SPECIAL ARTICLE

REGULATION OF SOMATIC-CELL THERAPY AND GENE THERAPY BY THE FOOD AND DRUG ADMINISTRATION

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SCIENTIFIC advances in the past decade have made the clinical testing of somatic-cell therapy and gene therapy a reality. Early trials in humans suggest that important new diagnostic and therapeutic tools are on the horizon. The objectives of this article are to examine the regulation of somatic-cell and gene therapy by the Food and Drug Administration (FDA) in the context of the agency's traditional role in the development of biologic products and to stimulate discussion in areas in which policy is still being formulated.

The technology of somatic-cell and gene therapy has moved from the bench to clinical evaluation with considerable speed. One striking aspect of current and planned clinical trials is the breadth of proposed indications. The flexibility of these new forms of technology allows the rapid tailoring of products for a variety of applications, including use as vaccines, diagnostic agents, drug-delivery systems, and treatments for malignant, infectious, and genetic diseases, as well as for organ failure. Gene therapy and somatic-cell therapy are discussed together here because of their close medical, scientific, and regulatory connection. Of 46 gene-therapy proposals reviewed by the FDA through mid-1993, 38 involved the ex vivo treatment of somatic cells with a gene-therapy vector, followed by the administration of the modified cells to the patient; only 8 involved direct administration of the vector.

SOMATIC-CELL THERAPY

The FDA defines somatic-cell therapy as the administration to humans of autologous, allogeneic, or xenogeneic living somatic cells that have been manipulated or processed to change their biologic characteristics.[1] The cellular products used in somatic-cell therapy meet the statutory definition of biologic products and are subject to regulation by the FDA under the Public Health Service Act.[2] These products also meet the definition of a drug under the Federal Food, Drug, and Cosmetic Act and are subject to applicable provisions of that law.[3]

Forms of somatic-cell therapy that are currently being studied include a wide spectrum of interventions. One approach involves expanding or activating autologous cell populations ex vivo. Clinical trials are being conducted at the National Cancer Institute to evaluate the use of tumor-infiltrating lymphocytes that have been expanded and activated ex vivo to treat patients with advanced cancers.[4] The use of activated T lymphocytes has been proposed as a new form of antiviral therapy to treat cytomegalovirus and other viral infections.[5] Ex vivo expansion of other cell types — e.g., autologous bone marrow progenitor cells — is also being attempted. A second approach to somatic-cell therapy involves the use of allogeneic or xenogeneic cells for replacement therapy. This includes the treatment of congenital or acquired diseases such as hemophilia, Parkinson's disease, and diabetes mellitus that are characterized by the deficient production of secreted factors. Rejection of the therapeutic cell population, the principal obstacle to this approach, has been overcome in animal models by the use of semipermeable barriers such as microcapsules or hollow-fiber culture systems. Many additional types of somatic-cell therapy, including partial organ regeneration or supplementation, are in the early stages of exploration.

GENE THERAPY

Gene therapy encompasses interventions that involve deliberate alteration of the genetic material of living cells to diagnose, prevent, or treat disease. The administration of cells that have undergone ex vivo genetic manipulation is considered a combination of somatic-cell therapy and gene therapy.[6] Although the majority of human gene-therapy trials to date have used this combination approach, gene-therapy products have also been administered directly to subjects to modify cells in vivo.

Current approaches to gene therapy use modified or attenuated viruses as vectors to carry the genetic material into the cell. Gene-therapy products based on viral vectors meet the statutory definition of biologic products and are subject to regulation by the FDA.[2,3] Other gene-therapy products that are under development use other delivery methods: DNA–liposome mixtures, directly administered DNA, and DNA combined with a targeted delivery system (e.g., a monoclonal antibody or cellular-receptor–targeted ligand–DNA conjugate). These products will also be regulated by the FDA.

Other gene-therapy interventions are also under clinical investigation. One application involves inserting a functional version of a missing or defective gene into a patient's cells. A number of such therapies for congenital genetic diseases are in the late preclinical

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stages of development. A clinical trial is currently evaluating the genetic treatment of severe combined immunodeficiency caused by insufficient adenosine deaminase. Preliminary results of this study, being conducted by Michael Blaese and coworkers at the National Institutes of Health, indicate that T lymphocytes transduced ex vivo with a retroviral vector containing the normal human adenosine deaminase gene have at least temporarily improved patients' immune function.[7,8] Other clinical trials are exploring the feasibility of inserting the cystic fibrosis transmembrane reporter gene by direct inoculation of patients' respiratory epithelium.

A conceptually quite different application of gene therapy involves using lymphocytes to target cytokine delivery to specific sites. Another use is to mark cells to measure their in vivo distribution and persistence.[9,10] An additional application involves creating individualized vaccines by modifying autologous cells to stimulate an effective immune response more efficiently through mechanisms such as the expression of new antigens on the cell surface, the secretion of certain cytokines, or both. This approach is being investigated to treat cancer and chronic infections such as human immunodeficiency virus (HIV) infection. A final example involves introducing a gene into tumor cells to render them susceptible to a drug.[11] Other genetic manipulations targeting diseases as disparate as atherosclerosis and hemophilia are undergoing preclinical testing.[12]

Trials currently under way are unlikely to define the ultimate role of somatic-cell and gene therapy in clinical medicine. As more is learned about the genetic control of growth and differentiation, as well as about genetic mechanisms of pathogenesis, an even broader range of approaches to the diagnosis, prevention, and treatment of disease will undoubtedly come under clinical evaluation.

Clinical Development of Biologic Products

Products that appear promising in early clinical trials of somatic-cell or gene therapy will usually enter a commercial development process with two important parallel components. The safety and efficacy of the products are tested in clinical trials of appropriate design. Concurrently, the manufacture and testing of the biologic product itself are refined to permit large-scale production and distribution of a pure material with reproducible qualities. Although the clinical aspect of this process is the focus of public attention, the product-development component is equally important.

The need for appropriate control of biologic products has been recognized since their first large-scale use in the late 19th century. Therapeutic antiserums were found to be effective in treating certain infectious diseases, but their potency and purity varied widely. In 1901, 13 children in St. Louis died of tetanus after they had been injected with diphtheria antitoxin. Their deaths were traced to tetanus contamination of the equine serum from which the antitoxin was prepared.[13] This and other less dramatic incidents led to the enactment of the Biologics Control Act of 1902 — also known as the Virus, Serum, and Toxin Act — which mandated the federal regulation of biologic products.[14] Since that time, the manufacturers of biologic products have been required to hold licenses both for the product and for all manufacturing facilities.

The control of biologic products has been progressively refined since the 1902 act was passed. Three principles are central: control of the biologic source or sources, control of the production process, and control of the bulk and final product. These principles have been successfully applied to quality control for products as diverse as human blood and vaccines against viruses, and they are also crucial to controlling the quality of products for somatic-cell and gene therapy.

Products for somatic-cell and gene therapy may be derived from a variety of biologic sources, including directly harvested autologous, allogeneic, or xenogeneic cells; cultured cell lines; genetically modified cell lines; and viral vectors. Product safety requires that such sources be well characterized, uniform, distinguishable from the sources of similar materials, and not contaminated by hazardous adventitious agents. At the time of the 1902 act, the control of biologic materials centered around microbiologic testing and animal husbandry. The importance of such controls was illustrated when foot-and-mouth disease occurred in animals used to produce smallpox vaccine.[13] Subsequently, the development of new forms of technology, beginning with the production of viral vaccines by tissue culture, generated additional scientific challenges. Viral seed-lot systems, which set the permissible number of passages from the well-characterized parent virus through vaccine production, were developed to control potential reversion to virulence by attenuated viral strains. In addition, the concept of the production-cell substrate, a defined cellular source material used to produce biologic agents, was developed. Strategies were devised to test for contaminants originating in cell substrates — for example, the simian virus 40 found in the monkey–kidney-cell cultures used to produce poliovirus vaccine. Adventitious viruses continue to be a problem in today's cell substrates. Currently, cell-banking and testing algorithms are used to evaluate the cell substrates used in the production of biologic agents such as vaccines, monoclonal antibodies, and recombinant-DNA products, as well as certain forms of somatic-cell and gene therapy.

Cells directly removed from humans may be used in somatic-cell and gene therapy and pose additional problems in preventing source-related contamination by adventitious agents. Safety issues related to the use of fresh cells first emerged with the advent of blood transfusion. Banking blood for transfusion saved countless lives during World War II, and whole blood subsequently became the first cellular material

approved as a biologic product by the FDA. However, the widespread use of a human-derived cellular product raised unique issues of quality control related to the transfusion-associated transmission of disease. Because blood could not be sterilized by filtration or other means, the development of strategies to control or prevent viral and bacterial contamination was essential. As a result, the evaluation of donor health through history taking, physical examination, and laboratory testing became central to protecting the safety of the blood supply. The recent emergence of HIV reinforces the importance of donor screening and testing procedures when human-derived biologic materials are used.

The concept of controlling the manufacturing process is the second cornerstone in ensuring the quality of biologic products. Rigorous control of the process is essential because of the difficulties inherent in assessing and controlling the consistency of biologic products. Source materials, such as cells, viruses, and blood, are often not uniform. In addition, seemingly minor changes in the conditions of cell cultures or in purification processes may significantly alter the biologic characteristics of the final product. Because of the complex nature of final products that consist of cells, microorganisms, or macromolecules, testing of final products alone cannot reliably detect, test, or control for variability. Manufacturers must therefore rely on controlled, reproducible manufacturing procedures and environments to produce a uniform product. The degree of reliance on a controlled process varies according to the nature of the product. For example, in the case of certain products containing living cells that may be prepared in single-donor, single-recipient batches, the small size of each batch and the need for timely administration of the cells impose special limitations on testing. As a consequence, control over the process and the facility has been particularly emphasized.

The third central principle of controlling biologic products involves control of the bulk and final product. Because the complete chemical characterization of biologic products is not ordinarily feasible for quality control, the testing of biologic potency receives particular emphasis. Controlling the potency of somatic-cell therapies will be particularly challenging and will probably require the development of new approaches.

As the preceding examples demonstrate, control of the production of biologic agents has had a key role in quality assurance from the earliest biologic therapeutic agents through today's scientifically complex interventions. The technical standards developed for the commercial production of somatic-cell and gene therapy will be based on these existing manufacturing and control principles.

The Approach to Regulation

The FDA is responsible for developing a regulatory framework and technical standards for products used in somatic-cell and gene therapy that apply the principles of product control discussed above. Technical requirements are less stringent in the early phases of clinical investigation and become more rigorous during later development.

The Investigational Phase

Clinical studies of investigational biologic agents are performed under an Investigational New Drug (IND) application filed with the FDA. IND applications for somatic-cell and gene therapy must contain information on product manufacturing and testing to ensure that trial subjects will not be exposed to an unreasonable and important risk of illness or injury. For example, an IND application for a gene therapy mediated by a retrovirus vector would be expected to contain detailed information on the molecular biology of the vector and insert, the production and testing of the producer cell banks, safety testing of the final viral supernatant used for transduction of the patient's cells, and any relevant safety or activity testing in animals. Specifications and required testing at each step of the production process would also be submitted.

Cells for somatic-cell therapy are distinguished from cells used for tissue transplantation for regulatory purposes, and questions about the distinction frequently arise. The extent and intent of the cell processing are one factor used in making this distinction. Ex vivo cell processing that involves expansion, selection, encapsulation, or pharmacologic treatment is viewed by the FDA as a manufacturing step that results in a product for somatic-cell therapy. Similarly, processing that alters the biologic characteristics of the cells — i.e., by inserting genetic material, inducing differentiation or activation, or causing the secretion of biologically active factors — defines the result as a product for somatic-cell therapy. However, unmodified autologous or allogeneic bone marrow cells intended for transplantation are not considered regulated products for somatic-cell therapy. Likewise, marrow purged of tumor cells or mature lymphocytes by monoclonal antibodies or drugs will not be considered products for somatic-cell therapy without further modification of the marrow, although the purging agents require FDA approval. In contrast, highly processed marrow cells, such as stem cells selected and expanded ex vivo, will be regulated as products for somatic-cell therapy. Similarly, genetically modified cells, such as transduced autologous hepatocytes, will be considered products for somatic-cell therapy. Issues concerning the regulation of tissue transplantation are under consideration by the FDA as a separate matter.

The Recombinant DNA Advisory Committee of the National Institutes of Health oversees investigational gene-therapy protocols that have received federal funding or are performed at institutions receiving federal funding. The committee and the FDA have important, complementary functions. Review by the committee ensures broad public discussion of the sci-

entific evaluation of this new technology, particularly with regard to social and ethical concerns. The FDA focuses on the development of safe and effective biologic products, from their first use in humans through their commercial distribution. Products used in protocols subject to review by the Recombinant DNA Advisory Committee must also undergo FDA review: no specific order is necessary, and the reviews may proceed simultaneously.

The Product License

Forms of somatic-cell and gene therapy that are successful in clinical trials will be produced commercially for use by qualified clinicians. Manufacturers of biologic products must hold licenses both for the products and for their manufacturing facilities. The FDA must therefore approve a sponsor's product-license application and establishment-license application for each product. Product-license applications contain detailed manufacturing information, product and labeling specifications, summaries of relevant preclinical data, and analyses of the design, conduct, and results of the clinical trials. The data are expected to demonstrate the ability to manufacture reproducibly a biologic product that provides overall benefit to patients when used in the clinic. The establishment-license application describes the manufacturer's facilities, including relevant procedures, equipment testing, and the qualifications of the personnel.

The pharmaceutical and biotechnology firms that are currently developing gene-therapy products will submit product-license applications and establishment-license applications for their products, as do producers of other biologic agents. The logistics of licensing cellular therapies will probably be more complicated because, like blood banking, cell processing may occur at local or regional facilities. For example, establishments that process and genetically modify patients' stem cells or other somatic cells might be located in or near tertiary care medical centers. Every such facility will need to be licensed by the FDA.

An Interactive Process

The FDA's Center for Biologics Evaluation and Research has worked with sponsors on hundreds of clinical research proposals for somatic-cell and gene therapy. Before IND applications are submitted, meetings between the center and sponsors planning clinical trials of new products are actively encouraged. Sponsors present the rationale for a particular approach, present preclinical data, discuss proposed trial designs, and otherwise describe their concepts and development plans. In the context of the specific product, the center's scientists describe standards for product characterization and quality control, comment on research strategies, pinpoint potential manufacturing problems, and suggest revisions in preclinical or clinical protocols.

To clarify some of the relevant issues, the Center for Biologics Evaluation and Research issued *Points to Consider in Human Somatic Cell Therapy and Gene Therapy* in 1991.[1] This document highlights many of the current scientific issues in the manufacture, testing, and clinical use of products for somatic-cell and gene therapy.

A Prudent Approach

Federal regulations provide that pharmaceutical research involving human subjects cannot begin until the FDA has determined that a clinical trial would not expose the subjects to an unreasonable and important risk of illness and injury, given the probability and magnitude of the risk and the potential benefits. This determination involves an assessment of both the product and the intended study population. For example, injecting genetically altered cells into a healthy person involves risk–benefit considerations different from those presented by studying an analogous therapy with possible antitumor properties in a patient with advanced cancer.

As the theoretical basis for somatic-cell and gene therapy has evolved, substantial concern has been voiced about its risks, both to individual patients and to the public at large, and its ethics. The public and the scientific community are well served, and the continuing development of new forms of technology is best ensured, by the independent, authoritative evaluation of risks that the FDA review process provides.

As these novel therapeutic applications are explored and knowledge about risks and benefits accumulates, the FDA's regulatory approach may well be modified. Nonetheless, early clarification of the agency's plan to apply its existing regulatory framework to products for somatic-cell and gene therapy is more prudent than waiting until the field has matured. This early discussion will facilitate product development by academic and commercial sponsors in line with FDA requirements and the demands of public health. The historical precedents for evaluating emerging forms of biologic technology are clearly established. Thoughtful and flexible science-based regulation under the statutory authorities that have evolved over the past century seems a consistent, reasonable, and prudent course.

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