Chapter 9

Regulatory Issues in the Therapeutic Use of Stem Cells

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1. Introduction

1.1. Stem cell tourism

Advances in stem cell research and media publicity of stem cell potential have raised the hopes of patients with severe disabilities and conditions which lack a cure. While stem-cell-based therapies are the clinical standard of care for a few conditions, such as leukemia and more recently for some burns and corneal disorders, stem cell tourism continues to rise worldwide.

Unfortunately, clinics around the world are exploiting patients' hopes by offering supposed stem cell therapies, without credible scientific rationale, oversight or patient protections. Occurring particularly in Asia and South America, treatments which are illegal in most counties are being offered for what are often considered incurable conditions, such as brain tumors, congestive heart failure or chronic obstructive pulmonary disease. In addition, countless other conditions are listed as candidates by these clinics including eye disease or orthopedic injuries or disease. In response to this, the International Society for Stem Cell Research (ISSCR) released "The *Guidelines for the Clinical Translation of Stem Cells"* which called for rigorous standards in the development of stem cell therapies and outlining what needs to be accomplished to move stem cells from promising research to proven treatments[1]. The goal of ISSCR in shining this light on the dangers of stem cell tourism is to ensure that the promise of stem cell research is delivered to patients in a safe, effective and fair manner. A number of professional organizations have also published guidance documents for the responsible conduct in translational stem cell research.

The general public receives information regarding stem cell potential from mainstream media and does not fully understand the risks associated with unproven treatments. In the

most desperate situations, patients may see no other options, or may view the years of continuing research as an obstacle to their potential cure. Yet, untested treatments can be dangerous and years of preclinical and clinical research are required to determine which novel stem-cell based therapies are effective and safe. In one example, brain tumors were discovered in a 9-year old boy who travelled to Russia to receive stem cell treatments to his brain; later it was found that the tumors were the result of cells from at least 2 different donors [2]. Even carefully planned and approved studies can go wrong and have unfortunate results, as in the fatal gene therapy case of Jesse Gelsinger, who received experimental therapy at University of Pennsylvania[3, 4].

Lau et al reported on the clinics around the world that are exploiting patients' hopes by professing to have effective stem cell therapies for seriously ill patients. These therapies often carry a hefty pricetag. However, they occur in counties which have limited oversight and allow treatment to occur in the absence of credible scientific rationale, transparency, oversight, or patient protections [5].

Comprehensive government regulations exist in the US, and several other countries. Below, we describe the U.S. and other government regulations associated with the use of human stem cell and tissues in regenerative medicine.

2. Cell Products must follow FDA regulatory guidelines

2.1. FDA's risk-based approach

To protect the public from risks associated with cell therapies and demonstrate the effectiveness of treatments, the U.S. FDA and other professional societies such as the ISSCR, and the United States Pharmacopia (USP), have established guidelines for therapies using human cellular and tissue-based products (HCT/Ps). The FDA has statutory authority to prevent the spread of communicable diseases granted under Section 361 of the Public Health Service Act (PHS Act, 42 U.S.C. § 264). HCT/Ps are regulated through a risk-based approach outlined predominantly in 21 C.F.R. Part 1271. Some HCT/Ps are regulated solely under Part 1271 while other HCT/Ps are regulated under both Part 1271 and FDA's Federal Food, Drug, and Cosmetic Act (FDCA, premarket and post- market regulation of medical devices and drugs), & section 351 of the PHS Act for biological products. FDA's regulation focuses on three general areas: 1) limiting the risk of transmission of communicable disease from donors to recipients; 2) establishing manufacturing practices that minimize the risk of contamination; 3) requiring an appropriate demonstration of safety and effectiveness for cells and tissues that present greater risks due to their processing or their use [6, 7].

Stem cell therapies show excellent promise for many types of treatments. However, scientific, manufacturing and safety challenges exist. Once the optimal stem cell type is identified for a given treatment (Table 1), there is a requirement to demonstrate the product's safety and efficacy in a clinical setting. Cell therapies must overcome several challenges before they can be considered safe for human use. First, most cell therapies will

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require large numbers of cells. Large cell doses are obtained by increasing cell harvest yields and by increasing ex vivo expansion yields. As cell cultures are expanded over long time periods, they show signs of aging that may be similar to human aging [8, 9]. Lengthy expansion periods can result in ineffective cellular products[10]. Cells may also be manipulated in other manufacturing steps that include cell-selection processes, genetic modifications, or encapsulation with another biological device. Cells that undergo ex vivo manipulation may lose potency, or acquire infectious contaminants, or become transformed / tumorogenic due to the cell culture conditions [11, 12]. Finally, the cells themselves may pose a risk, simply due to the novelty of the therapy and unknowns associated with their behavior in the body.

	Embryonic Stem Cells	***Adult iPS***	***Adult BM-MSCs***	***Adult Adipose MSC***
Ethical concerns	*[56-60]*	*[61-67]*		
Tumorogenic	*[68-72]*	*[59, 73-75]*		*[76-79]*
Scale-Up challenge	*[80-83]*		*[84-86]*	*[87]*
Genetically unstable	*[88, 89]*	*[34, 39, 90-94]*		*[95]*
Immunogenic difficulties	*[96, 97]*	[37, 98]		

Table 1. Scientific and Manufacturing Challenges in Stem Cell Sourcing *(numbers refer to literature references)* Several stem cell types are studied for their potential use in regenerative medicine, including, but not limited to, embryonic stem cells [20-27], inducible pluripotent stem cells [28-41], bone-marrow stem cells [42-46] and adipose-derived stem cells [47-55]. However, there are challenges with all stem cell types. A major concern with clinical application of iPSCs is their tendency to form tumors and cause cancer. Both ESC and iPSCs form teratoma in vivo, a major obstacle to stem-cell based regenerative medicine by the FDA. Also they are ethically controversial since they require genetic engineering using oncogenes. More recently, proteins have been used to generate piPSCs but the conversion efficiency us quite low. Adult derived BM-MSCs or adipose MSC are limited by their expandability.

In 1993, the US FDA began establishing regulatory and guidance documentation for cell therapies with the issuance of Application of Current Statutory Authority to Human Somatic Cell-therapy and Gene-therapy Products [13] which provided a biologics regulatory framework for the use of HCT/Ps. Table 2 provides a list of other key regulatory and guidance documents. The tiered risk-based approach means that products which present a lower perceived risk will be less regulated, while products with a larger perceived risk will undergo more extensive controls and examination. Both will require the cell products to be manufactured following Good Manufacturing Practices (GMP), and Good Tissue Practices (GTP). Additional regulatory requirements will depend on whether the cell product is minimally manipulated or more-than-minimally manipulated.

Guidance for Industry: Guidance for human somatic cell therapy and gene therapy		**1998**
GMPs	GMP	2001
Suitability determination for donors of HCT/Ps; proposed rule	GTP	1999
Current good tissue practice for manufacturers of HCT/Ps; inspection and enforcement; proposed rule		2001
Human cells, tissues and cellular and tissue-based products (HCT/Ps); establishment registration and listing; final rule		2001
Good clinical practice, GCP, ICH E6	GCP	1996
Validation of procedures for processing of human tissues intended for transplantation: final guidance		2002
Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products		2007
Guidance for Industry Potency Tests for Cellular and Gene Therapy Products		2011

Table 2. Key US FDA Regulatory and Guidance Documents. Over the past 15 years, the FDA has provided several guidance documents for HCT/Ps. A few products such as Genezyme's *Carticel* received approval prior to the issuance of these documents and has been grandfathered in. Many of these guidance documents are issued by CBER, the center within FDA that regulates biological products for human use following applicable federal laws, including the Public Health Service Act and the Federal Food, Drug and Cosmetic Act.

Minimal manipulation is defined by the FDA for cells or nonstructural tissue as processing that does not alter relevant biological characteristics of cells or tissues. HCT/Ps that meet 1271 criteria for regulation solely under section 361 of the PHS Act and the regulations in Part 1271 are called "361 HCT/Ps", and are not subject to any premarket review requirements. The Center for Biologics Evaluation and Research (CBER) has jurisdiction over 361 HCT/Ps.

According to 21 CFR 1271.10, minimal manipulation criteria include:

1. The HCT/P is minimally manipulated;

2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

3. The manufacture of the HCT/P does not involve the combination of the cell or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

4. Either:

i. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

ii. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

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a. is for autologous use;

b. is for allogeneic use in a first-degree or second-degree blood relative; or

c. is for reproductive use.

For cells, minimal manipulation means processing that does not alter the relevant biological characteristics of cells or tissues. Examples of products regulated as 361 HCT/Ps include bone marrow or blood transplants and organ transplants.

HCT/Ps that do not meet one or more of the four major criteria, are considered more-than-minimally- manipulated HCT/P. FDA has stated that density-gradient separation, cell selection, centrifugation, and cryopreservation constitute minimal manipulation. All processes that manipulate the cell / tissue product such as cell activation, encapsulation, ex vivo expansion, and gene modifications are considered more-than-minimal manipulations. Most advanced cellular therapies meet criteria for the more-than minimally manipulated category [14]. Finally, it is possible to request an informal jurisdictional determination on the level of manipulation from the Tissue Reference Group (TRG), or submit a formal Request for Designation (RFD) from the Office of Combination Products (OCP). Figure 1 is a schematic of regulatory pathway assessment to determine which guidelines apply to a given HCT/Ps product.

2.2. Manufacturing of HCT/Ps requires GTPs

For HCT/Ps that do not meet the criteria established in Section 1271.10, FDA premarket review is required; this includes obtaining FDA license, approval, or clearance.

All steps in the manufacturing of HCT/Ps will require compliance with Current Good Tissue Practice (cGTPs). cGTPs cover manufacturing facilities and processes. The manufacturing process can be broadly described as 1) procurement of HCT/Ps (donor screening and testing, product recovery), 2) processing of HCT/Ps (tissue or cell recovery /isolation, product handling, product labeling), 3) storage (e.g. cryopreservation), and 4) distribution. Many of these steps are common to GTPs and GMPs with the goal of safe and effective products via well-controlled processes and thorough supporting documentation. Requirements for standard operating procedures (SOPs), labeling controls, and storage requirements also exist.

2.2.1. Procurement

Therapies with HCT/Ps will require a determination of donor eligibility. For the FDA, donor eligibility is determined based on donor screening and testing for relevant communicable disease agents and diseases, and is required for all donors of cells or tissue used in HCT/Ps, with some exceptions listed in C.F.R. Part 1271.90.

As part of clinical or industry compliance with donor testing requirements, procedures to process, store, label, and package cell products also are needed. Hospitals and companies involved in cell/tissue therapeutics manufacturing must establish quality programs which consist of a comprehensive system for manufacturing and tracking HCT/Ps. The quality

program must follow CGTP requirements, and be designed to prevent, detect, and correct deficiencies that may lead to circumstances that increase the risk of introduction, transmission, or spread of communicable diseases.[6, 7]

2.2.2. Processing

The implementation of a Quality Assurance (QA) program includes principles of good manufacturing practice (GMP) and a quality control (QC) system. A QC system is required to ensure safety and efficacy of cell applications. GMP regulations apply to all phases of cell/tissue collection, processing and expansion, and storage. GMP quality practices are required for HCT/Ps to be used for clinical procedures and INDs. A compliant quality program for record and process control is a critical part of a QC system.

A compliant material control program is essential for FDA licensure. During review of new license applications, clinics and companies are asked to provide detailed descriptions of the manufacturing process and documentation of source country for all materials of animal origin. Additionally, for FDA-regulated products intended for administration to humans, companies must minimize any chance that BSE could be introduced into products during the manufacturing process and ensure that all materials are used as intended in the processing and are contamination free. Subsequently, a program for control of materials used in the process is necessary to meet FDA compliance and product safety.

2.2.3. Storage

If the HCT/P product involves cryopreservation, then compliance requires that the process includes an understanding of the shelf-life and how the freezing & storage process affects the HCT/Ps to complete the quality testing program. Banked cells should be stored under conditions shown to be suitable for long-term stability. Cell/tissue stability under the freezing and storage conditions should be validated using cell recovery or viability data. It is expected that establishment of a stability program for a banking process will lead to the development of quality products over a long term storage period and provide confidence that they will be effective in clinical applications.

2.2.4. Distribution testing

For the lot release of patient's cells/tissues for clinical use, standards for in-process and final product quality must be established. Specifically for FDA licensure, companies must submit their facility controls, process controls, and product standards designed with scientific principles to ensure the safety and effectiveness of all HCT/Ps products. This again is based on SOPs and controls for adherence to the cGTP, Current Good Manufacturing Practice (cGMP) and 21 CFR 1271 requirements. Product lot release specifications ensure that all products are produced in a safe and consistent manner and should be effective in clinical applications. In order to meet HCT/Ps regulations, product lot release specification should include testing for cell phenotype to confirm purity, potency, and identity.

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The application for licensure requires that companies demonstrate that the HCT/P product standards and procedures are based on good science, and thorough and extensive data. A comprehensive product characterization program is needed to understand the products and how they may be clinically beneficial. During the application process, the FDA may request that the hospital or company applicant expand on a concept or further explain the rationale/approach or provide additional data. FDA premarket review and licensing is considered a lengthy and arduous process, however new products applicants may benefit by the recent approvals of several cell-based products (Table 3).

Product **(Company)**	**Condition**	**Cell Type**	**Approval**
Carticel **(Genzyme BioSurgey)**	Articular cartilage damage in the knee	Autologous chondrocytes (adult/differentiated)	US FDA approval 1997 (grandfathered in)
Apligraf **(Organogenisis)**	Diabetic foot ulcers and venous leg ulcers	Neonatal foreskin allogeneic keratinocytes and fibroblasts in bovine collagen scaffold	US FDA approval 1998
Provenge **(Dendreon)**	Asypmptomatic or hormone refractory prostate cancer	Autologous dendritic cells (adult/differentiated)	US FDA approval 2010
Gintuit **(Organogenesis)**	Asypmptomatic or hormone refractory prostate cancer	Autologous dendritic cells (adult/differentiated)	US FDA approval 2010
La Viv **(Fibrocell Science inc)**	Moderate to severe nasolabial fold wrinkles	Autologous fibroblasts (adult/differentiated)	US FDA approval 2012
ChondroCelect® (**TiGenix**)	Single symptomatic cartilage defects in the knee	Autologous chondrocytes (adult/differentiated)	EMEA approval 2009
Prochymal (**Osiris**)	Graft vs. host disease in children who are refractory to steroid therapy post-BMT	Allogeneic mesenchymal stem cells from donor bone marrow	Health Canada/New Zealand grant conditional approval 2012
Hearti-cellgram-AMI (**FCB-Pharmicell**)	Heart repair post-myocardial infarction	Autologous bone marrow-derived mesenchymal stem cells	Korean approval 2011
Cartistem **(Medipost)**	Traumatic and degenerative osteoarthritis	Allogeneic mesenchymal stem cells from donor umbilical cord blood	Korean approval 2012
Cupistem **(Anterogen)**	Anal fistula in Crohn's Disease	Autologous fat-derived 'stem cells'	Korean approval 2012

Table 3. Approved Cell Therapy Products by the U.S. FDA and non-3rd World Countries. Several cell products have received US approval[99] and are in current use for a number of patients. Most US approved products are for autologous use, only Apilgrafs foreskin cells are used allogeneically. Osiris recently received conditional approval for allogeneic use of mesenchymal stem cells in pediatric graft-vs-host disease.

3. Non-U.S. regulatory systems

The European Union, Australia and Canada and other countries have established similar regulatory systems for the use of post-natal human HCT/Ps.

The European Medicines Agency (EMEA) is the regulating body with authorization and supervision of cell therapy products and other "advanced therapy medicinal products" [15]. As of January 2011, the EMA's Committee for Advanced Therapies (CAT) recognized the potential of stem cell therapies and released a reflection paper to work in conjunction with the *Guideline on Human Cell-based Medicinal Products* (EMEA/CHMP/410869/2006) for the Marketing Authorization Application (MA). Both the reflection paper and the guidance detail the quality and manufacturing, non-clinical, and clinical aspects required for MA approval. The quality and manufacturing considerations include starting and raw materials, manufacturing process, quality control, validation of the manufacturing process, development pharmaceutics, traceability and biovigilance, and comparability. Pharmacology and toxicology are the non-clinical development aspects to be considered. From a clinical development standpoint, general aspects, pharmacodynamics, pharmacokinetics, dose finding studies, clinical efficacy, clinical safety,pharmacovigilance, and risk management plans are necessary for approval.

In Australia, HCT/Ps or products (biologicals) are regulated by the Therapeutic Goods Administration (TGA) which is the Australian equivalent to the FDA. Similar to the FDA approach, the TGA's regulatory framework for biological imposes varying levels of regulation on the therapy or product depending on risk, extent of manipulation, and whether the intended use of the biological is its *usual biological function[16].* In order to gain approval a treatment that used a biological, and the biologicals intended use was not its normal function, a hospital or company would be required to submit substantial evidence that the particular therapy or product is safe, effective and of high quality.

In order for a stem cell therapy to be approved by Health Canada it must meet the regulations as stated in the Safety of Human Cells, Tissues and Organs for Transplantation Regulations (CTO Regulations[17]). The CTO Regulations detail requirements to ensure safety in processing; storage; record keeping; distribution; importation; error, accident and adverse reaction investigation and reporting. Requirements for donor screening, testing, and suitability assessment are described in the processing regulations as well as the testing and measurements performed on the products after retrieval or in preparation for use, preservation, or packaging[17].

Health Canada, the FDA equivalent in Canada, is the first approving body in the world to approve a manufactured stem cell based drug intended to treat a systemic disease -acute Graft versus Host Disease (aGvHD) [18]. Osiris Therapeutics of Columbia, Maryland developed Prochymal [remestemcel-L, adult human mesenchymal stem cells (hMSCs) for intravenous infusion], a liquid cell suspension of ex vivo cultured adult MSCs derived from the bone marrow of healthy adult donors. Prochymal is the first stem cell therapy approved for clinical use in patients, specifically pediatric patients. Health Canada required Osiris to continue a Risk Management Plan to demonstrate that the benefits of Prochymal continue to outweigh

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risk, the addition of post-market studies, and maintenance of a treated patient registry for approval[19].

Table 3 provides a list of cell therapy products that have received U.S. FDA approval or other government approval. Despite extensive stem cell research over the past 15 years, most cell products are not stem cell derived. Only Osiris' BM-MSC product and 3 Korean products are stem cell based products.

4. Conclusions

This report examines the different processes involved in HCT/Ps manufacturing and highlights the guidelines that must be followed to obtain FDA or other country specific regulatory approval. Ex vivo expansion, cell selection or gene modification will likely be necessary for most advanced cell and tissue therapies. These modifications increase the risk associated with the treatment and render the product to be regulated under a higher risk category of more-than-minimally-manipulated product. Key to biomanufacturing is the implementation of a QA/QC program including a quality control system and GMP principles which apply to all phases of manufacturing.

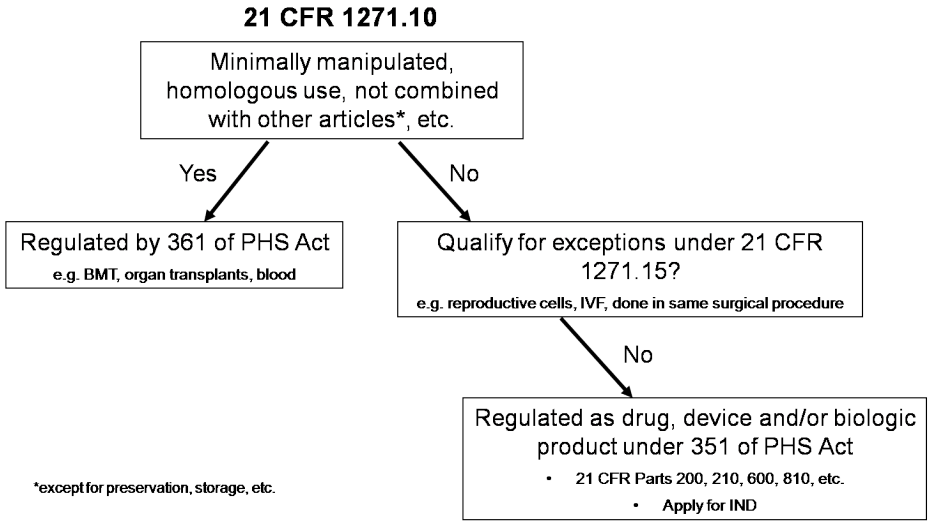

Figure 1. Regulatory Pathway Assessment If an HCT/Ps product is minimally manipulated it is regulated as a "361 HCT/Ps", and it is not subject to any premarket review requirements. However, if the HCT/Ps is more-than-minimally manipulated, and does not qualify for exemptions under 21 CFR 1271.15, it will be regulated as drug, device and/or biologic product under 351 of the PHS Act.

Many counties actively regulate the use of stem cell products, however, there are still a number of areas around the world that have little regulations and unregulated treatments

pose risk to patients and the careful development of the field. The current challenge to deliver safe cell and tissue therapies and curb unregulated treatments may soon apply to gene therapy and other innovative technologies. Early government regulation and active education by a number of professional organizations should reduce the spread of medical tourism and aid in the development of safe and effective treatments in the field of regenerative medicine.

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