

# Bringing safe and effective cell therapies to the bedside

Robert A Preti

**New rules to assess the safety and efficacy of human cell- and tissue-based products are the culmination of a multiyear, cooperative effort between the US government and the biotech industry.**

With relatively little fanfare, the current Good Tissue Practices (cGTP) Final Rule<sup>1</sup> finally came into force in the United States in May. Under its legal authority, the US Food and Drug Administration (FDA) now inspects entities involved in the manufacture of human cells, tissues, and cellular and tissue-based products (collectively referred to as human cell/tissue-based products from hereon) and ensures cGTP compliance. Although cellular medicines present formidable challenges to regulators, I argue here that the FDA's new regulation strikes the right balance between safety and encouragement of the development of new experimental medicines for unmet needs. Even so, questions linger over the capacity of current technologies to ensure product consistency and quality and the ability of companies to achieve compliance.

## A new medical paradigm

Cellular medicines show great promise for replacing defective, damaged or missing metabolic and anatomic functionality, with the potential to treat hundreds of millions of patients each year in the United States alone. Perhaps more than any other experimental medicine, cell/tissue-based therapies take a bewildering array of forms, depending on the starting material, the methods of preparation and provision used, and whether off-the-shelf or individualized treatments are envisaged.

Several different types of cells and tissues can be exploited as starting material for

*Robert A. Preti is President & Chief Scientific Officer of Progenitor Cell Therapy, 292 Atlantic Street, Hackensack, New Jersey 07601, USA and 291 North Bernardo, Mountain View, California 94043, USA.*



Genzyme's Carticel is one of the few commercialized cell therapies approved for use in humans in the US. (Source: Genzyme, Cambridge, MA).

cellular medicines, including differentiated cells derived from the organs of living adult humans and adult cadavers, adult stem and progenitor cells derived from live donors, or embryonic stem (ES) cells extracted from developing embryos and cells derived from the fetus. For some types of cell/tissue-based products destined for treatment of the donor or a suitably matched recipient, only minimal manipulation during purification and storage is required to obtain a product that is similar in nature and function to the particular cell type extracted from its niche in the body. For others, more intense manipulation may be necessary, either through proliferation and/or differentiation in specially designed

culture systems to expand a particular cell type or function or through genetic modification at one or more loci. In the case of therapeutic cloning, manipulation will require replacement of the entire genome using nuclear transfer techniques.

## The challenges of cell therapies

Because cell/tissue-based products are derived from these diverse and complex biological sources, their conversion into therapies is not trivial. Challenges include their potential to spread communicable disease, the difficulty in adequately identifying the 'active agent' for identity and potency purposes, the expense associated with large clinical trials to test these complex products and the difficulties associated with stability of the incoming cellular raw material and final formulation. From the point of view of regulators, cell/tissue-based products present several problems.

**Comparability.** Product characterization is a key problem for these complex biologics. At the heart of the issue lies the paucity of demonstrable *in vitro* surrogates for assessing the functional viability, or potency, of cells and tissues as they are processed into the final 'medicine'. Such surrogates are needed to establish testing criteria at the various stages in manufacture of the cell/tissue-based product: acceptance testing to determine the suitability of incoming cellular raw materials; in-process testing to use as process controls; and release testing to define the adequacy of a finished formulation for distribution to patients. Surrogates are also required as a basis for comparisons when evaluating the impact of changes in the manufacturing procedures.

A further complication to this issue of comparability is that many cell/tissue-based

### Box 1 Gestation of the final rule

Although to an 'outsider' the Good Tissue Practices Final Rule may just have registered on the radar, it is in fact the fruit of many years of a cooperative effort between the FDA and stakeholders in the biotech industry. The US regulatory agency and biotech industry representatives began this creative dialog in 1993 with the FDA's publication of its thoughts in the *Federal Register*<sup>2</sup>. This initiated a period of mutual education and cooperation between regulators and practitioners, each of whom had at the outset little appreciation for opposing positions. These ongoing discussions led, in January 2001, to the publication of the first of subparts A and B of the rule (Table 1). Finally, in November 2004, the Final Rule containing the last of the subparts (otherwise collectively known as 21 CFR Part 1271) was published, coming into force (after the customary one-half year interval) on May 25, 2005.

products are heterogeneous, containing a variety of cell types, with one or more of them being the active agent, or component. These heterogeneous products best demonstrate their clinical value through their use in patients, and determining the contribution of the 'inactive' or 'contaminating' cell populations is difficult. Although this is an issue for all therapeutics, the ability to purify the final cell product to a high degree of purity with only the active cell ingredient becomes more difficult as one proceeds from chemical pharmaceuticals to biologics to cells, mostly because of the lack of available technology to do so, the normal variability inherently characteristic of biologic systems and the increased fragility of complex cell/tissue-based products (and thus their functional robustness during isolation, preparation, manufacture and processing).

When relevant *in vitro* test methods are available, often these tests have read-out times that exceed the product expiration, highlighting the need for developing and validating real-time test methods for relevant functional release criteria.

#### Intrinsic properties of cells as therapies.

Typically, the readily definable final formulation of traditional therapeutics is manufactured in large batches from well-characterized raw materials. These large batches are quarantined, and a representative portion is tested and released when predetermined specifications are met. The released lots are then packaged and delivered to wholesale distributors that ultimately deliver the products to point-of-care facilities.

For many cellular medicines, however, the therapeutic is patient-specific, with a lot size for the final formulation of one. Given the biologic variability in the cellular raw materials and in the characteristics of the final formulation, the time-critical and transit-environment sensitivity of the raw materials and final formulation, and the inevitable coordination with patient and clinical schedules, this one-off treatment model will require a tailored manufacturing and delivery infrastructure for the cell to reach the right patients at the right time.

**Source material—the donor as vendor.** A key distinguishing component of the cGTP rules is the emphasis on donor eligibility as

described in Subpart C of the rule (Table 1). This demonstrates that the FDA recognizes that cells and tissues taken from a donor as raw material for the manufacture of a cellular medicine may carry communicable disease risks both for the recipients of those cells and for recipients of cells manufactured and/or stored in the same place or time.

Given that these live, cellular medicines provide no opportunity for terminal sterilization before delivery, the donor eligibility determination serves as a *de facto* safety qualification and entails both product testing and prescreening donors for high-risk behaviors or medical histories that would place the donor at a high risk for transmitting communicable diseases. Product testing includes evaluation for human immunodeficiency virus (HIV-1 and HIV-2), hepatitis B and C, *Treponema pallidum* (syphilis), human T lymphocyte virus (HTLV-1 and HTLV-2) and cytomegalovirus (CMV). In addition, for donors of reproductive cells or tissue, testing is required for communicable diseases of the genitourinary tract, such as *Chlamydia trachomatis*.

**Getting therapies to patients.** Manufactured cell/tissue-based products and their cellular source materials are currently transported in an unregulated manner by various means, including ground couriers, commercial air and cargo airlines. Shippers of the cell/tissue-based products typically contract 'freight forwarders' to coordinate the logistics of delivering the cell product from origin to destination. Cell products that are shipped fresh are time sensitive and have special handling requirements. Commercial air carriers typically do not operate in a sufficiently tailored flight network to accommodate the medicines

**Table 1 The genesis of the Good Tissue Practices Final Rule**

Date effective	Subpart of rule and description
January 21, 2001	Registrations Final Rule <i>Part A. General Provisions.</i> Describes the purpose and scope of the part, defines terms used in the part and describes its applicability <i>Part B. Registration and Listing Requirements.</i> Describes when and how a facility must register with the FDA and how often and under what circumstances registration must be amended and renewed.
November 24, 2004	Donor Eligibility Final Rule <i>Part C. Donor Eligibility Requirements.</i> Sets out the requirements for determining donor eligibility, including donor screening and testing, and identifies the subpart as a component of the cGTP requirements. cGTP Final Rule <i>Part D. Good Tissue Practices.</i> Describes the core cGTP requirements necessary to prevent the introduction, transmission or spread of communicable disease by HCT/P. Requires establishments to maintain a high-quality program to address requirements for personnel, procedures, facilities, environmental control and monitoring, equipment, supplies and reagents, recovery, processing and process controls, storage and distribution. <i>Part E. Labeling/Reporting Requirements.</i> Defines and describes requirements and methods for reporting deviations and adverse events, and defines product labeling requirements. <i>Part F. Inspection/Enforcement Provisions.</i> Provides the agency with the authority to inspect establishments that manufacture HCT/Ps. Describes the purpose and method of inspections and the required response of the establishment during an inspection. Outlines the range of recourse available to the agency in the event that an inspection identifies noncompliance to the Rules.

they are charged to deliver, and few, if any, of the transportation systems have been qualified under manufacturing controls to ensure the quality of the cell products from the point of collection to the processing facility, and of the final products to the patient.

Furthermore, inspection and/or exposure to radiation could adversely affect the viability of the cell product. More sophisticated and 'approachable' transportation systems tailored to the shipment of cellular medicines, with their special handling needs and tight temporal requirements, are currently in development all over the world.

To obtain public trust in cellular medicines, the cellular source materials and finished formulations must be fully integrated into a chain of control from the time of cellular collection to the time the manufactured biologic agent is used in the patient.

### A tiered regulatory framework

As existing regulatory protocols were set up to assess much simpler chemical (such as small molecules and natural products) or biological entities (such as monoclonal antibodies or recombinant proteins), it became apparent early on that cellular medicine might pose problems for the traditional Investigational New Drug (IND) or Biologic License Application (BLA) US regulatory approval pathways.

As with any other new experimental therapy (for example, monoclonal antibodies, recombinant proteins, recombinant vaccines, antisense or gene therapies), the regulatory priority for the FDA has been to ensure a mechanism whereby only safe and effective new cellular medicines enter the market. And in terms of cellular medicines, one of the agency's main safety concerns is to ensure the creation of a regulatory system that can prevent cell/tissue-based products containing communicable pathogens or agents from entering the clinic. At the same time, however, it is in the interests of patients that regulations should be designed to not be so stringent and complex that they stifle innovation and compromise the commercial viability of these promising experimental therapies.

By the late 1990s, the FDA and industry—not willing to yield the critical features of the traditional, tried-and-tested approval process—began reevaluating the need for stringent regulation across the board for cell/tissue-based products (**Box 1**). Rather than a blanket approach, it was determined that a hierarchical regulatory approach was preferable, enabling cell/tissue-based products of higher potential risk to be overseen more rigorously than those of lower potential risk.

Products have thus been divided into three broad classifications on the basis of the relative safety risks that their manufacture and distribution pose to the public health.

**Category 1 products.** The first tier, cell-based products that are not considered human cell/tissue-based products, and therefore are not regulated through the 21 CFR 1271 rules, includes human organs for transplantation, whole blood and blood-derived products, extracted human products (such as milk or collagen) and bone marrow. For a product to fall within this first category, its manufacture must involve no or minimal manipulation *and* its use must be considered homologous (that is, it is used to directly replace the function for which it was biologically intended). "Minimal manipulation" refers to any procedure that does not alter the relevant biological characteristics of the cells.

For instance, the use of a purified population of human bone marrow-derived stem cells to replace those lost during high-dose chemotherapy is considered homologous because the cells are intended to repopulate the cells damaged during chemotherapy. The same cell preparation, however, used to replace endothelial function in damaged heart muscle after myocardial infarct is not homologous use, and this 'bumps up' the relative risk and consequent regulatory classification of the cells.

**Category 2 '361' products.** The second category is the first risk class directly affected by the GTP rules and represents a slightly higher risk classification of cell-based products (commonly referred to as '361 products' because they are regulated solely under the authority provided by Section 361 of the Public Health and Safety Act). This category includes human cell/tissue-based products that are minimally manipulated *and* are intended for homologous use, but includes all tissues other than bone marrow. 'Manufacturing requirements' for these types of cells include autologous transfer of tissue to perform its natural biologic role elsewhere in the patient (surgical replacement of left-knee cartilage with cartilage derived from the right knee of the same patient or a first-degree cousin), manipulation of hematopoietic cells that do not alter their biologic function (specific cell purification of CD34<sup>+</sup> hematopoietic progenitor cells derived from autologous peripheral blood progenitor cell apheresis products) and storage of tissue for these purposes (cryopreserved cornea for transplantation).

For a human cell/tissue-based product to be included in this category, its manufacture

must not involve cell combinations or the mixing of tissues with another entity or agent such as a biodegradable scaffold or other agent that could pose new safety risks to the recipient. In addition, the cell/tissue-based product cannot have a systemic effect and may not be dependent upon the metabolic activity of living cells for its primary function. If it does have a systemic effect, and is dependent on the metabolic activity of living cells for its primary function, it must be for reproductive use, autologous use or allogeneic use in a first- or second-degree relative (that is, the category extends as far as the transfer of tissue between cousins of the first degree).

A seminal feature of the GTP rules is that the FDA makes a distinction between these '361 products' and those that pose a higher risk to public health and safety. As such, 361 products, although guided by the 21 CFR Part 1271, are not required to follow the BLA pathway; do not require an IND (21 CFR Part 312); and are not subject to the pharmaceutical current cGMP. However, manufacturers of 361 products are bound by additional subparts (D, E and F) of the GTP rules that describe the current Good Tissue Practices, Labeling and Reporting requirements and Inspection and Enforcement provisions.

**Category 3 '351' products.** The third and final classification includes those cellular medicines in which cells or tissues are cultured and/or manipulated in a manner that would cause them to be regulated as biologic drugs or medical devices under the Federal Food, Drug, and Cosmetic Act and/or Section 351 of the Public Health Services Act (42 U.S.C. 262; '351 products'). This category includes cell/tissue-based products modified by such procedures as gene transduction and tissue culture and/or that are intended for non-homologous use (for example, the use of knee cartilage to provide bladder support to treat incontinence or the use of blood-derived hematopoietic progenitor cells from donors unrelated to the recipient). Increased scrutiny is warranted because of the possible unintended and unanticipated consequences related to the use of cells that have been altered in some way or are intended for use in ways for which there is no biologic precedent.

Category 3 products are subject to pre-market review procedures (BLA), among other requirements, as they are considered akin to pharmaceutical 'products'. Those entities involved in the recovery, screening, testing, processing, storing, labeling, packaging or distribution of these products would be considered 'manufacturers', as defined in the FDA's regulations; therefore, they are subject to full

cGMPs (21 CFR 210 and 211) and applicable parts of the 21 CFR 1271 cGTP rules, particularly donor eligibility.

As with traditional pharmaceuticals, after the development phase of a Category 3 cell/tissue-based therapy, clinical testing must be performed in a series of clinical trials designed to test the safety, purity, potency, efficacy and stability of the biologic agent or drug. Such clinical testing is typically performed in three stages (phase 1, phase 2 and phase 3), each involving a successively greater number of patients: advancement to a new clinical phase depends upon the successful completion of the previous one. In contrast to traditional pharmaceuticals, cell/tissue-based therapy trials may involve only a fraction of the number of patients because of the expense and available supply of the treatment. Thus, a cell/tissue-based product developer must use limited data sets and creative clinical study designs to achieve the statistical significance required to gain approval.

### Striking a balance

After publication of an earlier version (containing only parts A and B) in 2001 (see **Table 1**), important additions have been introduced into the Final 21 CFR 1271 Rule. These additions are presented in the context of a paradigm shift in the agency's thinking, as the FDA has chosen to focus on the safety and communicable disease aspects of the delivery of cell/tissue-based products and to de-emphasize product identity and efficacy standards traditionally associated with the cGMP requirements for pharmaceuticals and Category 3 therapies. Consequently, the Final Rule does not require a developer interested in distributing a Category 2 therapy (361 product) to enter into phased clinical testing toward the submission of a BLA. As a result, Category 2 products are not subject to the full cGMPs regulations. Nonetheless, in addition to the general provisions, registration and donor eligibility requirements (as described in subparts A, B and C, respectively, of the Final Rule), manufacturers of 361 products are still bound by the additional subparts D, E and F that describe the current Good Tissue Practices, Labeling and Reporting requirements and Inspection and Enforcement provisions, respectively (see **Table 1**).

Subparts C and D of the Final Rule are intended to prevent the introduction, transmission or spread of communicable disease by human cell/tissue-based products by

ensuring that they do not contain communicable disease agents, are not contaminated and do not become contaminated during manufacturing. In this regard, cGTP governs the methods used in, and the facilities and controls used for, the manufacture of cellular medicines, including environmental controls, equipment, supplies and reagents, recovery, processing and process controls, labeling controls, storage, receipt and predisposition, and shipment and distribution.

Whereas significant regulatory hurdles associated with demonstrating product efficacy have been removed for Category 2 products, the distinction between the overt manufacturing requirements of cGTP and cGMP, as they each relate to communicable diseases, is somewhat blurred. Thus, although the cGTP tiered system aims to provide a less onerous regulatory environment, in the final analysis manufacturers of Category 2 products must satisfy the Rule's core requirements by establishing an adequate quality system and controlled environment that shares many of the elements required by manufacturers of products covered by more stringent cGMPs.

What's more, in an odd twist, the cGTP requirements actually add to the level of regulatory oversight for Category 3 (351 products) by extending compliance into the realm of donor eligibility. At the current time, few 361 facilities are equipped with adequate infrastructure, either systems or people, to meet with compliance in this regard.

In recognition of these difficulties and the line they blur between drug production and the practice of clinical medicine for Category 2 products, the FDA provides a concession through a liberal use of the 'Urgent Medical Need' determination. This provides a physician with the authority to both evaluate the risks associated with certain cell/tissue-based product 'failures' in comparison to the risks associated with a lack of treatment options and determine whether there is a sufficient medical need to proceed with treatment. Because product failures could potentially include the exposure of a patient to incompletely tested (or, worse still, contaminated) products, any recipients undergoing such therapy would need to be fully informed of any potential risks through adequate labeling of product. This arrangement is something of a radical departure from traditional regulatory models that simply prohibit the use of products not meeting safety specifications.

### The road ahead

The success of the cGTP Final Rule ultimately depends on its ability to protect the public from the introduction or spread of communicable disease through the means of cell/tissue-based products. Attempts to incorporate these cGTP regulations will require implementation of GMP-quality systems to ensure that the viral and microbial content of each product is well understood, controlled, contained and traceable through defined systems and tight documentation.

Because cell/tissue-based products are so difficult to fully characterize, sophisticated cGMP systems will also be needed to rigorously control the process by which such products are generated. These systems will serve as the most reliable mechanism to ensure as much consistency in the final formulation as possible. Without consistency, it is difficult to imagine cell/tissue-based products gaining the public trust as therapies.

As the FDA and biotech industry work to develop the most appropriate mechanisms to achieve consistently high cell product quality, discussions continue regarding the methods and controls used in the manufacturing process. The FDA's collaborative stance with the biotech industry is demonstrated by the interactive nature of its discussions and the forums it supports; examples include the annual Somatic Cell Therapy Symposium (which it cosponsors with the International Society for Cellular Therapy) and the recent establishment of a biannual liaison meeting between industry and the Office of Cellular, Tissue and Gene Therapies.

Just a few years ago, the practical implementation of commercialized cell/tissue-based products in the clinic was far from reality; now these products are being evaluated at all phases of clinical trials, with some, such as Cambridge, Massachusetts-based Genzyme's autologous cultured chondrocyte product (Carticel), even in commercial production. Looking back, one might marvel at what has been achieved in so short a time: an infrastructure to harvest, manufacture, test and deliver an entire new class of medicines that not so long ago was unimaginable.

1. Department of Health and Human Services, Food and Drug Administration. Human cells, tissues, and cellular and tissue-based; donor screening and testing; and related labeling. *Fed. Regist.* **70**, 29949–29952 (2005). <<http://reform.house.gov/UploadedFiles/FDA%20Regulation%2021%20CFR%201271.pdf>>
2. Department of Health and Human Services, Food and Drug Administration. Application of current statutory authorities to human somatic cell therapy products and gene therapy products, Docket 93N-0173. *Fed. Regist.* **58**, 53248–53251 (1993). <<http://www.fda.gov/cber/genadmin/fr101493.pdf>>