. Congress had provided the Agency with authority to regulate products regardless of how they were manufactured. Therefore, under the Federal Food, Drug and Cosmetic Act and the Public Health Service Act, FDA's regulatory review of the products developed by biotechnology was based on the intended use of each product. Evaluations were made on a case-by-case basis.

At this point, I would like to "take a walk through the Agency", to define the Agency's mission, to present an overview of its regulatory history, and then to concentrate on the important role of science in the regulatory process and the FDA regulatory framework for biotechnology products. I will not discuss specific regulations or details of the regulatory process, but rather the basic philosophy and policy that the FDA has adopted for regulation of biotechnology products. Since biotechnology has led to products in the international marketplace, this information may be helpful for the development of certain common international regulatory policies and principles which will facilitate product commercialization worldwide.

The FDA is a scientific regulatory agency in the U.S. Public Health Service whose mission is to promote and protect public health by assuring that food is safe and wholesome and that medicines and medical devices are safe and effective for their intended use. The Agency accomplishes this by exercising legislative authority in both premarket approval and postmarket surveillance of the products that it regulates. The very effective postmarket surveillance program continues to monitor the performance of approved products in the marketplace. In essence, the Agency reviews new products before they enter the marketplace, inspects manufacturing facilities, and takes corrective action to remove products from commerce when they are unsafe or ineffective.

The FDA is organized into Centers, each responsible for specific product areas and research efforts. In addition to the Centers headquartered in the Washington, D.C. metropolitan area, the National Center for Toxicological Research is located in Arkansas, and field laboratories and office components are located in specific regions throughout the U.S. These regional offices and laboratories serve a very important function. They monitor activities and potential problems throughout the country and communicate regularly with Agency components at headquarters.

The science and research programs of the FDA are the foundation upon which rests the Agency's ability to bring to the public safe and effective products. As recommended in the 1991 Report of the Advisory Committee on the FDA, "the FDA is, and increasingly must be, a scientific knowledge-based Agency in a world undergoing rapid and significant scientific and technological change." We can see this reflected in the regulatory and legislative history of the Agency. The Food and Drug Act was passed in 1906 largely based on the in-house research of Dr. Wiley, a chemist in what was then the Department of Agriculture. His research led to this legislation that prohibited the interstate commerce of misbranded and adulterated foods and drugs. Since that time, the Agency's legislative authority has expanded considerably, and it continues to update and streamline its regulatory procedures. The latest legislation is the Safe Medical Device Act of 1990 which provides for additional FDA regulatory authority for medical devices. Historically, the Agency has taken the steps necessary, in an orderly, logical fashion, to protect the public health while at the same time making certain that regulations are not overly burdensome to the industry.

To accomplish these activities, the FDA maintains up-to-date expertise in many areas of the basic sciences, engineering, epidemiology, and clinical medicine. This expertise provides the Agency with a strong institutional research capability that can quickly fulfill needs that are unique to the FDA regulatory mission. FDA's research, for example, develops rapid, accurate, sensitive, and reproducible methods that can be applied in response to public health emergencies such as the detection of contaminants in drugs, pathogens in foods, or system failure with devices. In addition, the FDA conducts applied and problem solving research necessary to assess product safety, effectiveness, and quality as well as to form the basis for science-based regulations and guidance for the industrial community.

Thus, research in FDA is unique and specialized in that it is aimed at providing information specifically related to the Agency's mission. As a result, FDA's research is performed in-house, in each of the Centers. Although the Agency uses information generated from other research efforts, its regulatory activities are based to a great extent on scientific information generated from the intramural research program.

FDA has emphasized the need for maintaining this active in-house research program, and supports facilities and programs for its scientific staff in order to maintain expertise in state-of-the-art science. Research scientists have an important role in the Agency's review functions for resolving scientific problems relative to judgements on the safety, reliability, and significance of research data to support product submissions. Sound science leads to sound regulatory decisions. Without it, consumer protection would degrade and the credibility of Agency decisions would suffer.

Usually the advent of a new technology, and biotechnology is no exception, is frequently accompanied by regulations to ensure public safety and protect the environment. In the case of biotechnology, however, I believe the Agency adopted a far-sighted view in its decision to regulate the product not the process used in its manufacture. FDA's regulatory review of all new products, including those employing specialized biotechnology methods in their manufacture, is, as I have mentioned, based on the intended use of each product on a case-by-case basis. It has been the Agency's position that there is no evidence showing that biotechnologies used to produce useful products make it necessary for the FDA to impose new or different criteria in the evaluation of such products. The procedures used for reviewing and approving conventional products are the same procedures used for biotechnology products and, no additional requirements are contemplated. The FDA is not the only body to adopt this regulatory position. A similar philosophical approach on regulating the environmental release of recombinant organisms is expressed in the U.S. National Academy of Sciences 1987 policy statement, "Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues".

The FDA has identified certain principles that are essential for a sound regulatory framework for products encompassed by the FDA evaluation system. These include:

1. A predictable review process that is readily understood by all constituencies and available through published "points to consider" documents or guidelines. Many of you are no doubt aware of the Points to Consider documents, the most recent being the one for gene and somatic cell therapy, and the guidance documents published by the Center for Devices and Radiological Health, Division of Small Manufacturers Assistance.

2. An efficient review process performed by well qualified regulatory reviewers that evaluate new products expeditiously to ensure safety and effectiveness.

3. An interactive process that can be responsive to queries about uncertainty on regulatory procedures or on scientific issues. Dialogue between FDA research and regulatory review scientists with industry and others in the outside community is encouraged.

4. A clear determination of what constitutes a "new molecule" for various discrete purposes, including patentability.

5. Development of regulations for combination products which are composed of a drug/device or biologic/device combination.

6. The availability of sufficient well-trained inspectors to ensure that appropriate control of the manufacturing process is maintained during the clinical testing phases of product development.

Of course, new technological achievements have led to the development of many products to improve public health. Nowhere is this more evident than in biotechnology whose powerful tools have created myriad biomedical products. Techniques have been applied to products for clinical diagnosis and therapy in different medical areas and FDA has approved many of these products. These include drugs, biologics, and vaccines. They range from tissue plasminogen activator, an anti-clotting agent to recombivax HB, a second generation hepatitis B vaccine. On the average, it requires seven to ten years to bring a therapeutic, a drug or biologic, to the marketplace.

Much developmental work takes place before a new drug application (NDA) is filed with the Agency. This includes in vitro and animal studies as well as limited clinical studies. From the time a NDA is filed, the approval time can vary from five to thirty months.

While a number of different therapeutics are under active development, by far the greatest application of biotechnology has been in medical devices, specifically the in vitro clinical laboratory diagnostic assays employing monoclonal antibodies and DNA probe or recombinant DNA technology. For the most part, these products are regulated as medical devices under the purview of the Center for Devices and Radiological Health (CDRH). A medical device is any health care product that does not achieve its primary, intended purposes through chemical action in or on the body or by being metabolized. They range from in vitro diagnostic assays to prostheses and heart valves. This regulatory purview presents a considerable scientific challenge to the staff of this Center. However, the active bioengineering, materials science and biophysics expertise coupled with talents in cell and molecular biology make the CDRH a strong scientific organization with the capability of assessing the safety and effectiveness of such diverse products.

The FDA has approved more than 400 biotechnology devices, drugs, and vaccines. These include over 350 monoclonal antibody and over 60 DNA probe or recombinant DNA-based diagnostic kits. More than 800 clinical trials on potential new biotechnology–based therapeutics are undergoing review. In fact, fifty percent of all the Investigational New Drug Applications (INDs) for biologics involve products made by monoclonal antibody or recombinant DNA techniques. One might say that the Agency has already experienced the early effects of the surge in biotechnology research during the 1970's and 1980's.

In the next century, biotechnology will exert a stronger influence than ever on the direction and level of product development in FDA-regulated industries. The frontiers of biotechnology continue to be explored with research and development yielding new products such as anticoagulants, colony stimulating factors, interferons, interleukins, monoclonal antibodies, growth factors, and vaccines. In addition, other exciting and evolving areas that have yielded products include gene and somatic cell therapy, biological-response modifiers, engineered tissues, new biomaterials for implants, and biosensors and new diagnostics for detection purposes.

An area of current interest to the Agency is that of combination products which I mentioned previously. The combination of epidermal growth factor and other soluble factors that mediate inflammation and wound healing processes with implanted prostheses are products under active development. In addition, a material can be coated with adhesion factors and used to create 'organiods', that is, collections of living cells that mimic some aspects of whole organs. We can also envision the coupling of diagnostics to therapeutics. Approaches for evaluating and regulating such products are currently being discussed, and the Agency should have regulations for combination products by the end of this year. Certainly, these developments will add significantly to the complexity of FDA evaluations, because they will present new products with

complex safety and efficacy questions for which there are no easy answers. Such products will also cross regulatory jurisdictions between the FDA Centers.

The in-house research expertise has contributed greatly to forecasting trends in research and development and evaluating biotechnology–derived products. The biotechnology research programs in therapeutics, vaccines, medical devices, and diagnostics will continue to provide the information necessary for such evaluation.

There is no doubt that the techniques of biotechnology will be applied to products in many areas. What are the future perspectives for biotechnology — its development and product commercialization? How do we ensure that the standards and regulations that we develop further the technology for developing products to benefit public health while at the same time do not impede industrial development and commercialization?

The FDA, recognizing its important role in product commercialization will continue to use science and scientists as the primary means for decision making with regard to the evaluation of conventional products and biotechnology–derived products. To this end, the Agency's research programs will continue to provide the information necessary for such decision making. The regulatory review of all products will continue to be based on a case–by–case basis. There are essentially three critical elements that will continue to be important in any regulatory review: the manufacturer's claim, the manufacturer's quality control procedures, and product performance.

Although scientific consideration may dictate generic concerns for certain biotechnological means to develop products, FDA will continue to use the same regulatory procedures for biotechnology products as for conventional ones.

The US Presidents's Council on Competitiveness, made up of representatives from the Federal Agencies issued a Report on National Biotechnology Policy in February of 1991. The report recommends a harmonization of regulations to eliminate many of the differences in current regulatory practices. It also recommends that additional regulatory burdens such as state and local laws or technical barriers to international free trade be removed.

In addition to this report, a Presidential "biotechnology initiative" seems highly likely for 1992. It is hoped that this special initiative will lead to substantially increased funding for biotechnology research, streamlined federal regulations where appropriate, tax incentives, and new programs aimed at greater cooperation among all groups.

US Congressional initiatives include the Congressional Office of Technology Assessment recent report "Biotechnology in a Global Economy" which was discussed earlier in this conference. This report has examined biotechnology relative to the commercial activity and industrial policy in sixteen different countries.

Another indication of increased Congressional interest in biotechnology is the recent formation of the Congressional Biotechnology Caucus which was formed to encourage the U.S. biotechnology industry and recommends broadening support for biotechnology and increasing awareness of the economic benefits of this technology.

In the international arena, the time has come to seriously address how regulations in different countries can be harmonized to ensure free trade of goods produced through the new biotechnology.

Two promising events have occurred. First, the Organization for Economic Cooperation and Development has formed a Group of National Experts on Safety in Biotechnology. A major contribution entitled "Recombinant DNA Safety Considerations" describes conditions in which organisms of negligible risk could be propagated safely under good industrial large-scale practice. More recently, a discussion document has been developed that describes Good Developmental Practices that are to be employed when planned release of organisms occurs in the environment.

Second, the European Community has focused on biotechnology as one of the major new

technologies to be reviewed centrally. It is possible that the evaluation of new biotechnology products may occur in more uniform fashion under these new procedures.

An enhanced level of commitment of the US to this field should ensure that these important issues both in the US and in other countries can be resolved, thereby enabling the commercial fruits of research in biotechnology to continue to be harvested safely and effectively.

Regulacje prawne dla biotechnologicznych produktów biomedycznych w USA

Streszczenie

W artykule przedstawiono aspekty legislacyjne w USA dotyczące produktów biotechnologicznych.

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