

Current regulatory issues in cell and tissue therapy

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Summary

Cell-based therapies have grown dramatically in power and scope in recent years. Once limited to blood and BM transplantation, these therapies now encompass tissue repair and regeneration, metabolic support, gene replacement, and immune effector functions, with established and investigational clinical applications in disorders affecting nearly every tissue and organ system. The complexity and novel applications of human cells, tissues, and cellular and tissue-based products (HCT/Ps), however, present potential risks for adverse events. The US Food and Drug Administration, responding to these concerns, has established a tiered, risk-based regulatory structure, in which more rigorous controls and safeguards are required for products thought to pose increased risk. The proposed good tissue practices (GTP) rule and existing good manufacturing practices (GMP)

requirements form the principal elements of this regulatory framework. The proposed GTPs are intended to prevent HCT/P contamination with infectious disease agents, and to ensure that these cells and tissues maintain their integrity and function. GMPs focus on production of safe, pure, and potent products, and entail a higher level of process control and product characterization. All HCT/Ps will be required to comply with GTPs. HCT/Ps considered to present greater risks of adverse events, however, will be subject to both GTPs and GMPs, and must obtain premarket approval using the Investigational New Drug (IND) mechanism established for biologics. Although these requirements will present significant challenges for clinician–investigators and laboratories producing HCT/Ps, the regulations fundamentally support good clinical care by increasing safety and control, and enable good science by improving the quality and reliability of data.

Introduction: potential and risks of advanced cell therapies

Cellular therapies in recent years have grown dramatically in sophistication, power, and scope. No longer limited to enabling myeloablative chemotherapy by immune and hematopoietic reconstitution, applications for advanced cell therapies now include structural tissue repair and regeneration, metabolic support, immunomodulatory and effector cell functions, and gene replacement, for disorders affecting nearly every tissue and organ system [1–4].

Preparing advanced cell therapy products often requires complex procedures, such as multiple cell-selection steps, *ex vivo* expansion, cell activation, encapsulation, and genetic modification [2,4–6]. This has led to a fundamental change in cell-therapy laboratories. In the past, when product cryopreservation was the predominant or sole procedure, operations often were based in a hospital blood bank, or a BMT investigator's research laboratory. Standardization, process control, training and documentation typically were limited. Today, however, laboratories

producing advanced cell therapy products cannot be viewed as simply processing cells, and increasingly function as cell-engineering manufacturing establishments, with extensive validation, process control and documentation. This evolution reflects the increasing sophistication of cell therapies and their production methods, but also has occurred in response to the potential risks and increasingly rigorous regulatory requirements for these novel biological therapies.

It is likely that no technology can grow more powerful and capable without also developing a greater potential for problems. Enhanced abilities may function in unintended, undesired ways, and more elaborate systems typically contain more elements that may break. The growing sophistication of advanced cell therapies, similarly, has been accompanied by increased risk of adverse events. In years past, for example, when clinical trials did not involve administration of *ex vivo* cultured cells, there was no reason for concern about adverse events due to cultured-cell contamination. This situation has changed dramatically.

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The complex processes used to manufacture today's advanced cell therapies present more opportunities for something to go amiss, and hence warrant additional safeguards and control measures. Beyond these known or foreseeable manufacturing-related risks, some advanced cellular therapies present concerns simply by virtue of being innovative or new, as the degree of clinical risk associated with these products is more difficult to predict than for established therapies.

Regulatory agencies and standard-setting organizations have attempted to address concerns and often unknown risks associated with production and clinical use of advanced cell therapies, by increasing regulatory oversight and stringency. Accordingly, the growth and development of cellular therapies has been accompanied by a parallel evolution in the regulations governing them.

Regulatory framework for cell and gene therapies

In the USA, the Food and Drug Administration (FDA) is the principal agency with regulatory oversight over cell, gene, and tissue therapies. The FDA definition of human cells, tissues and cellular and tissue-based products (HCT/Ps): “products containing or consisting of human cells or tissues, intended for implantation, transplantation, infusion, or transfer into a human recipient”, includes a broad range of cell- and tissue-based therapies.

Several types of cell- or tissue-based therapies are, however, specifically excluded from FDA regulation of HCT/Ps. Transplantation of minimally manipulated BM and vascularized whole organs is regulated by the Health Resource Services Administration (HRSA) [7], while allogeneic unrelated BMT falls under the authority of the National Marrow Donor Program standards [8], under HRSA administration. Blood components and derivatives are subject to other FDA regulations and hence are not considered HCT/Ps [9,10]. Xenogeneic cells and tissues also are excluded.

The FDA responded to the challenges of advanced cell therapies by establishing a tiered, risk-based regulatory structure, in which more rigorous controls and safeguards are required for products that are thought to pose increased risk. The foundation for this structure was prepared with a 1993 publication [11] describing the FDA's authority and intent to regulate cell- and gene-therapy products. This document outlined a basic regulatory framework for these products, based on the existing

biologics regulatory structure. This specified establishment and product licensure, and clinical trials under the Investigational New Drug (IND) mechanism, and required compliance with current good manufacturing practices (cGMPs) [12,13]. A comprehensive regulatory structure for cellular therapies, the *Proposed approach to regulation of cellular and tissue-based products* [14,15] (*Proposed Approach*), was published in 1997. These and subsequent FDA major regulatory and guidance documents regarding HCT/Ps are listed in Table 1.

The intent of the *Proposed Approach* was to prevent potential infectious disease transmission, by preventing improper processing that could result in product contamination or other adverse effects, and to ensure clinical safety and effectiveness — particularly for products with greater risk for adverse events. The regulatory structure of the *Proposed Approach*, accordingly, is tiered and risk-based, in that products thought to present greater risk receive more regulatory oversight, and require more extensive controls in manufacturing and clinical studies — and more rigorous product characterization. Products thought to present less risk are stringently regulated, but less so than higher-risk products [14,22,23].

HCT/Ps in the lower risk category are regulated under Public Health Service Act 361 [24], and hence are sometimes termed ‘361 HCT/Ps’, or minimally manipulated products. Manufacturers of minimally manipulated HCT/Ps are not obliged to operate under full GMPs, or to follow the biologics IND pathway, but must comply with good tissue practice (GTP) regulations. These regulations will be discussed more extensively below. Clinical trials of higher-risk, “more-than-minimally manipulated” HCT/Ps must use the IND mechanism established for biologics, and must comply with both GTPs and GMPs. Devices composed of more-than-minimally manipulated HCT/Ps must seek premarket approval through the Investigational Device Exemption (IDE) mechanism, and comply with GTPs and Quality System Regulations. For the purpose of regulation, HCT/Ps in this category may be thought of as cellular drugs.

The risk-based approach

This tiered regulatory approach necessitates stratifying HCT/Ps according to their known or projected risks for causing adverse events. The *Proposed Approach* considers a variety of risk factors when evaluating the potential for any HCT/P to cause adverse events. Fundamentally, these

Table 1. US FDA cell and gene-therapy related regulatory requirements and guidance documents (based in part on Read [23])

| Date | Title | Specifics |
|------|--|--|
| 1993 | Application of current statutory authority to human somatic cell-therapy and gene-therapy products [11] | Legal authority to regulate cell- and gene-therapy products Background for development of regulatory structure for cell therapies, based on biologics regulatory requirements INDs required for clinical trials Compliance with cGMPs Establishment and product licensure required for commercialization |
| 2001 | GMPs [12,13] | Ensure consistent manufacture of safe, pure, potent products |
| 1997 | <i>Proposed approach to regulation of cellular and tissue-based products, HCT/Ps</i> [14] | Rationale for HCT/P regulatory structure Tiered, risk-based approach to regulation of cells and tissues based on estimated public health risk, need for FDA review cGTP regulations |
| 1998 | <i>Guidance for human somatic cell therapy and gene therapy</i> [16] | Definitions of somatic cell and gene therapy Collection, production, quality control testing, vectors for gene therapy, preclinical testing of cell-therapy products and gene-therapy vectors |
| 1999 | <i>Suitability determination for donors of HCT/Ps; proposed rule</i> [17] | Requirements for HCT/P donor screening and testing Emphasis on preventing infectious disease transmission. First of three GTP rules |
| 2001 | <i>Current good tissue practice for manufacturers of HCT/Ps; inspection and enforcement; proposed rule</i> [18] | Infectious disease testing for human donors of cell and tissue-based products Preventing contamination of cells and tissues during manufacturing Testing—demonstrate that cell and tissue therapy products maintain function, viability, are free from contamination, and have other appropriate characteristics Second of three GTP rules. |
| 2001 | <i>Human cells, tissues and cellular and tissue-based products (HCT/Ps); establishment registration and listing; final rule</i> [19] | Requirements for HCT/P manufacturer establishment registration, product listing Third of three GTP rules |
| 1996 | Good clinical practice, GCP, ICH E6 [20] | Ethical and scientific quality standard for clinical trials Protection of clinical trial subjects Assure credibility of clinical trial data |
| 2002 | <i>Validation of procedures for processing of human tissues intended for transplantation: final guidance</i> [21] | Validation practices for tissue processing. Assure controlled, consistent processing, products free of contamination |

factors and their use in risk assessment is based on very straightforward reasoning, which takes into account:

- The potential for manufacturing-related problems that could result in adverse clinical effects
- The likelihood of predicting accurately the product's behavior after administration
- The extent of the product's clinical effects
- The product's intrinsic potential for causing adverse clinical effects [14].

The concern about potential for manufacturing-related problems is addressed by stratifying products according to the degree of cell or tissue manipulation in processing: the first major risk factor. Complex, extensive manufacturing procedures involve greater risk than simple, brief processes, and so HCT/Ps that are extensively processed are assigned the higher-risk category. These products are, in the terminology of the FDA, 'more-than-minimally manipulated', a description that includes *ex vivo* culture, cell activation, genetic modification, and encapsulation. HCT/Ps may not be processed in any of these ways, and hence may be placed in the lower risk category [14].

Another risk factor, combination with a non-tissue component, drug or device, also reflects the issue of manufacturing-related problems, and perhaps also the question of predicting the product's behavior *in vivo*. Combining cells or tissues with another agent, such as a drug, device, or other non-tissue component, adds an additional level of complexity to the process, and adds to the variables involved in predicting product function and safety. To address these points, such products too are assigned to the higher-risk category. Note that HCT/Ps may be combined with certain preservative agents, such as cryopreservative solutions, without being considered higher-risk products [14].

The question of predicting *in vivo* product characteristics and behavior leads to another risk factor: whether the product is intended to perform a homologous or non-homologous function. Homologous use, in which the product performs a function identical to its native function, is considered lower risk, as the product's *in vivo* characteristics should be relatively predictable. Hematopoietic stem and progenitor cells used for hematopoietic reconstitution following myeloablation would be considered to be performing a homologous function, but would be viewed as performing a non-homologous function if used for treatment of a metabolic deficiency. In the latter instance, the cells would not be used to perform hematopoiesis, but instead would provide a different metabolic function, with less predictable characteristics [14].

Consideration of the scope of a product's activity leads to the risk factors of systemic versus localized effect, and metabolic activity. HCT/Ps that function systemically, and hence have the opportunity to interact with a diverse range of living and non-living agents, and to exert intended and unintended effects widely, are thought to have greater potential for causing adverse effects than localized pro-

ducts. HCT/Ps that perform a primary function that requires the metabolic activity of viable cells also represent a broader and less predictable range of activity. Accordingly, the higher-risk category includes systemically acting HCT/Ps, and HCT/Ps that perform their primary function through the metabolic activity of viable cells [14,22].

Certain risks are, in some sense, intrinsic to the nature of the HCT/P. Autologous HCT/Ps are considered lower risk than unrelated allogeneic HCT/Ps, due to immunologic compatibility issues. Allogeneic HCT/Ps typically also involve more extensive manipulation than autologous products. The FDA has, however, included closely related allogeneic HCT/Ps, as from a first or second degree blood relative, in the lower-risk category, with autologous HCT/Ps [14,22].

Determining whether an HCT/P is in the lower or higher risk category becomes relatively straightforward when considered in terms of risk factors. The distinctions between lower-risk, minimally manipulated HCT/Ps and higher-risk, more-than-minimally manipulated HCT/Ps are outlined in Table 2. It must also be remembered that any one of the risk factors described is sufficient to place an HCT/P in the higher-risk category. For an HCT/P to be considered in the lower-risk, minimally manipulated category, it must not have *any* of the characteristics of the higher-risk, more-than-minimally manipulated products.

Lower risk, minimally manipulated HCT/Ps, by definition, may not be manufactured using complex processes, may not be combined with a drug or device, other than certain preservative agents, and must be intended for homologous use. In general, lower-risk, minimally manipulated HCT/Ps must not have a systemic effect, or have a primary function depending on metabolic activity of viable cells.

Autologous, or closely related allogeneic HCT/Ps, or HCT/Ps for reproductive use are a partial exception to this rule. In these instances, the use of the patient's own cells, or those of near-relatives, may reduce overall risk, permitting HCT/Ps with systemic effects or metabolic activity to remain in the lower-risk, minimal manipulation category. HCT/Ps in this lower-risk category include cryopreserved autologous PBSC/progenitor cells, closely related allogeneic UC blood for transplantation, and minimally manipulated cadaveric tissues and reproductive tissues [14,22,23].

Table 2. Applicability of US FDA regulations to cell, tissue, and gene therapy products, HCT/Ps [14,22,23]

| | Minimally manipulated '361' HCT/Ps | More-than-minimally manipulated HCT/Ps |
|--------------------------------|---|--|
| Definition | <p>Must meet criteria 1 <i>and</i> 2 <i>and</i> 3, <i>and</i> 4a, 4b, or 4c.</p> <p>An HCT/P which is</p> <p>1 Minimally manipulated (not activated, encapsulated, expanded <i>ex vivo</i>, or genetically modified) <i>and</i></p> <p>2 Intended for homologous use <i>and</i></p> <p>3 Not combined with a drug or device <i>and</i></p> <p>4a. Does not have a systemic effect, <i>and</i></p> <p>Primary function does not depend on metabolic activity of viable cells</p> <p><i>or</i></p> <p>4b. Has a systemic effect <i>and</i> is intended for autologous, related-allogeneic, or reproductive use</p> <p><i>or</i></p> <p>4c. Primary function depends on metabolic activity of viable cells) <i>and</i> is intended for autologous, related-allogeneic, or reproductive use</p> | <p>Do not meet one or more of the four major criteria for minimally manipulated HCT/P.</p> <p>Note that cell activation, encapsulation, <i>ex vivo</i> expansion, and gene modification are considered more-than-minimal manipulations.</p> <p>Nearly all advanced cellular therapies meet criteria for the more-than-minimally manipulated category.</p> |
| Regulatory requirements | <p>HCT/Ps regulated under the US Public Health Service Act, 42 USC Section 361</p> <p>cGTP establishment registration, product listing</p> <p>cGTP donor suitability criteria</p> <p>cGTP manufacturing requirements</p> | <p>Regulated under US FDA authority. Federal Register 1993;58:53248-53251.</p> <p>cGTP establishment registration, product listing</p> <p>cGTP donor suitability criteria</p> <p>cGTP manufacturing requirements</p> <p>cGMP regulations (biologics, drugs)</p> <p>Quality System regulations (devices)</p> <p>IND or IDE required for clinical trials</p> <p>Premarket approval</p> <p>BLA (biologics)</p> <p>PMA (devices)</p> |
| Examples | <p>Minimally manipulated autologous or closely related allogeneic cord blood or PBSCs</p> <p>Minimally manipulated cadaveric musculoskeletal tissue, cornea, heart valves, dura mater</p> <p>Minimally manipulated reproductive tissue (donor eggs, sperm)</p> | <p>Allogeneic unrelated cord blood and PBSCs, even if minimally manipulated</p> <p>Autologous HSC/HPC for cardiac repair</p> <p>Mononuclear cells activated <i>ex vivo</i></p> <p>Genetically modified cells (lymphocytes, HSC/HPC, other)</p> <p>Autologous BM stromal cells combined with synthetic scaffolding</p> |

Nearly all advanced cell, gene, and tissue therapies would be considered more-than-minimally manipulated, as this category specifically includes products containing cells that have been cultured *ex vivo*, activated, genetically modified, or combined with a drug or device — common procedures in manufacturing advanced cell-therapy products. In addition to HCT/Ps produced using one or more of these more-than-minimal manipulations, allogeneic cord blood and allogeneic unrelated-donor PBSC/progenitor cells for transplant also fall into the higher risk, more-than-minimally manipulated category.

Regulatory requirements — minimally and more-than-minimally manipulated HCT/Ps

GMPs and GTPs are the principal US governmental regulations for HCT/Ps. As the specific requirements of GMPs in cell-therapy product manufacturing have been discussed in previous reviews [25–28], these will not be discussed extensively here.

GTPs focus on preventing cell-therapy product contamination with infectious diseases, and ensuring that these cells and tissues maintain their integrity and function

(Table 3). While this is a somewhat narrower focus than for GMPs (Table 4), compliance with GTPs will be required for all HCT/Ps, whether in the lower-risk, minimally manipulated, or the higher-risk, more-than-minimally manipulated group. As such, the GTPs are by far the most rigorous and comprehensive regulations yet seen in cell, gene, and tissue therapies. GTPs cover manufacturing methods and facilities, donor screening and testing, product recovery, processing, storage, labeling, and distribution. Many of these elements are common to both GTPs and GMPs, reflecting common goals — safe and effective products, well-controlled processes, comprehensive supporting documentation. Requirements for standard operating procedures (SOPs), labeling controls, and storage requirements also will be familiar to any clinical laboratory.

The GTP regulations, 12 CFR 1271, presently are defined in three regulatory documents — *Suitability determination for donors of human cellular and tissue-based products; Proposed rule*, [17]; *Current good tissue practice for manufacturers of human cellular and tissue-based products; inspection and enforcement; Proposed rule*, [18]; and *Establish-*

Table 3. Current GTPs [18]

| GTP elements | Specifics |
|--------------------------------------|--|
| Quality program | Formal quality program evaluating all aspects of operations to assure GTP compliance |
| Organization and personnel | Personnel qualification, training |
| Procedures | SOPs for all significant steps in manufacturing, authorization of deviations |
| Facilities | Facility and equipment operations, cleaning, validation |
| Environmental control and monitoring | |
| Equipment | Equipment and environmental monitoring |
| Supplies and reagents | Requirements, qualification and control of materials used in processing |
| Process controls | Validation and control of manufacturing processes, process modifications |
| Process changes | |
| Process validation | Corrective action plan for failure to meet expected outcomes |
| Labeling controls | Controlled product labeling, prevention of mix-ups |
| Storage requirements | Provisions for adequate and appropriate raw material and product storage |
| Receipt and distribution | Record keeping and data management |
| Records | Product tracking — from donor to recipient, and from recipient to donor |
| Tracking | |
| Complaint file | Outcome analysis, deviation tracking, adverse event reporting |

Table 4. Current GMPs [12,13]**GMP elements**

General provisions
 Organization and personnel
 Buildings and facilities
 Equipment
 Control of components
 Production and process controls
 Packaging and label controls
 Holding and distribution
 Laboratory controls
 Records and reports
 Returned and salvaged product

ment registration and listing for manufacturers of human cellular and tissue-based products; *Final rule* [19]. The three GTP rules may be better appreciated in light of the 1997 *Proposed Approach*. While developing the regulatory structure for HCT/Ps, five aspects of these products became sources of particular concern. These were:

- The potential for transmission of infectious disease
- Control of processing
- Clinical safety and effectiveness
- Product labeling and promotion
- The need for a baseline knowledge of the cell and tissue therapy industry [22].

The proposed rule on *Suitability determination for donors of HCT/Ps* [17] responds to the concern about potential for

infectious disease transmission, by specifying requirements for donor testing and screening. Similarly, the FDA's concern that it requires knowledge of the cell and tissue therapy industry is addressed by the *Establishment registration and listing rule* [19], which requires that all HCT/P manufacturing establishments register with the FDA and list their HCT/P products. The issues of processing controls, evaluation of clinical safety and effectiveness, and product labeling and promotion are covered by the proposed rule specifying current good tissue practices (cGTPs) for HCT/P manufacturers [18], and by the tiered, risk-based regulatory structure itself.

Beyond GTPs and GMPs, other regulatory requirements, guidance documents, and standards also apply to HCT/Ps (Table 5). Clinical trials of HCT/Ps must operate in compliance with good clinical practices (GCPs) [20], and with Institutional Review Board oversight and approval [35], to assure protection of the rights of research subjects.

Gene therapies require additional review and approval by the NIH Recombinant DNA Advisory Committee [29]. FDA-CBER has issued guidance documents addressing somatic cell therapy and gene therapy [16], and validation of procedures for processing human tissue for transplantation [21]. The Foundation for Accreditation of Cellular Therapy (FACT) [30] and American Association of Blood Banks [31] each publish standards for cell therapies, and operate inspection and accreditation programs. The US Pharmacopeia (USP) provides a general information

Table 5. Non-FDA cell- and gene-therapy related Standards and Regulations

| | Standard-setting organization | Specific interests | Reference |
|------|--|---|-----------|
| 2002 | Recombinant DNA Advisory Committee (RAC); NIH Office of Biotechnology Activities (OBA) | Requirements covering essentially all aspects of clinical trials involving recombinant genetic material | [29] |
| 2002 | Foundation for the Accreditation of Cellular Therapy (FACT) accreditation standards | Cell therapy product collection, processing, and transplantation | [30] |
| 2002 | American Association of Blood Banks (AABB) accreditation standards | Cell therapy product collection, processing, administration | [31] |
| 2001 | American Association of Tissue Banking (AATB) accreditation standards | Tissue processing and banking | [32] |
| 2002 | National Marrow Donor Program | Allogeneic unrelated BMT | [8] |
| 1988 | Clinical Laboratory Improvement Amendments (CLIA): Laboratory Requirements | Clinical laboratory standards and requirements | [33] |
| 2001 | College of American Pathologists. Laboratory Accreditation Program | Clinical laboratory standards | [34] |
| 2002 | USP General Information Chapter, Cell and Gene Therapy | Practices and recommendations for cell, tissue, and gene therapies | [6] |

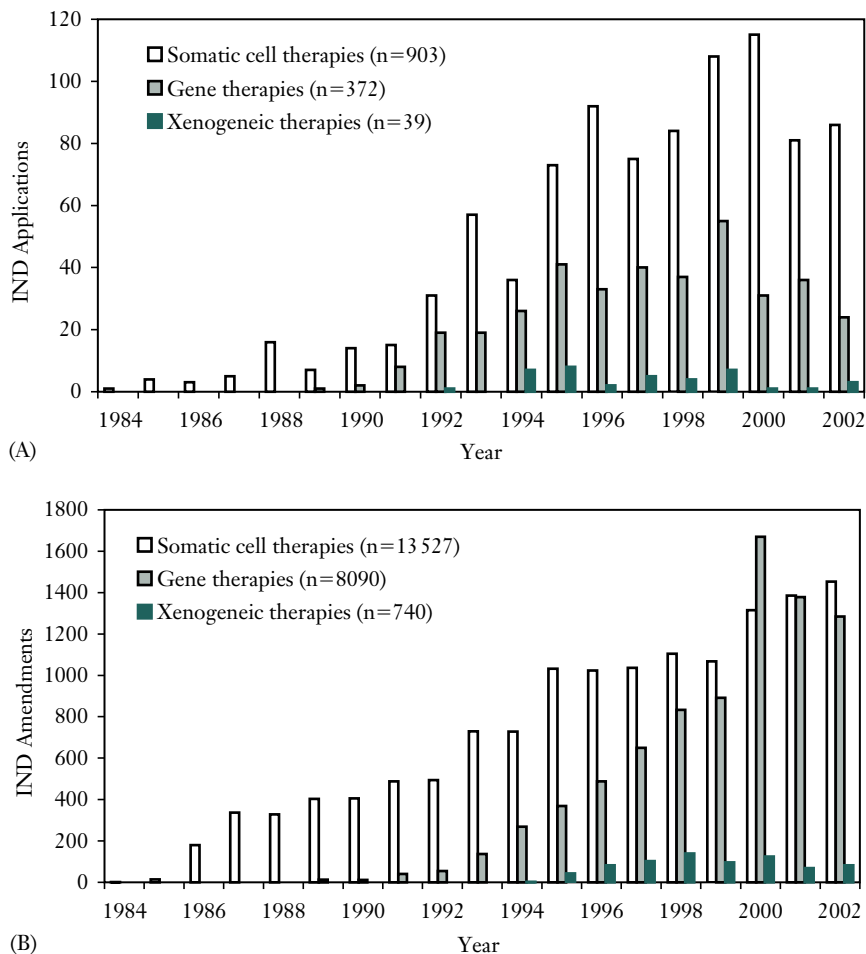


Figure 1. A. Total annual IND applications for cell therapies, gene therapies, and xenogeneic therapies, 1984–2002 [36]. B. Total annual IND amendments for cell therapies, gene therapies, and xenogeneic therapies, 1984–2002 [36].

chapter on cell and gene therapy [6], while the American Association of Tissue Banking publishes standards for tissue therapy [32]. Cell-therapy clinical laboratories, like other clinical laboratories, have long been accustomed to the requirements of the Clinical Laboratory Improvement Amendments (CLIA) [33], and accreditation by the College of American Pathologists [34].

Regulatory requirements and HCT/P process development

HCT/P manufacturing processes, analytical methods, and product specifications inevitably evolve over the course of clinical trials. Critical raw material, particularly patient-specific cells and tissues, often cannot be available for preclinical development studies. The inherent biological variability and heterogeneity of this living raw material,

and of cell and tissue therapy products, add further challenges. Clinical trial material, data and experience are essential for process and analytical development of HCT/Ps, and product characterization.

This point is illustrated by a simple comparison between numbers of cell therapy and gene therapy INDs, depicted by annual total in Figure 1A, and amendments to those INDs, shown in Figure 1B.

For the period 1984 to 2002, FDA-CBER recorded 903 INDs in cell therapy, but 13 527 amendments to those INDs — an average of 15 amendments for every cell therapy IND [36]. Gene therapies involve still greater complexities, and hence undergo a still more complex development process. FDA-CBER recorded 372 gene therapy INDs by the end of 2002, but these 372 gene therapy INDs accounted for 8090 IND amendments — an

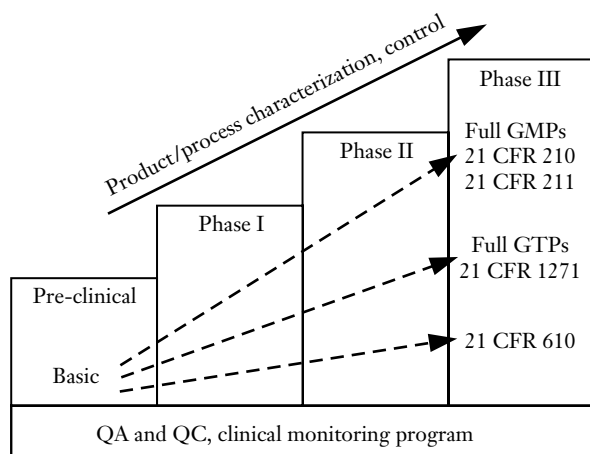


Figure 2. FDA regulatory requirements for product characterization and process control increase with ongoing product development [36].

average of nearly 22 amendments for every gene therapy IND [36]. Development activity evidently continues long after IND submission.

It is expected, then, that HCT/P manufacturing and analytical methods will change with clinical trial experience, becoming more controlled, more reproducible, and more fully characterized. Accordingly, FDA regulatory requirements for product characterization and process control increase with ongoing process development, as illustrated in Figure 2. The level of compliance with GMP and GTP requirements is expected to increase with progress through the different phases of clinical trials. While full compliance with GMP requirements is almost certainly unattainable for an HCT/P at Phase I, a more basic level of process control and product characterization, in keeping with the fundamental principles of GMPs, is both possible and expected. Aseptic processing, thorough documentation, and quality assurance/quality control (QA/QC) programs should be in place. While full process validation would not be feasible at this stage, process qualification runs would be expected. More extensive process and analytical development and validation should take place over time, to result in full GMP compliance by the pivotal trial stage.

Conclusions

To date, only one of the three GTP rules has been issued in final form, but certainly it will not be long before the remaining two rules are also finalized. GTP and GMP regulations, and IND/IDE premarket approval mechanisms, applied according to FDA's risk-based regulatory

strategy, provide a rational regulatory pathway for cell, gene, and tissue therapies. Although compliance with these requirements will be a significant challenge for clinician–investigators and laboratories producing HCT/Ps, the regulations fundamentally support good clinical care by increasing safety and control, and enable good science by improving the quality and reliability of data. These outcomes are in everyone's interest.

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