

Boston College Law School

From the Selected Works of Mary Ann Chirba

February, 2015

FDA Regulation of Adult Stem Cell Therapies as Used in Sports Medicine

Mary Ann Chirba, *Boston College Law School*

Berkly Sweetapple, *Boston College Law School*

Charles P. Hannon

John A. Anderson

Available at: https://works.bepress.com/maryann_chirba/51/



FDA Regulation of Adult Stem Cell Therapies as Used in Sports Medicine

Mary Ann Chirba, JD, DSc, MPH¹ Berkley Sweetapple, JD¹ Charles P. Hannon, BS²
John A. Anderson, MD, MSc³

¹ Boston College Law School, Newton Centre, Massachusetts

² Georgetown University School of Medicine, Washington, District of Columbia

³ Department of Sports Medicine, Rothman Institute, Philadelphia, Pennsylvania

Address for correspondence Mary Ann Chirba, JD, DSc, MPH, 855 Centre Street, Newton Centre, MA 02459 (e-mail: maryann.chirba@bc.edu).

J Knee Surg 2015;28:55–62.

Abstract

Keywords

- ▶ mesenchymal stem cells
- ▶ adipose stem cells
- ▶ HCT/Ps
- ▶ FDA Section 361
- ▶ FDA Section 351
- ▶ minimal manipulation
- ▶ sports medicine
- ▶ cartilage
- ▶ ACL
- ▶ meniscus

In sports medicine, adult stem cells are the subject of great interest. Several uses of stem cells are under investigation including cartilage repair, meniscal regeneration, anterior cruciate ligament reconstruction, and tendinopathy. Extensive clinical and basic science research is warranted as stem cell therapies become increasingly common in clinical practice. In the United States, the Food and Drug Administration (FDA) is responsible for regulating the use of stem cells through its “Human Cells, Tissues, and Cellular and Tissue-Based Products” regulations. This report provides a brief overview of FDA regulation of adult stem cells. Several common clinical case scenarios are then presented that highlight how stem cells are currently being used in sports medicine and how current FDA regulations are likely to affect the physicians who use them. In the process, it explains how a variety of factors in sourcing and handling these cells, particularly the extent of cell manipulation, will affect what a physician can and cannot do without first obtaining the FDA’s express approval.

Over the past decade, interest in regenerative medicine and adult stem cell therapies in sports medicine has expanded rapidly around the world. With the ability to self-renew and differentiate into multiple types of cells and tissues, adult stem cells hold significant promise. In sports medicine, basic science and clinical research is investigating the use of stem cells in several areas including, but not limited to: osteoarthritis,^{1,2} articular cartilage repair,^{3,4} anterior cruciate ligament (ACL) reconstruction,^{5–8} tendon healing,^{9–12} and meniscus regeneration.^{13–15}

To the authors’ knowledge, the first randomized control trial on the intra-articular injection of human mesenchymal stem cells into the knee was recently published, and demonstrated their safe use and potential ability to regenerate meniscal tissue.¹⁵ A review of clinicaltrials.gov indicates that in May 2014, over 45 clinical trials were being conducted

worldwide on the use of stem cells in orthopedic pathologies of the knee. Interest in the field of regenerative medicine has even prompted elite athletes to travel worldwide to receive intra-articular therapies such as Regenokine[®] and Regenexx[®], which are advertised as containing adult stem cells. With great promise, however, comes potentially great risk. Safety concerns remain because the process of differentiating into so many cell and tissue types is not well understood, and the means of regulating these pathways are often unknown.

Pluripotent stem cells may hold the greatest therapeutic potential because they can differentiate into virtually any cell type. Pluripotent stem cells are isolated in three ways: (1) directly from human embryos (embryonic stem cells, ESCs), (2) from cloned embryos through somatic cell nuclear transfer (SCNT), or (3) from adult cells reprogrammed to a pluripotent state (induced pluripotent stem cells; iPSCs).¹⁶ As

received

May 21, 2014

accepted after revision

November 19, 2014

published online

January 20, 2015

Copyright © 2015 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0034-1398470>.
ISSN 1538-8506.

pluripotent stem cell work can involve the creation and destruction of embryos and the possibility for reproductive cloning of entire organisms, and raises concerns about uncontrolled growth (such as teratomas), their use has been complicated by serious ethical concerns and significant technical challenges. This has led to varying regulatory approaches by different countries. Some regulatory bodies will allow the use of ESCs derived from discarded embryos or in vitro fertilization.¹⁶ A smaller number will permit the creation of new ESC lines for research purposes.¹⁶ Others ban SCNT research, limit research to existing cell lines, or ban pluripotent work altogether. In the United States, research on ESCs was previously limited because federal funds could not be used to create new ESC lines. However, this has changed under the Obama administration.

Although more limited in their ability to differentiate, multipotent adult stem cells create less ethical and political controversy, tend to carry less risk, and pose fewer technical challenges than their pluripotent counterparts. In recent years, many specialties, including sports medicine and orthopedics, plastic and reconstructive surgery, cardiology, and ophthalmology, have been increasingly active in researching and developing adult stem cell therapies. Much of this work has focused on mesenchymal stem cells (most commonly bone marrow-derived and also adipose-derived stem cells [ASCs]). Bone marrow-derived mesenchymal stem cells can differentiate into several types of connective tissue including cartilage, bone, tendon, ligament, and muscle.^{17,18} Other sources of adult stem cells that have common characteristics, but are distinctive and reflective of their tissue of origin include synovium, umbilical cord, muscle, and adipose tissue.^{18,19} Each of these distinctive cell types has shown varying ability to differentiate into cartilage, bone, muscle, tendon, ligament, as well as fat.¹⁸ Interest in using ASCs in sports medicine continues to grow as they are readily accessible, abundant, and a reliable source for isolation of adult stem cells.^{20,21} To date, however, research on their use in the field of sports medicine has been limited to proof of concept/basic science studies, case reports, and phase I safety trials.^{20,22}

In the United States, the growing enthusiasm for using adult stem cell therapies in sports medicine and other areas of medical practice is often coupled with significant legal and regulatory obstacles to doing so. It is therefore important for the physician to understand how adult stem cells are regulated in the United States, and how these complex rules are likely to affect what can and cannot be done in clinical practice. The aim of this discussion is to explain the Food and Drug Administration's (FDA) current regulatory framework in the adult stem cell context and evaluate its impact on the use of stem cells in the sports medicine today.

Regulation of Adult Stem Cell Therapies in the United States

The U.S. Food and Drug Administration (FDA) regulates cell and tissue products as part of its implementation of two federal laws: the Public Health Service Act (PHSA) and the

Food Drug and Cosmetics Act (FDCA). An adult stem cell is a "biological product" under the PHSA because like a "therapeutic serum, ... blood, blood component or derivative, ... protein ... or analogous product," it is "applicable to prevention, treatment or cure of a disease or condition in human beings."²³ An adult stem cell also falls within the FDCA's definition of a "drug" because it is an "articl[e] intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease" and "intended to affect the structure or function of the body"²⁴ Finally, stem cells can constitute a "medical device," which the FDCA defines as "any product or equipment used to diagnose a disease or other conditions, to cure, to treat or to prevent disease."²⁵ Products that satisfy more than one definition can also function as combination products.

The FDA oversees cell therapies through its Center for Biologics Evaluation and Research (CBER) and Center for Devices and Radiological Health (CDRH). Since 2001, the FDA has used a three-tiered, risk-based regulatory framework to promote the safety and efficacy of human cells, tissues, and cellular and tissue-based products (HCT/Ps).²⁶ Current good tissue practices (cGTPs) apply throughout. Otherwise, the extent of regulation varies directly with the product's potential risk, especially with regard to the risk of introduction, transmission, and spread of communicable disease. Thus, depending on how a particular cell or tissue product is categorized, a physician may face relatively simple registration requirements or be held to the demanding premarketing approval requirements that bind the likes of Pfizer, Merck, and other global pharmaceutical companies when commercializing a product for mass consumption.

Before examining the regulations more closely, it is helpful to define four key terms: manufacturer, establishment, combination with another article, and minimal manipulation.²⁷ A physician becomes a "manufacturer" of HCT/Ps by engaging in any or all steps in HCT/P recovery, processing, storage, labeling, packaging, or distribution. An "establishment" is a physician's office, clinic, or any place of business under one management that manufactures HCT/Ps. As explained later, combining HCT/Ps with other "articles" can increase safety concerns and thereby increase the degree of regulatory oversight. For this reason, the regulations exempt combining the HCT/P with "water, crystalloids, or a sterilizing, preserving, or storage agent, provided that their addition poses no additional concerns regarding clinical safety."

The most important term, and the most difficult to determine in practice is "minimal manipulation." The regulation defines it separately for structural tissue and cells/nonstructural tissues,²⁷ and both are relevant to sports medicine although manipulation of cells and nonstructural tissues is the focus of this discussion. For structural tissue, minimal manipulation involves "processing of the HCT/P [that] does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement." For cells or nonstructural tissues, minimal manipulation is "processing of the HCT/P [that] does not alter the relevant biological characteristics of cells or

tissues.” The degree of cell manipulation is critical in determining where an HCT/P will fall in the following three-tiered framework.

Category 1: No HCT/P Oversight

Products in this category are not regulated as HCT/Ps because they are deemed to be of low risk. Category 1 includes vascularized human organs for transplantation, whole blood and blood-derived products, and extracted human products such as collagen and bone marrow that are minimally manipulated, for homologous use and not combined with another article (except for the purpose of sterilizing, preserving, or storing).²⁷ By default, Category 1 also includes cells that are expressly exempted from Categories 2 and 3, described later. For this discussion, the most significant exemption covers “an establishment that removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure”²⁸—but again, this applies only if HCT/Ps are minimally manipulated, for homologous use and not combined with other articles. Physicians or clinicians who use Category 1 products must follow cGTPs, but otherwise need not register as an establishment with the FDA’s CBER or submit a list of the HCT/Ps used.

Category 2: Section 361 Products with Minimal Oversight

The FDA views Section 361 products as posing a greater risk with regard to safety and regulates them more extensively to prevent contamination, infection, and disease transmission. Section 361 products that are commonly used in sports medicine include bone, cartilage, ligament, tendon, and skin.²⁹ However, to fall within Section 361, these products must be:

1. No more than minimally manipulated which, again, for structural tissue, means preserving the “original relevant characteristics of the tissue relating to the tissue’s utility for reconstruction, repair, or replacement”²⁷ and for cells or nonstructural tissues, prevents a change in the “relevant biological characteristics of cells or tissues”²⁷ during processing, storage, etc.
2. Used for a homologous purpose.
3. Combined with no other cells, tissues, or articles except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that their addition poses no additional concerns regarding clinical safety.
4. These products must also have either
 - a. No systemic effect or otherwise depend on the metabolic activity of living cells for their primary function or
 - b. A systemic effect or depend on the metabolic activity of living cells for their primary function, and for
 - i. Autologous use
 - ii. Allogeneic use in a first- or second-degree blood relative, or
 - iii. Reproductive use

For cells and nonstructural tissues, certain methods have been expressly characterized as minimal manipulation; that is, as involving no change in cell function or characteristics

during processing, storage, and the like. They include the following:

- Centrifugation
- Cutting, grinding, or shaping
- Soaking in antibiotic solution
- Sterilization by ethylene oxide treatment or irradiation
- Cell separation
- Lyophilization
- Cryopreservation or freezing

Physicians who use or “manufacture” Section 361 HCT/Ps must employ cGTPs, register their office or clinic as an “establishment,” and submit an annually updated list of each HCT/P manufactured to CBER.^{30,31} They need not obtain premarketing approval before using the product or follow current Good Manufacturing Practices (cGMPs) in preparing them.

Category 3: Section 351’s Extensive Regulation of HCT/Ps as Biologics and Drugs

Products are most likely to shift from the comparatively relaxed oversight of Section 361 to the more stringent requirements of Section 351 if—at least in the FDA’s view—they present greater risks. While Section 361 focuses on safety and preventing infection and disease transmission, Section 351 concentrates on both safety and effectiveness. For the clinician, this imposes more onerous requirements (such as cGMPs and premarketing approval) with little distinction between individuals and small physician practices versus larger pharmaceutical industries. Thus, cells or processing methods that fail to satisfy any of Section 361’s requirements will cast a product into the heavily regulated Section 351 track.

A product will fall within Section 351 if it is one or more of the following:

1. More than minimally manipulated, which for cells and nonstructural tissue means to present a risk of change in cell morphology, function, expression, or other relevant biological characteristics during processing, storage, etc.
2. Used for a nonhomologous purpose.
3. Combined with other articles that may pose additional concerns regarding clinical safety.
4. Have a systemic effect or otherwise rely on the metabolic activity of living cells for its primary function, and be used in a context other than autologous use, allogeneic use in a first or second degree relative, or reproductive use.

Like Section 361, Section 351 requires an establishment to register and file a list of its HCT/Ps with CBER each year. The main reason why Section 351 is more problematic in the clinical setting, however, is that, it also requires the physician or clinic to complete the burdensome and expensive process of obtaining formal premarket approval from the FDA. This can involve submitting a New Drug Application, an Investigational New Drug Application, Biologics License Application, or, when dealing with a Section 501k medical device, a premarket approval application or premarket notification. Costly and time-consuming controlled

clinical trials may be needed to establish product safety, purity, potency, efficacy, and stability. In addition, physicians using Section 351 HCT/Ps must follow the FDA-prescribed cGMPs and prescription drug labeling requirements that govern commercial pharmaceutical manufacturers. Without premarket approval, cGMPs, and/or proper labeling, a Section 351 HCT/P is an “adulterated” and/or “misbranded” drug and biologic under the FDCA and the PHSA, respectively. This remains true even if the patient is being treated with her own cells. Using such adulterated and misbranded products exposes the physician and the clinic to FDA sanctions including orders of retention, recall, destruction of the HCT/P, cessation of manufacturing, and/or shutdown of the entire facility.³²

It must be emphasized that Section 351 applies equally to autologous and allogeneic use in contrast to Section 361, which treats autologous and allogeneic use differently. Consequently, treating a patient with a Section 351 HCT/P means that the physician as “manufacturer” and the office, clinic, or hospital as “establishment” are “marketing” the cell product. Treatment of this kind requires premarket approval even if those cells are to be injected into the same patient from which they were harvested.

Adult Stem Cells in Sports Medicine: The Physician, the Regulator, and the Courts

The FDA’s authority to promulgate, interpret, and enforce its three-tiered, risk-based HCT/P regulations was recently tested in the *U.S. v. Regenerative Sciences, LLC*, where, after years of litigation, a federal appellate court upheld the agency’s power to regulate adult stem cells as drugs and biologics.³³ The decision demonstrates the longstanding legal principle that courts will defer to the broad discretion of an agency to regulate matters within its scope of authority, especially in matters that demand scientific expertise. The court therefore affirmed the FDA’s decision to categorize a mixture of cultured mesenchymal stem cells and doxycycline as a Section 351 product that needed to comport with cGMPs and prescription labeling requirements, and obtain premarketing approval before it could be used to treat various orthopedic injuries.

Specifically, Drs. Christopher Centeno and John Schultz, through their company Regenerative Sciences and the Colorado-based Centeno-Schultz Clinic, used their “Cultured Regenexx Procedure” to isolate mesenchymal cells from bone marrow or synovial fluid, transport them off-site to a separate laboratory, culture the cells for several weeks (so as not to involve the “same surgical procedure”), mix them with other products including doxycycline and heparin, and transport them back to the clinic where they would be reinjected into the same patient. The court found that:

1. The Regenexx cell product satisfied the statutory definitions of a “drug” under the FDCA and a “biologic” under the PHSA and, therefore, fell within the FDA’s authority to regulate HCT/Ps.
2. The Regenexx Procedure could be regulated simultaneously under state law as the practice of medicine, and under federal law through the FDA’s HCT/P regulations. Although derived from bone marrow (often exempted from HCT/P oversight under Category 1) and intended for autologous use (often covered by Section 361), the Regenexx cell product was properly regulated under Section 351 because it was more than minimally manipulated insofar as it was: cultured; exposed to different temperatures and media; and “combined” with other “articles” (including doxycycline and heparin)—all of which could affect relevant biological characteristics of the cell, including cell function, and differentiation; and, with regard to doxycycline, cause infection, severe allergic reaction, or other adverse events.
3. Under Section 351, the physicians as “manufacturers” and the clinic as an “establishment” were required to:
 - a. Register the establishment with CBER
 - b. Submit an annually updated list of all HCT/Ps used (or “marketed”) to CBER
 - c. Obtain formal premarket approval before using (i.e., “marketing”) the cell product to treat patients—even when the cells were for autologous use
 - d. Fulfill all requirements regarding manufacturing/cGMPs, processing, and packaging
 - e. Fulfill all labeling requirements for a prescription drug, including labeling it as “Rx only” and providing adequate “directions under which the layman can use a drug safely and for the purposes for which it is intended.”³⁴
4. By violating Section 351’s requirements for manufacturing, processing, and premarket approval, the physicians and clinic had engaged in the unlawful distribution of an “adulterated drug.”
5. They had also distributed a “misbranded drug” because Section 351’s labeling requirements had not been satisfied.
6. The FDA was therefore within its authority to enforce its HCT/P regulations for Section 351 cell products which, in this case, resulted in permanently enjoining the physicians and clinic from using the Regenexx procedure in the United States to treat orthopedic injuries.

Impact of HCT/P Regulations on Sports Medicine Going Forward

To ensure compliance with these complex regulations and avoid the kinds of sanctions and expensive litigation that ensued in the Regenerative Sciences case, a physician must evaluate whether a particular procedure involves a less regulated Category 1 “non-HCT/P,” a Category 2/Section 361 HCT/P, or a Category 3/heavily regulated Section 351 product. Unfortunately, this can be quite difficult for a variety of reasons. Under the HCT/P regulations, a Section 361 versus Section 351 product may result from the same substance being subjected to different conditions that—again, at least in the FDA’s view—present different degrees of risk so as to warrant different levels of oversight. The physician must therefore remember that how a particular adult stem cell

therapy is categorized and regulated will depend, at least in part, on:

- The source of that cell (e.g., bone marrow vs. fat)
- The degree of cell manipulation in isolating or processing that cell (e.g., centrifuge vs. culture)
- The homologous or nonhomologous use of that cell, and
- The ultimate recipient of that cell (autologous vs. allogeneic).

Accordingly, the same cell from the same source in the same donor may be a Category 1/non-HCT/P or Category 2/Section 361 product if it is minimally manipulated; homologous; not combined with articles involving safety concerns; and for autologous use, allogeneic use for a close blood relative or reproductive use. Alternatively, that same cell from the same source in the same donor may qualify as a heavily regulated Category 3/Section 351 HCT/P if it is more than minimally manipulated, and used in a way that is nonhomologous, nonreproductive and/or allogeneic beyond a first- or second-degree relative.

Determining which regulatory track applies is also difficult because as therapies evolve and technologies improve, definitional ambiguities remain unresolved. In this respect, one of the most difficult challenges is defining what qualifies as minimal versus more than minimal manipulation because this distinction is a key factor in determining whether premarketing approval is required under Section 351. Therefore, to evaluate the Section 361 versus Section 351 divide as it presents in clinical practice and illustrate how FDA oversight will increase with increasing degrees of cell manipulation, we present the following examples of manipulating adult stem cells for use in sports medicine:

1. Isolation by centrifugation
2. Stromal-vascular fracture with collagenase
3. Culture and expansion

In the process, we also discuss the impact of the following:

- a. Bone marrow versus adipose-derived cells
- b. Homologous versus nonhomologous use
- c. Autologous versus allogeneic use
- d. Harvested, processed, and reinjected during “the same surgical procedure”
- e. Harvested, processed, and reinjected in the United States versus another country.

Before proceeding, we must emphasize that our evaluation of the following hypotheticals is predictive, not definitive. To date, the technical and therapeutic capabilities of researchers and physicians have outpaced the ability of regulators to respond to the particular challenges and opportunities of adult stem cell therapies (especially for autologous use). Existing regulations were created to address other kinds of clinical applications and often provide an awkward fit for adult stem cell therapies. With regard to the procedures discussed later, there is little in the way of actual agency enforcement or formal guidance. As a result, we have had to rely on the few resources that do exist: the HCT/P regulations, the Regenerative Sciences litigation, and the FDA’s draft and

final guidance documents and warning letters. In this context, however, the agency’s finalized guidance documents are few to none and guidance documents are, by definition, merely suggestive and subject to change. Looking to tentative draft guidances to predict future regulatory enforcement is even more problematic, especially where the agency has yet to evaluate public comments on its most recent draft guidances. Despite these uncertainties, we offer our best prediction of how the FDA would view the following scenarios—some of which differ only to a small degree. We include them because one small change in clinical practice can unleash a significant jump in regulatory demands.

Application of Current FDA Regulations to Adult Stem Cell Use in Sports Medicine

1A. Intraoperative Isolation of Autologous Bone Marrow–Derived Stem Cells by Centrifugation and Injection

Using cells under these conditions is likely to qualify as a Category 1 “non-HCT/P” because the cell product involves a specifically exempted product (bone marrow), is autologous, used for a homologous purpose, and not combined with other articles. Moreover, the FDA has long viewed centrifugation as minimal manipulation. Recent draft guidances,^{35–37} however, have created some confusion as to whether it will continue to do so. In our view, it is likely that the ambiguous wording of these draft guidances will be clarified to continue to characterize centrifugation and other means of physical separation as forms of minimal manipulation. Under these circumstances, this cell product should be exempted from oversight under Category I. Therefore, clinicians can most likely use this cell product without having to comply with either Section 361’s requirements to register as an establishment and list all HCT/Ps used with CBER, or satisfy Section 351’s additional requirements regarding premarket approval, cGMPs, and labeling.

Should the bone marrow and/or same surgical procedure exemptions not apply so as to disqualify the cell product from Category 1, it should at most be covered by Category 2/Section 361 because it is still autologous, used for a homologous purpose, and most likely not more than minimally manipulated.

1B. Intraoperative Isolation of Autologous Adipose-Derived Stem Cells by Centrifugation and Injection of Stromal Vascular Fraction

Current regulations treat stem cells derived from bone marrow and fat differently. Bone marrow–derived stem cells explicitly qualify as Category 1/non-HCT/Ps but only if they are for autologous and homologous use, minimally manipulated, not combined with articles that raise safety concerns, and have no systemic effect. Adipose tissue–derived stem cells are not expressly exempted and, therefore, are typically regulated as Category 2/Section 361 or Category 3/Section 351 products depending on the level of manipulation, intended use, etc. A recent draft guidance would subject adipose stem cells, which are obviously cellular, to the structural

as opposed to cellular definition of minimal manipulation.^{35–37} This immediately incited a broad array of concerns among clinicians that may sway the FDA to alter its position.

The scenario described here, however, should involve the kind of “same surgical procedure” that is exempt from Sections 361 and 351 because—again, presuming the FDA clarifies or dismisses its recent draft guidances—it most likely entails minimal manipulation with homologous and autologous use, and is harvested, processed, and reinjected without interruption of the overall process. For this and any clinical fact situation, a question could be raised as to whether using an adipocyte technically qualifies as homologous use as the cell source—fat—arguably has little to do with the object of repair. To date, this has not been a regulatory focus but the FDA has signaled that it will examine this more closely. For now, this procedure would most likely fall within Category 1’s same surgical procedure exemption as the cells are withdrawn, centrifuged, separated, and reinjected into the same patient, and completed within the same room during a time frame of several hours. Under Category 1, the treatment could go forward with no need to register the establishment, submit lists of HCT/Ps, obtain premarket approval or follow manufacturing or labeling requirements.

At most, it is likely to fall within Category 2’s relatively minimal Section 361 oversight as cell separation is accomplished through centrifugation, a form of minimal manipulation, and the resulting product will be used autologously. Should Section 361 control, the physician as “manufacturer” would need to register the office, clinic, or hospital as an “establishment” with CBER, and also provide CBER with an annually updated list of all HCT/Ps used at that establishment.

2. Intraoperative Selective Isolation of Adipose-Derived Stem Cells through Treatment of the Stromal-Vascular Fraction with Collagenase and Albumin and Injection

The aim of adding collagenase is to produce a higher yield of stem cells than would otherwise be obtained by centrifuge alone. The FDA has not formally defined whether or not this constitutes more than minimal manipulation. However, several agency warning and nonbinding guidance documents issued by the FDA indicate that introducing an enzyme to increase yield may qualify as more than minimal manipulation as it may pose a risk of changing cell behavior or characteristics.

Should the introduction of collagenase be viewed as minimal manipulation, the procedure will fall within Category 2/Section 361 and require establishment registration and HCT/P listing with CBER. It must be emphasized that when evaluating risk in order to predict a procedure’s regulatory status, what matters most is how the FDA views a procedure. Consequently, even if a physician or group of physicians deems the introduction of collagenase to present little risk to cell morphology and behavior, the FDA has broad discretion to disagree. Its informal statements to date suggest that it will characterize SVF with collagenase as more than minimal manipulation, thereby triggering Category 3’s Section 351 requirements. As a result, the clinic/establishment has two

choices. First, it can attempt to persuade the FDA to classify this or any specific procedure as minimal manipulation under Category 2/Section 361. Unless that effort succeeds, its second and only remaining option is to abide by Section 351 and complete all of the following:

- Register with CBER
- Submit lists of HCT/Ps used to CBER
- Follow cGMPs for pharmaceutical drugs
- Follow prescription drug labeling requirements
- Undertake the time and expense involved in obtaining premarket approval (including controlled clinical trials)

Failing to satisfy any of these requirements will expose the physician and clinic to increasingly stiff sanctions, ranging from site inspections and warning letters to a permanent injunction of the procedure or a shutdown of the entire establishment.³²

3A. Harvest, Culture, and Expansion of Autologous Bone Marrow-Derived Stem Cells with Delayed Injection in the United States

These facts parallel those of *U.S. v. Regenerative Sciences, LLC*,³⁵ as discussed earlier. That case makes it fairly certain that, absent full satisfaction of Section 351’s premarketing approval, cGMPs and labeling requirements, this patient would have to leave the United States to be treated with cells that have been cultured and expanded. This would apply even though the cells are her own. As previously discussed, the FDA has long viewed centrifugation alone as minimal manipulation and will hopefully clarify recent draft guidelines to maintain this position. In *Regenerative Sciences*, however, removing the cells from the place of treatment, culturing, and expanding them over several weeks, and adding such “articles” as doxycycline and heparin to the culture product and returning them to the clinic for use in the patient was, in the FDA’s view, clearly more than minimal manipulation as these measures escalated the risk of contamination, infection, disease transmission, and change in the cell’s composition and behavior. Physicians who use this or similar processes should comply with Section 351, shift to alternative Category 1 or Category 2 methods of processing, or conduct this work outside the United States.

3B. Harvest of Autologous Bone Marrow-Derived Stem Cells in the United States with Culture, Expansion, and Delayed Injection Overseas

Foreign travel for the sake of undergoing treatment may reduce the likelihood of FDA enforcement, but it does not necessarily eradicate it. Harvesting cells in the United States may be enough, and preparing the cell product in the United States should be more than enough to subject the physician to Section 351 premarketing approval requirements—and penalties for noncompliance—even if the actual administration of the resulting cell product occurs offshore. A physician should err on the side of caution and presume that performing even a small step in the sequence between cell harvest and reinjection will support the FDA’s jurisdiction to enforce its HCT/P regulations in full.

3C. Harvest, Culture, and Expansion of Autologous Bone Marrow–Derived Stem Cells with Delayed Injection Overseas

In this case, the entire process of harvesting, culturing, expanding, and injecting the patient's own stem cells occurs overseas. This is beyond the scope of FDA jurisdiction. However, through its formal Global Initiative, the FDA is currently forging collaborations with countries around the world to harmonize regulations. The central goal of this effort is to build regulatory capacity and develop international standards so that all the countries will employ similar approaches when regulating medical drugs and devices, including adult stem cell therapies.

3D. Allogeneic Bone Marrow–Derived Stem Cell Harvest, Culture, Expansion, and Injection

Bone marrow-derived autologous stem cells are typically harvested from the iliac crest. The bone marrow aspirate is then centrifuged, stem cells are isolated and then injected into the same patient's injury site. In contrast, allogeneic stem cells are isolated from a donor other than the patient and then injected into the patient's injury site. If the allogeneic donor is a first- or second-degree blood relative, the procedure may be treated as if it were autologous, meaning that it could qualify for minimal Section 361 oversight if it is also homologous and not more than minimally manipulated. The clinic would need to register as an establishment and submit HCT/P lists to CBER, but it would not need to follow cGMPs or labeling requirements, or obtain premarket approval.

A donor other than a first- or second-degree relative would shift this procedure into the realm of Section 351. Consequently, in addition to Section 361's registration and listing requirements, the physician/manufacturer and clinic/establishment would be required to fulfill cGMPs and labeling requirements for prescription drugs, and obtain formal premarket approval before using the cell product to treat a patient.

Future of Adult Stem Cell Therapies in Sports Medicine

The current enthusiasm for the use of adult stem cells in sports medicine will surely grow as the basic science and clinical applications advance. At the same time, there is great confusion about the meaning and enforcement of the FDA's complex scheme for regulating stem cell therapies—and this confusion will also grow as therapeutic options expand. It is therefore imperative that the sports medicine physician be familiar with current regulations; remain mindful that regulations evolve over time regarding both content and interpretation; and remember that the FDA's rationale is not always obvious to those who are regulated.

Thus, when dealing with HCT/P regulations, the physician would be wise to err on the side of caution: assume that a regulation applies, and assume that the FDA will be risk-adverse in its interpretation and enforcement (particularly with regard to minimal vs. more than minimal manipulation). Furthermore, given the great promise of cell therapies, the complexity of their regulation, the ease of derailing from the

Section 361 track into Section 351, and the high stakes for noncompliance, obtaining regulatory updates from an attorney or compliance officer is not just beneficial, but increasingly necessary. In this way, physicians can focus their resources on counseling patients who need the more effective and less invasive treatments that adult stem cells can offer. Failing to seek regulatory guidance sooner rather than later does not avoid risk; it creates its own risk—one that is significant, probably expensive, and largely avoidable.

References

- 1 Koh YG, Choi YJ, Kwon OR, Kim YS. Second-look arthroscopic evaluation of cartilage lesions after mesenchymal stem cell implantation in osteoarthritic knees. *Am J Sports Med* 2014;42(7):1628–1637
- 2 Jo CH, Lee YG, Shin WH, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. *Stem Cells* 2014;32(5):1254–1266
- 3 Anderson JA, Little D, Toth AP, et al. Stem cell therapies for knee cartilage repair: the current status of preclinical and clinical studies. *Am J Sports Med* 2014;42(9):2253–2261
- 4 Gobbi A, Karnatzikos G, Sankineani SR. One-step surgery with multipotent stem cells for the treatment of large full-thickness chondral defects of the knee. *Am J Sports Med* 2014;42(3):648–657
- 5 Fan H, Liu H, Toh SL, Goh JCH. Anterior cruciate ligament regeneration using mesenchymal stem cells and silk scaffold in large animal model. *Biomaterials* 2009;30(28):4967–4977
- 6 Kanaya A, Deie M, Adachi N, Nishimori M, Yanada S, Ochi M. Intra-articular injection of mesenchymal stromal cells in partially torn anterior cruciate ligaments in a rat model. *Arthroscopy* 2007;23(6):610–617
- 7 Figueroa D, Espinosa M, Calvo R, et al. Anterior cruciate ligament regeneration using mesenchymal stem cells and collagen type I scaffold in a rabbit model. *Knee Surg Sports Traumatol Arthrosc* 2014;22(5):1196–1202
- 8 Proffen BL, Haslauer CM, Harris CE, Murray MM. Mesenchymal stem cells from the retropatellar fat pad and peripheral blood stimulate ACL fibroblast migration, proliferation, and collagen gene expression. *Connect Tissue Res* 2013;54(1):14–21
- 9 Beitzel K, Solovyova O, Cote MP, et al. The future role of mesenchymal stem cells in the management of shoulder disorders. *Arthroscopy* 2013;29(10):1702–1711
- 10 Ruzzini L, Longo UG, Rizzello G, Denaro V. Stem cells and tendinopathy: state of the art from the basic science to clinic application. *Muscles Ligaments Tendons J* 2012;2(3):235–238
- 11 Pascual-Garrido C, Rolón A, Makino A. Treatment of chronic patellar tendinopathy with autologous bone marrow stem cells: a 5-year-followup. *Stem Cells Int* 2012;2012:953510
- 12 Isaac C, Gharaibeh B, Witt M, Wright VJ, Huard J. Biologic approaches to enhance rotator cuff healing after injury. *J Shoulder Elbow Surg* 2012;21(2):181–190
- 13 Zellner J, Hierl K, Mueller M, et al. Stem cell-based tissue-engineering for treatment of meniscal tears in the avascular zone. *J Biomed Mater Res B Appl Biomater* 2013;101(7):1133–1142
- 14 Hatsushika D, Muneta T, Nakamura T, et al. Repetitive allogeneic intraarticular injections of synovial mesenchymal stem cells promote meniscus regeneration in a porcine massive meniscus defect model. *Osteoarthritis Cartilage* 2014;22(7):941–950
- 15 Vangness CTJ Jr, Farr J II, Boyd J, Dellaero DT, Mills CR, LeRoux-Williams M. Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: a randomized, double-blind, controlled study. *J Bone Joint Surg Am* 2014;96(2):90–98

- 16 Bongso A, Lee EH. *Stem Cells: From Bench to Bedside*. Singapore: World Scientific Publishing Co. Pte. Ltd; 2011
- 17 Caplan AI. New era of cell-based orthopedic therapies. *Tissue Eng Part B Rev* 2009;15(2):195–200
- 18 Murray IR, Corselli M, Petrigliano FA, Soo C, Péault B. Recent insights into the identity of mesenchymal stem cells: Implications for orthopaedic applications. *Bone Joint J* 2014;96-B(3):291–298
- 19 da Silva Meirelles L, Chagastelles PC, Nardi NB. Mesenchymal stem cells reside in virtually all post-natal organs and tissues. *J Cell Sci* 2006;119(Pt 11):2204–2213
- 20 Gimble JM, Guilak F, Bunnell BA. Clinical and preclinical translation of cell-based therapies using adipose tissue-derived cells. *Stem Cell Res Ther* 2010;1(2):19
- 21 Guilak F, Estes BT, Diekman BO, Moutos FT, Gimble JM. 2010 Nicolas Andry Award: Multipotent adult stem cells from adipose tissue for musculoskeletal tissue engineering. *Clin Orthop Relat Res* 2010;468(9):2530–2540
- 22 Koh YG, Jo S-B, Kwon OR, et al. Mesenchymal stem cell injections improve symptoms of knee osteoarthritis. *Arthroscopy* 2013; 29(4):748–755
- 23 42 U.S.C. § 262 (i)(1)
- 24 21 U.S.C. § 321(g)(1)(B)-(C)
- 25 21 U.S.C. § 360(c)
- 26 21 CFR. 1271
- 27 21 CFR. 1271.3
- 28 21 CFR. 1271.15(b)
- 29 21 CFR. 1271.10
- 30 21 CFR 1271.3(b) and (e), respectively
- 31 21 CFR. 1271.(1)
- 32 32 CFR. 1271.440
- 33 *US v. Regenerative Sciences, LLC*, 741 F.3d 1314 (D.C. Cir. 2014)
- 34 21 C.F.R. 201.5
- 35 FDA. *Minimal Manipulation of Human Cells, Tissues and Cellular and Tissue-Based Products*; December 2014
- 36 FDA. *Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations*; December 2014
- 37 FDA. *Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception*; October 2014
- 38 *Declaration of Steven R. Bauer, PhD, US v. Regenerative Sciences, LLC*. (D.D.C. January 7, 2011)