Journal of Cellular Biochemistry Supplement 38:104–112 (2002)

Regulatory Issues in Cellular Therapies

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Abstract Cellular and gene therapies offer considerable promise as new treatment modalities. The Food and Drug Administration has been developing strategies to regulate these rapidly evolving fields in a manner that sustains progress and also ensures minimization of potential risks. The death of a patient on a gene therapy study highlighted a number of potential problems that have galvanized the agency to examine their strategy and to review current regulations for gene therapy. Meanwhile, a unified regulatory approach is emerging for cell-based therapies. This stratifies the level of regulation based upon the potential risk to the donor of the cells and the recipient. In this article the history and status of regulation of cellular therapy is briefly reviewed. J. Cell. Biochem. Suppl. 38: 104–112, 2002.

The excitement engendered by the promise of new cellular and gene therapies has recently been somewhat tempered by the death of a patient on a new gene therapy protocol [Carmen, 2001], and by the resulting revelation of numerous previously-unreported adverse events [American Society of Gene Therapy, 2000; Balter, 2000; Fox, 2000]. The true significance of these incidents has undoubtedly been exaggerated by hyperactive media reports, however, the result has been an increase in regulatory scrutiny of these types of therapies [Vogel, 2000; Friedman et al., 2001; McCarthy, 2001].

In fact, in the United States, regulatory policy for cellular and gene therapy has been under development for a number of years by the Center for Biologics and Research (CBER) of the federal Food and Drug Administration (FDA) [CBER, 1991; Marti et al., 1994]. In the case of gene therapy, several other bodies, including the Recombinant Advisory Committee (RAC), have also been intimately involved in the development of the strategy [Steele, 2000]. This article focuses primarily on the history and the current status of regulations related to cellular therapies, and assesses the impact of these regulations on the average academic cell processing facility.

REGULATIONS VERSUS STANDARDS

It is important to distinguish between standards and regulations pertaining to a field. The former are usually developed by interested professional organizations and are voluntary. In most cases, there is a related inspection and accreditation program by which member institutions or facilities can demonstrate that they are operating in compliance with the standards. In the case of hematopoietic cell therapies, the most widely followed standards are those developed by the Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT) [FAHCT, 1996] and the American Association of Blood Banks (AABB) [AABB, 2000]. The former covers all aspects of hematopoietic progenitor cell (HPC) collection, processing, and clinical transplantation, whereas the AABB standards focus on HPC collection and processing. Recently, the FAHCT standards have been extended, in collaboration with the NetCord cord blood banking cooperative, to cover the collection, processing, banking, and transplantation of HPC from umbilical and placental cord blood [NetCord/FAHCT, 2001]. The development of standards is usually a process internal to the individual organization. In practice, most will publish draft standards for public comment, and incorporate appropriate changes in the final version of their document.

The voluntary nature of standards does not, however, insulate the standard-setting organ-

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Received 4 September 2001; Accepted 6 September 2001

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jcb.10028

ization from liability, as was shown when the AABB was found to be negligent in considering currently available medical and scientific knowledge when developing its blood banking standards [Noble et al., 1998].

In contrast, regulations are developed by governmental bodies and have the force of law. Agencies involved in regulation may be at the local, state, or federal level. In reality, most states will defer to the federal government, although, New York [New York State Department of Health, 1991; Ciavarella and Linden, 1992] has developed specific regulations for HPC therapies. Other states may mandate that facilities under their jurisdiction must comply with standards set by the various professional organizations. In this article, the focus is on federal regulations developed by CBER.

Compliance with regulations is mandatory and is usually enforced by inspection or audit of a facility by the relevant agency, in this case the FDA. These audits are usually unexpected, or may come as a result of an adverse event reported to the agency by the facility. Failure to comply with regulations can result in suspension of activities or even closure of a facility.

DEVELOPMENT OF REGULATIONS

A primary force driving regulation of cellular therapies has been the risk of transmission of communicable diseases. CBER has a mandate to "protect and enhance the public health through the regulation of biological and related products including blood vaccines and biological therapeutics according to statutory authorities". In exercising that mandate it has reviewed the potential risk to the donor and recipient that is posed by the collection, processing, storage, and infusion of products used for cellular therapies. The first step in such a process is to examine existing legislation to determine whether it is adequate to achieve these intended goals [CBER, 1993]. Surprisingly, relevant regulations date from as early as 1902 when the Biologics Control Act defined blood and blood components as biologics, and from 1912, when the United States Public Health Service Act included "any virus, therapeutic serum, toxin, vaccine, blood, blood component, or derivative...applicable to the prevention, treatment, or cure of diseases or injuries of man" in the biologics category.

GOOD MANUFACTURING PRACTICES

Over the years one of the central tenets of all of the proposed regulatory strategies, was one first expounded in the Food, Drugs and Cosmetics Act of 1936, which established current good manufacturing practices (cGMP) for drug products for administration to humans or animals. This Act became law following the death of more than 100 people who had received a toxic preparation of sulfanilamide. Its intent was to ensure that, in future, drugs would be safe. Although, cGMP is frequently perceived as the use of a specific type of facility to prepare drugs or cell products, it is, in fact, much more comprehensive. It consists of a set of current, scientifically sound methods, practices, or principles that are implemented and documented during product development and production to ensure consistent manufacture of safe, pure, and potent products [CBER, 2001] (Table I). The application of cGMP to an academic cell processing facility does not, therefore, mandate demolition and/or reconstruction of the laboratory, but rather implementation of a number of processes and systems that can document that a controlled and auditable procedure is being used to prepare a safe and effective cellular product. In spite of a number of changes of direction in the strategy for regulating cell therapies, the implementation of cGMP has remained central to all.

SPECIFIC REGULATIONS

Following their review of existing applicable regulations, CBER felt that additional guidance was required on how these regulations would be implemented in the area of cellular therapy. In October 1993, CBER published "Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products" [CBER, 1993]. Somatic cell therapy products consisted of cells that had been manipulated ex vivo, and manipulation was defined as "ex vivo propagation, expansion, selection, or pharamacologic treatment or alteration of biological characteristics."

This approach would effectively regulate cells that had been cultured ex vivo, and/or been genetically altered, selectively enriched, or purged or treated with drugs. Specifically excluded from approval prior to marketing were "minimally manipulated or purged bone marrow transplants," which would include auto-

TABLE I. Essential Elements of Good Manufacturing Practices (for Blood Banking Establishments Part 600, Title 21, Code of Federal Regulations)

Staff	Adequate number
	Appropriate training and experience
	Exclude unauthorized staff from area
	Qualified and knowledgeable Director for supervision, discipline, and training
Facilities	Adequate space for all activities
	Clean, orderly, construction suitable for cleaning and maintenance
	Adequate lighting and ventilation, bathroom facilities and drains
	Safe and sanitary disposal of trash, blood, and components
Supplies and reagents	Safe, orderly, and sanitary storage
	Surface in contact with blood must be sterile, pyrogen-free, and non-reactive
	Observe containers for damage and contamination before and after filling
	Use oldest lots first
	Use sterile disposable materials where possible
	Written procedures for receipt, identification, storage, handling, sampling, testing etc.
	Store off floor and in manner to prevent contamination
	Record lot numbers and test lots
Equipment	Maintain in clean orderly manner and locate to facilitate cleaning and maintenance
	Regular calibration and cleaning
Laboratory controls	Establish specification and test to ensure safety, purity, potency and effectiveness
	Monitor test reliability, accuracy, precision and performance
	Adequate identification of product and test samples to allow tracking
	Compatibility testing between donor/product/recipient
Finished product controls	Separate areas to prevent mix-ups
	Use labeling controls
	Provide instruction circular
Records and reports	Maintain concurrently with each step of the procedure
	Include identity of person performing work, test results and interpretation, product expiration dates, history of work performed, lot numbers, donor records, information on storage and distribution, compatibility testing, infusion reactions etc.

logous marrows purged of tumor using an approved product, or enriched for stem cells by immunodherence, as well as allografts that had been depleted of T cells using an approved monoclonal antibody.

In February 1995, in a meeting at the National Institutes of Health, this approach changed. Dr. Katherine Zoon, Director CBER, stated that the definition of manipulation was to be radically altered in response to CBERs concern about the emergence of new sources of HPC, new methods for purification, a lack of accepted standards, and general confusion over the definition of manipulation. Under the new proposals, manipulation was defined as "one or more procedures performed to intentionally purge or enrich the starting material of a subset(s) of nucleated cells."

By default, minimal manipulation would now only include procedures such as centrifugation, density gradients, red cell lysis, and basic cryopreservation and storage of cells. Any other type of manipulation was likely to require an Investigational New Drug (IND) or Investigational Device Exemption (IDE).

This approach was consolidated further in a draft proposal on cord blood regulation published in December 1995 [CBER, 1995]. Citing its feeling that cord blood HPC represented a special case, CBER proposed that these products would be subject to IND regulations regardless of the degree of ex vivo manipulation. In February of the following year, CBER circulated a draft document on the regulation of peripheral blood progenitor cells (PBPC). Using the 1995 definitions of manipulation, it was proposed that non-or minimally-manipulated cells, as defined by the 1995 proposal, would not require an IND application, but if the product was intended for interstate commerce, licensure of the product, and the establishment would be required. Facilities preparing these products would be expected to operate under cGMP and would be subject to FDA inspection.

RISK-BASED REGULATION

This somewhat complicated situation was clarified by the publication of three documents. The first, which appeared in February 1997 was "Tissue Action Plan—Reinventing the Regulation of Human Tissue," outlined a new regulatory framework. More details were provided in the second document, also published in February—"Proposed Approach to Regulation of Cellular and Tissue-Based Products" [CBER, 1997]. This was prompted by what the agency described as "the highly fragmented" existing regulatory approach to these products, that had resulted in confusion to both industry and FDA reviewers. The aim was now to provide a new regulatory framework that would provide a

unified approach. Specifically excluded from the proposal were vascularized organs or minimally manipulated bone marrow, transfusable blood products, and tissues derived from animals. The emphasis was to be on three general areas: (1) preventing unwitting use of contaminated tissues with the potential of transmitting infectious diseases; (2) preventing improper handling and processing that might contaminate or damage tissues; and (3) ensuring the clinical safety and effectiveness for tissues that are highly processed and are used for other than their normal function, or which are combined with non-tissue components, or used for metabolic purposes.

The distinction was again made between extensively and minimally manipulated cells or tissues. Minimal manipulation would consist of processing that does not alter the original relevant characteristics of the tissue. Included in this category would be procedures such as cell separation and cryopreservation. This effectively moved procedures such as selection of stem cells from lymphocytes and mature cells of other lineages, into the minimal manipulation category. To resolve confusion as to whether a technique constituted minimal or extensive manipulation, CBER proposed to establish a Tissue Reference Group. Conversely, processes that alter the biological characteristics of the cells would include cell expansion, encapsulation, activation, or genetic modification. These types of manipulations would be subject to processing controls (covering chemistry, manufacturing, and controls), and to premarket requirements i.e., use of the IND or IDE mechanism.

The distinction was also made between cells used for homologous and non-homologous functions. The latter would comprise cells that are being used for a purpose different from that which they fulfill in their natural state, or in a location of the body where their function would not normally occur, for example, the use of amniotic membranes for wound healing in the cornea. The latter would be subject to more stringent regulation than the former. The same strategy was applied to cells that are required to exert metabolic function for efficacy. These products would be considered to raise greater regulatory concerns, even when minimally manipulated and would, therefore, be subject IND or IDE and marketing application procedures.

In the area of the potential for the transmission of communicable diseases, the agency would not assert any regulatory control over cells or tissues that are used autologously in a single surgical procedure. The use of allogeneic cells or autologous cells that are banked, processed, or transported in a facility that handles other cellular or tissue-based products would be considered to increase the risk of disease transmission. A distinction was also made between allogeneic cells obtained from an unrelated donor versus those from a close blood relative, the latter being considered to be more similar to those from an autologous donor. Unrelated donors would have to undergo specific screening for communicable diseases, and the product may require testing and quarantine if testing was positive or unavailable at the time of storage.

From these proposals it was possible to construct a regulatory matrix based upon the degree of risk posed by each of the three areas (disease transmission, degree of processing, and homologous/non-homologous/metabolic use). This is shown in Table II.

In March 1998, CBER published "Guidance for Human Somatic Cell Therapy and Gene Therapy" [CBER, 1998]. The intent of this document was to provide manufacturers with current information regarding regulatory concerns for production, quality control testing, and administration of vectors for gene therapy, and of preclinical testing of both cellular therapies and vectors. As a guidance document, these proposals did not have the force of law, but were intended to indicate the thinking of the agency. Emphasis was placed on the importance of quality control of the manufacturing process, rather than specific requirements for the product, because of the difficulty of defining the specific composition and properties of many biological products. The document contains detailed recommendations on the selection and testing of donors, quality control of cell culture procedures (including screening for adventitious agents), monitoring of cell identity and heterogeneity, characterization of the therapeutic entity, management and testing of materials used during manufacturing, and extensive information on the establishment of cell banks. Individual sections cover the characterization and release testing of cellular gene therapy products and vectors (including specific details on different classes of gene therapy

TABLE II. A Risk-Based Approach to Regulation of Somatic Cell Therapy

Product type	Action required	FDA submission
Risk of transmission of communicable diseases		
Autologous that is processed, banked, or shipped	Follow cGTP, recommend donor screening	None required
Allogeneic	Follow GTP, require donor screening	None required
Risk posed by processing		
Autologous or family member that is minimally manipulated ex vivo	Follow GTP	None
Unrelated allogeneic or extensively manipulated	> GTP regulation	IND/IDE–PMA/BLA compliance with standards?
Clinical safety considerations		
Unrelated donor or extensively manipulated and/or non-homologous function and/or combined with non-tissue (device)	Generate safety and efficacy data	IND/IDE–PMA/BLA
Labeling and registration		
All products EXCEPT autologous transplantation single surgical procedures	Clear, accurate, and non-misleading labeling, notify FDA of existence of facility and products manufactured	Depends on the type of product, facility registration, and annual listing of products

vectors), modification of vectors, and preclinical evaluation of cellular and gene therapies.

These proposals essentially left unmentioned the regulatory strategy for allogeneic umbilical cord blood HPC and PBPC.

CBER indicated that these regulations would be phased in by first requiring registration and listing with the FDA of facilities that recover, screen, test, procure, bank, process, transport, or distribute these cells. This would be followed by requirement to test blood samples from allogeneic donors to assess the risk for transmission of communicable diseases. Thirdly the agency intended to promulgate establishment controls, processing controls, and product standards. They invited professional groups and individuals to submit data and standards that would ensure product safety and effectiveness. Once such standards were in place, the FDA would issue licenses based upon certification by the applicant that the standards are met.

CURRENT GOOD TISSUE PRACTICES

Much of what has been described above was distilled into a single proposed rule published by CBER in January 2001. "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products: Inspection and Enforcement" [CBER, 2001a] would provide core requirements that would be applicable to all human cellular and tissue based products regardless of their regulatory category. They would be supplemented by other subparts of Part 1271 of Title 21 of the Code of Federal Regulations. Subpart A describes the scope and purpose of Part 1271 and provides definitions. Subpart B would cover facility registration [CBER, 1998a], Subpart C would describe the screening and testing of donors in order to determine their suitability [CBER, 1999]. Subpart E describes labeling and reporting requirements, and Subpart F contains inspection and enforcement provisions [CBER, 2001]. cGTP would form Subpart D and provide a new form of cGMP that would be more appropriate to the preparation of cellular and tissue-based therapeutic products, and aimed primarily at preventing the transmission of communicable diseases. The document calculates the potential risk to a recipient from receiving a contaminated product and the potential cost in terms of providing treatment and lost productivity. The accuracy of these calculations is open to debate, as is the claimed cost of implementing the proposals in an academic environment.

Facilities preparing products that require and IND or IDE application would, in addition, be subject to the provisions of cGTP. Similarly cGTP are considered to supplement rather than supersede existing cGMP regulations.

The proposals are comprehensive, containing sections on establishment of a quality program (including functions, authority over the program, audits, computers, and procedures); organization and personnel (including competency, training, and records); procedures; facilities, environmental control and monitoring; equipment; supplies and reagents; process controls, changes, and validation; labeling controls; storage; receipt and distribution; tracking; and complaint files. For those familiar with cGMP, there were not too many surprises. The sections dealing with quality are perhaps more detailed

and receive a higher prominence, and the data tracking provisions are explicit in what is required. The proposal is intended to cover all forms of cellular and tissue-based therapies and some provisions may be difficult to comply with for certain products. An example occurs in Subpart E which indicates that any product offered for import (e.g., an unrelated bone marrow provided by a foreign registry) would be held in tact under conditions necessary to maintain product function an integrity and prevent communicable disease, until it is released by the FDA.

ACHIEVING COMPLIANCE IN AN ACADEMIC ENVIRONMENT

Most cellular and gene therapies have their origins in academic research laboratories, which then take on the responsibility of transitioning them to Phase 1 clinical trials. This confronts the investigator with a daunting task of obtaining all of the necessary regulatory approvals to initiate the study and scale-up of the technique to clinically appropriate cell numbers. The prospect of how to comply with required manufacturing conditions, and the development of the required infrastructure, may seem an impossible task both organizationally and economically. In a smaller institution it may make more sense to contract manufacturing to a larger academic or a commercial facility, however, it is possible to achieve compliance by the development of certain core systems.

Documentation

Documentation is at the heart of cGMP and cGTP, since it provides the evidence that systems are in place and functioning as required. A central component of documentation is the Standard Operating Procedures manual, which describes all of the procedures that are used by the facility in a manner that allows a suitably qualified staff member to perform a procedure. There is an art to writing such a manual, since procedures should be sufficiently detailed to allow them to be performed properly, without being so detailed that any minor change would require the generation of a variance to document what deviations occurred. The manual must also be comprehensive, including sections on qualification of supplies and reagents, inventory management, equipment cleaning and maintenance, environmental monitoring, cell or tissue processing, testing and release criteria, storage and transportation of products, and recall procedures.

Documentation of each procedure is also required. This is generally achieved by the completion of a worksheet that lists all of the reagents used (their manufacturer, lot number, and expiration date), the equipment used in the procedure, and the performance of each of the key steps in the procedure, together with the raw data that was acquired. The worksheet is signed by the staff member performing the procedures and also reviewed by the supervisor or laboratory director. These records must be available at all times and should be audited for compliance with regulations and standards.

Facilities

Many academic centers have focused on the nature and design of the facility as the key to GMP/GTP compliance. This is generally a misplaced concern, since the current regulations do not specify the environmental conditions that must be used to prepare these types of products. Compliance can be achieved in most suitably sized, clean, and well-organized laboratories. The key is to demonstrate that the area is managed in a manner that minimizes the risk of contamination or cross-contamination of the products that are being prepared or stored. This can be achieved by careful cleaning and decontamination procedures for the facility and equipment (including calibration and regular maintenance), use of designated areas for particular activities, and careful management and storage of supplies and reagents. If a facility has systems for controlling air quality, however, it is important to document that these are routinely operating within specifications and that appropriate air balances are being maintained. This will require measurement of particle and viable counts within processing areas, together with the use of fall-out and RODAC plates to monitor specific areas and surfaces respectively.

Staff Training

Another essential component of compliance is staff training. The facility is required to provide evidence that the staff are suitably qualified and trained to perform procedures, and that they maintain competency. This is usually achieved by establishing a training file for each staff member. This contains a copy of the job

description, the staff member's curriculum vitae, documentation of training on relevant SOPs and of competence testing, together with details of annual retraining, or retraining following changes to a procedure and details of continuing education activities.

Quality Program

The regulatory authorities continue to emphasize the importance of a quality program. The functions of this program include ensuring: (1) that appropriate procedures are established and maintained to ensure compliance with regulations; (2) that there are procedures for sharing information on potential contamination with upstream and downstream organizations and facilities, for recalling the product, and for notifying the FDA, and (3) that effective corrective actions are taken and documented following revelation of a problem. The program should also perform and document quality audits at least annually. This should be done by individuals who do not have direct responsibility for the processes being audited.

One of the simplest methods to implement such a program is to leverage existing quality improvement programs that exist within most academic hospitals. They can provide invaluable advice on the selection of appropriate quality indicators, design of the program, and independent evaluation of its performance. In the absence of an institutional program, a facility can identify critical steps in the performance of key procedures and use these as basic quality indicators that are monitored and trended on an ongoing basis. Examples could include maintenance of sterility during processing, performance of donor screening within the required timeframe, variances from SOPs etc.

INSTITUTIONAL COMMITMENT

If an institution is to participate in the development and implementation of cellular therapies it must find a mechanism to comply with the regulations described above. This commitment must be both philosophical and financial, especially during the initial stages of establishing a GMP/GTP facility. Even if there is no construction or renovation of facilities, investment is required to provide the basic infrastructure, which must be maintained even during periods of minimal manufacturing activity. In addition, many of the procedures performed in such a facility are classified as research, and cannot be reimbursed by charging the patient. Some costs may be offset by using the facility to prepare HPC grafts for use in "standard" protocols, however, there is no doubt that continuing investment is essential to maintain such a facility, regardless of its size or level of activity.

Successful implementation of cGMT/GTP also requires a philosophical commitment in an academic environment. Research staff in these settings are usually unfamiliar with the level of documentation and record-keeping required to ensure compliance. They are often puzzled or frustrated by some of the limitations that may be imposed when they attempt to transition a research procedure into early clinical application. It is, therefore, the responsibility of GMP/GTP staff to become involved as early as possible in the development of a procedure that is destined for the clinic. This can facilitate transition by, for example, (1) ensuring that GMP-friendly reagents are selected early in the course of research, (2) that cells are handled, wherever possible, in closed systems; (3) that the use of additives, such as cytokines, should be fully justified and minimized, and (4) that the researchers follows GLP during this phase of development of the therapy.

GENE THERAPIES

The regulatory situation in gene therapy has recently been further complicated by the death of a patient on a clinical trial, and by erroneous findings in another study that clinical vector preparations may have been cross-contaminated with other viruses [Washington Post, 2000]. The resulting investigations stimulated numerous belated reports of adverse reactions in patients on gene therapy trials. A misunderstanding of the significance and severity of the types of reactions by the media lead to widespread public concern about the safety of gene therapy in general. This, in turn, has resulted in increased regulatory scrutiny, and more rigorous release criteria for clinical viral vectors. It is clear that an already complex approval process has been made all the more difficult by the number of governmental agencies now involved in the approval and regulatory process. The result is that the investigator is now faced with a tortuous system of often contradictory and vague requirements. In the

present climate it is mandatory to maintain close contact with CBER to ensure that the most current requirements are being met. For more generic information on the regulations covering the preparation of viral vectors, master and working cell banks, master viral banks, and final vector products, the reader is referred to CBER publications [CBER, 1993a, 1998].

CONCLUSIONS

There is no doubt that cellular and gene therapies hold considerable promise for the prevention and treatment of a variety of diseases. Their future is, however, inextricably entangled with oversight by regulatory authorities. The regulatory strategy has been evolving, complex, and subject to revision in the light of clinical incidents. It now appears that a more unified approach is emerging that will address most types of somatic cell and gene therapies. It is incumbent on the investigator to become intimately familiar with these regulations, if he or she is to be successful in developing and implementing these types of treatments. These same investigators also have the responsibility to provide feedback to the regulatory agencies on the appropriateness and utility of existing and proposed regulations.

A more generic concern is whether the level of regulation is appropriate for these still highly investigational types of therapy. Of course, the primary concern must always be the protection of the patient, but there will always be a risk benefit ratio to be considered. One has to ask whether it is appropriate to require the same level of testing for investigational products that will be administered to a relatively very small number of patients, as is required for widely used pharmaceuticals or vaccines that may be given to hundred of thousands. We live in a world where economics cannot be ignored, and a real concern should be whether we will end up with a regulatory system that is both so complex and expensive for compliance that we are likely to destroy the types of academic investigational studies that are essential for the growth and development of the field. The trick will be to minimize the risk in a cost-effective manner and to ensure that potential patients are fully informed of the realistic balance between those risks and the potential benefits.

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