Biotechnology regulatory policy for biomedical products: the United States perspective

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In the next century, biotechnology will exert a stronger influence than ever on the direction and level of product development in industries regulated by the US Food and Drug Administration (FDA). The agency's philosophy with regard to the regulation of biotechnology products is that the biotechnology methods used to develop such products are extensions of refinement of older techniques. The prevailing FDA policy has been that the agency's extensive experience in reviewing the products and processes of conventional methods is relevant and adequate for reviewing new biotechnology products and no additional regulatory requirements are needed. The regulatory review of all new products, therefore, is based on the intended use of each product on a case-by-case basis. Once a sponsor submits data to establish product safety and efficacy, the FDA evaluates the biotechnology product using procedures developed for review and approval of conventional products. For example, before industry can market new drugs or biologics for human use, FDA must first approve the appropriate new drug application and product licence application. New medical devices require a premarket approval application or a reclassification petition if they are not substantially equivalent to legally marketed devices. For any substantially equivalent new device, a premarket notification is sufficient. As a science-based regulatory agency, the FDA uses science as the basis for regulatory decision-making. It relies on and conducts applied and problem-solving research necessary to assess product safety, effectiveness and quality as well as to form the basis for science-based regulation and guidance for the regulated industrial community. Since biotechnology has led to products in the international marketplace, the regulatory approach adopted by the FDA for biotechnology products may be helpful in the development of certain common international regulatory policies and principles which will facilitate not only product commercialization worldwide but also the development of cooperative research and development programmes.

Background

Within two years of the synthesis of recombinant DNA (rDNA) in 1973, the pathway for US regulation of the new biotechnology began at the Asilomar Conference in February 1975 when guidelines for recombinant DNA experiments were first developed. This was an historic conference, whose potential impact was hardly anticipated by the organizers. Three fundamental principles emerged from this conference which shaped the US 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 National Institutes of Health (NIH) guidelines of 1976 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 experiments and organisms on a case-by-case basis. As new knowledge became available and the concerns about the risk associated with this technology diminished, progressive exemptions were developed particularly with regard to laboratory research and to developments in pharmaceuticals and diagnostics.

The United States Food and Drug Administration (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

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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 US 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.

The FDA regulatory system as it has evolved is set out in the succeeding paragraphs.

The FDA—a scientific regulatory agency

The FDA is a scientific regulatory agency in the US Public Health Service. The mission of the FDA is to promote and protect public health through the methods of science. Its mandate is to protect the public health by assuring the safety of foods and the safety and effectiveness of medicines and medical devices, as assessed and evaluated by scientific principles and methods. Its authority, derived from legislation, extends to pre-market approval and post-market surveillance of all products which are covered by its mandate. The post-market surveillance programme continues to monitor the performance of products in the field (market). In essence, the agency reviews new products before they get to the market place, inspects manufacturing facilities and takes corrective action, flowing from its authority derived from legislation, to remove products from commerce when they are unsafe or ineffective. The FDA has six centres:

- Centre for Drug Evaluation and Research
- Centre for Biologic Evaluation and Research
- Centre for Devices and Radiological Health
- Centre for Food Safety and Applied Nutrition
- Centre for Veterinary Medicine
- National Centre for Toxicological Research.

Apart from performing science-based pre-market approval and post-market surveillance, the FDA conducts studies on bioeffects analysis and testing and undertakes the development of methods that support scientific evaluation of products.

The mission of the FDA is enabled and supported by research which:

- tests products
- enables scientific reviews of approvals of new products in order to assess their safety, effectiveness and quality
- identifies hazards associated with products or hazards to public health
- develops new and/or improved rapid, accurate, sensitive and reproducible tests in order to ensure the safety of products that use new technology
- develops product standards and/or enables the determination of compliance with such standards
- clarifies and elucidates the mechanisms of toxicological and pharmacological effects.

To accomplish the above activities, the FDA maintains up-to-date expertise in many areas of the basic sciences, engineering, epidemiology and clinical medicine. The expertise provides the agency with a strong institutional research capability that can quickly fulfil 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 geared to providing information specifically related to the agency's mission. Although the agency uses information generated from other research efforts, its regulatory activities are based to a great extent on scientific information generated from its own intramural research programme which supports facilities and 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 issues which arise when considering the safety and reliability of products and data, and the significance of research data supplied by manufacturers in support of product approval applications. Sound science leads to sound regulatory decisions, upon which the credibility of the decisions of the agency (and its answerability to the public) depends.

Regulatory history and policy

The science and research programmes 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 legislation that prohibited interstate commerce in misbranded and adulterated food 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 over medical devices.

The regulatory history of FDA is set out briefly in the following date-wise sequence of events.

Date	Event	Impact
1906	Food and Drug Act of 1906	Based on in-house research (Dr Wiley); prohibited interstate commerce of misbranded and adulterated foods and drugs
1927	Legislative responsibility for 1906 Act transferred from Department of Agriculture to new Food, Drug, and Insecticide Administration; renamed Food and Drug Administration (FDA) in 1934	
1937	Problems with Sulfa led to Food, Drug, and Cosmetic Act of 1938	Required pre-marketing proof of drug safety by manufacturers
	Research and technology leads to FDA amendments and new interpretations, strengthened the law and government's role in consumer protection	
1976	Medical Device Amendments to FD&C Act	Required pre-market evaluation and post-market surveillance of diverse medical devices
1982–84	Center organizational structure established	Streamlined FDA for more effective management and administration
1986–87	Regulatory initiatives	Streamlined products for FDA product approvals
1990	Safe Medical Device Act of 1990	Greater FDA authority for evaluation of medical devices

[Readers familiar with the Indian system, such as it is, will doubtless be sobered by this regulatory history in a nation often considered in India to be 'devoid of governmental controls'—Editor]

The policy of the FDA with regard to regulation of products is based on the intended end use of the product. The regulatory review is conducted on a case-by-case basis and, the burden of proof with regard to the safety and effectiveness of the product is on the manufacturer.

So far as products made by biotechnological processes are concerned, the policy is identical. 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 biotechnology products are the same as those used for conventional products. The mere fact that a product is made by a biotechnological process does not imbue the product with any additional or special risk with regard to the intended end use of such product. 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 1987 policy statement of the US National Academy of Sciences, 'Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues'.

Approved biotechnology products

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 anticlotting agent) to recombivax HB, a second-generation hepatitis B vaccine.

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 an 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 defined as any health care product that achieves its primary, intended purposes by means other than through chemical action in or on the body or by being metabolized. They range from *in vitro* diagnostic assays to prostheses and heart valves.

As of end-1991, the FDA had approved more than 600 biotechnology products. These included more than 500 monoclonal antibodies and over 60 DNA probe or rDNA-based diagnostic assays. The time taken by the FDA to approve a product has a wide spread, as the following table shows:

Product	Company	Approval date	New drug application review (months)
Humulin	Lilly (Genentech)	1982	5.3
Protropin	Genentech	1985	25.5
Intron A	Schering (Biogen)	1986	11.0
Roferon-A	Roche (Genentech)	1986	19.5
Orthoclone OKT3	Ortho	1986	27.0
Recombivax HB	Merck (Chiron)	1986	6.0
Humatrope	Lilly	1987	5.0
Activase	Genentech	1987	18.0

Product categories whose development is in the pipeline, which will come up for FDA review and some of which will pose new regulatory challenges include the following:

Anticoagulants	Vaccines
Colony stimulating factors	Gene and somatic cell therapy
Human growth hormones	Biological response modifiers
Interferons	Engineered tissues
Interleukins	Biosensors
Monoclonal antibodies	New diagnostics
Growth factors	Combination products

In the next century, biotechnology will exert a stronger influence than ever on the direction and intensity 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. 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 'organoids', 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 have been developed and the agency now has regulations for combination products. 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.

Research programmes of the FDA

The research programmes of the FDA are designed to provide the knowledge necessary for the FDA to accomplish its mission using the methods and tools of science. To this end, the FDA supports research programmes that encompass the following areas:

- Therapeutics: Elucidation of mechanisms of action for review of products. Development of assays for Product Control testing.
- Vaccines: Evaluation of immune response and identification of antigens for new vaccines. Development of methods for control testing.
- Medical devices: *In vitro* methods for assessment of mechanisms of host system–device interaction; biomaterial degradation and performance; evaluation of biosensor technology.
- Diagnostics: Method development for assay evaluation: infectious agents; cancer and other disease markers; blood-donor screening.
- Evaluation of MAb for *in vivo* diagnostic imaging.

Future perspectives

From the viewpoint of the FDA, the future development of biotechnological products will be limited only by one's imagination and by the state-of-the-art technology. The FDA is, and will continue to be, a gatekeeper for the commercialization of products which are safe and efficacious. Science and scientists will remain the primary means for making decisions regarding the evaluation of 'biotechnology products'. The regulatory regime for all products will continue to be based on case-by-case review. To this end, the agency's research programmes will continue to provide the information necessary for such decision-making. There are essentially three critical elements that will continue to be important in any regulatory review; the manufacturer's claim, his quality control procedures, and the performance of his product.

Although scientific considerations 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.

On the US national plane, the 1991 Report on National Biotechnology Policy called for harmonization of regulatory practices; removal of additional regulatory burdens; protection of process patents and increased governmental support for basic research and generic pre-competitive technologies. Pursuant to these recommendations, the Presidential Biotechnology Initiative 1992 increases funding for federal biotechnology programmes, has streamlined federal regulations, and provides tax incentives for investments in biotechnology.