**Boston College Law School**
**Digital Commons @ Boston College Law School**

Boston College Law School Faculty Papers

1-1-2011

# FDA Oversight of Autologous Stem Cell Therapies: Legitimate Regulation of Drugs and Devices or Groundless Interference with the Practice of Medicine?

Mary Ann Chirba
*Boston College Law School*, chirbama@bc.edu

Stephanie M. Garfield

Follow this and additional works at: http://lawdigitalcommons.bc.edu/lsfp

Part of the Administrative Law Commons, and the Health Law Commons

Recommended Citation
Mary Ann Chirba and Stephanie M. Garfield. "FDA Oversight of Autologous Stem Cell Therapies: Legitimate Regulation of Drugs and Devices or Groundless Interference with the Practice of Medicine?." *Journal of Health & Biomedical Law,* 7, (2011): 33-272.

This Article is brought to you for free and open access by Digital Commons @ Boston College Law School. It has been accepted for inclusion in Boston College Law School Faculty Papers by an authorized administrator of Digital Commons @ Boston College Law School. For more information, please contact nick.szydlowski@bc.edu.

*Journal of Health & Biomedical Law, VII (2011):233-272*
*© 2011 Journal of Health & Biomedical Law*
*Suffolk University Law School*

# FDA Oversight of Autologous Stem Cell Therapies: Legitimate Regulation of Drugs and Devices or Groundless Interference with the Practice of Medicine?

Mary Ann Chirba, J.D., D.Sc., M.P.H.*

Stephanie M. Garfield, J.D.**

## I. Introduction

> [T]he term 'stem cells' is inexact. And it's really more akin to the term 'seeds.' We appreciate that not all seeds are alike. An apple seed makes apple trees, an orange seed makes orange seeds. And when we talk about apples and oranges, we don't get them confused. Well, the distinctions between seeds are essential to the biologist, just as the distinctions among different stem cell types are essential.[1]
>
> Excerpt from Senate testimony of George Q. Daley, MD, PhD.

Just as slight variations between different sources of stem cells are crucial to understanding the real policy debate over when life begins under the law, slight permutations in the federal regulations and guidelines for stem cell research can have

---

* Associate Professor of Legal Reasoning, Research, & Writing; J.D., Boston College Law School; D.Sc. and M.P.H. Harvard School of Public Health.
** Attorney; J.D., Boston College Law School.

[1] *Can Congress Help Fulfill the Promise of Stem Cell Research?: Joint Hearing Before the Comm. of Health, Education, Labor, and Pensions, and the Subcomm. on Labor, Health and Human Services, Education, and Related Agencies of the Comm. on Appropriations*, 110th Cong. 13 (2007) (statement of George Q. Daley, M.D., Ph.D.), *available at* http://www.gpo.gov/fdsys/pkg/CHRG-110shrg32808/pdf/CHRG-110shrg32808.pdf [hereinafter Daley Testimony].

serious ramifications for advancing the science of stem cell research and therapeutic applications. As human embryonic stem cell ("ESC") research has garnered widespread press coverage and generated enormous public controversy for over a decade,[2] scientists and physicians have been finding generous amounts of less controversial, adult stem cells ("ASCs") in an increasingly wide array of human tissue. These discoveries promise new and urgently needed therapies for patients but also pose novel challenges for regulators. This is especially so here, where many ASC therapies are emerging from the offices of practicing physicians instead of the laboratories of university or commercial research scientists.

All stem cells are "undifferentiated" or unspecialized; beyond that, different categories of stem cells are characterized by their source. Embryonic stem cells are derived from the blastocyst stage of an embryo, which means the embryonic stem cell is developed prior to the implantation in the uterine wall.[3] ESCs are "pluripotent" because potentially, a single embryonic stem cell can be coaxed into differentiating into any kind of cell found in the developed organism.[4] Therapeutic applications include directing ESCs to become specific kinds of cells for the purpose of understanding a particular disease or medication, replacing or repairing a certain kind of tissue, or creating an entirely new organ for transplantation.[5] Adult stem cells qualify as stem cells because they too are undifferentiated, but they are adult in that they are found among cells that have already differentiated into a particular kind of tissue.[6] ASCs are "multipotent" in that they are able to differentiate, but they are more limited in their ability to develop into cell types and tissues that differ from the original tissue from which they were derived.[7] ASCs function primarily to restore dying cells and repair damaged tissue.[8] Unlike the more controversial ESC therapies, many ASC treatments rely on autologous cells, i.e., stem cells which are harvested from an individual patient and later re-injected

---

[2] Christine Vestal, *Stem Cell Research at the Crossroads of Religion and Politics*, PEW FORUM (Jul. 17, 2008), http://pewforum.org/Science-and-Bioethics/Stem-Cell-Research-at-the-Crossroads-of-Religion-and-Politics.aspx (last visited May 11, 2011) (discussing the history of the ESC debate in the United States).

[3] NAT'L INST. OF HEALTH, *Stem Cell Information-The Embryonic Stem Cell*, (Mar. 24, 2009), http://stemcells.nih.gov/info/scireport/chapter2.asp (last visited May 11, 2011).

[4] Li-Fang Chu & Thomas P. Zwaka, *Human Pluripotent Cells: The Biology of Pluripotency*, HUMAN STEM CELL TECH. & BIOLOGY: A RESEARCH GUIDE & LAB. MANUAL 313, 313 (2011).

[5] *See* Richard Mollard, *Embyonic Stem Cells*, INT'L SOC'Y FOR STEM CELL RES., *available at* http://www.isscr.org/public/ES_cells.pdf.

[6] NAT'L INST. OF HEALTH, *Stem Cell Basics: What Are Adult Stem Cells?* (Mar. 24, 2009), http://stemcells.nih.gov/info/basics/basics4.asp (last visited May 11, 2011).

[7] *See* Maria Borowski & Gary S. Stein, *Pluripotent Stem Cells: Biology & Applications*, HUMAN STEM CELL TECH. & BIOLOGY: A RESEARCH GUIDE & LAB. MANUAL 3, 5 (2011).

[8] *See* NAT'L INST. OF HEALTH, *Stem Cell Basics: What Are Adult Stem Cells?*, *supra* note 6.

into that same patient to restore deteriorated tissue.[9] ASCs are believed to have vast reparative potential due to their undifferentiated state and ability to self-renew; further, ASCs have recently been located in more organs and tissues than previously thought possible, including the brain, heart, bone marrow, skeletal muscle, skin, teeth, and—a surprisingly rich source of ASCs—human adipose tissue, or fat.[10] To date, ASCs have been used to accelerate wound repair,[11] restore degenerated discs or joints in animal studies,[12] and may soon assist in reversing degenerative diseases like age-related macular degeneration and Parkinson's disease.[13]

Developing ASC therapies have been so promising that the technology is no longer confined to the clinical laboratories of academic institutions or pharmaceutical manufacturers. Practicing physicians and surgeons are increasingly taking the lead in treating patients with ASC therapies, particularly with the patient's own autologous ASCs.[14] In theory, this may seem like a brave new world, but in practice, extracting and re-injecting a patient's own cells is not that different from other reparative or surgical procedures. For instance, coronary artery bypass graft surgery typically removes the saphenous vein from the patient's leg with the purpose of using that vein to re-route coronary circulation to bypass an occluded artery.[15] Spinal surgery often uses bone from a patient's pelvis or rib to fuse vertebrae.[16] Further, withdrawing adult stem cells from adipose tissue is much less invasive than either of these or many other procedures

---

[9] *See* NAT'L INST. OF HEALTH, *Stem Cell Basics: What Are the Potential Uses of Adult Stem Cells and the Obstacles that Must Be Overcome Before These Potential Uses Will Be Realized?* (Mar. 24, 2009), http://stemcells.nih.gov/info/basics/basics6.asp (last visited May 11, 2011).

[10] *See id.*

[11] *See, e.g.*, Mario Cherubino, et al., *Adipose-Derived Stem Cells for Wound Healing Applications*, 66 ANNALS OF PLASTIC SURGERY 210, 210-15 (2011).

[12] *See, e.g.*, Timothy Ganey et al., *Intervertebral Disc Repair Using Adipose Tissue-Derived Stem and Regenerative Cells: Experiments in a Canine Model*, 34 SPINE 2297 (2009) (reporting effective lumbar disc regeneration from autologous stem and regenerative cells in study consisting of twelve dogs).

[13] *See, e.g.*, Michael Day, *Stem Cell Research: A New Age Dawns in Healthcare*, TELEGRAPH (Oct. 19, 2010), http://www.telegraph.co.uk/health/8072484/Stem-cell-research-a-new-age-dawns-in-healthcare.html (last visited May 11, 2011).

[14] *E.g.*, DANA-FARBER CANCER INST., *Dana-Farber Stem Cell Transplantation* (2011), http://www.dana-farber.org/Adult-Care/Treatment-and-Support/Treatment-Centers-and-Clinical-Services/Stem-Cell-Transplantation-Program.aspx (last visited May 11, 2011) (discussing Dana-Farber/Brigham and Women's Cancer Center's ASC transplantation program).

[15] NAT'L HEART LUNG & BLOOD INST., *What Is Coronary Artery Bypass Grafting?*, http://www.nhlbi.nih.gov/health/dci/Diseases/cabg/cabg_whatis.html (last visited May 11, 2011).

[16] Peter F. Ullrich, *Autograft: The Patient's Own Bone*, SPINE-HEALTH (Nov. 25, 2009), http://www.spine-health.com/treatment/spinal-fusion/autograft-patients-own-bone (last visited May 11, 2011).

relying on the patient's own tissue. The fact that such procedures have recently become a matter of routine is largely attributable to the innovations of physicians and surgeons involved in the practice of medicine (who, for the sake of this discussion, along with other health care providers will be collectively referred to as "physicians"). Obviously, autologous ASC therapies have yet to reach such widespread acceptance since understanding where ASCs exist and how they can be used is relatively new.[17] Nevertheless, as they have for so many other therapies, doctors have made significant strides in understanding where to find ASCs and developing therapeutic treatments, especially for autologous ASCs. [18]

In recent years, the federal Food and Drug Administration ("FDA") has quietly asserted its regulatory authority over physicians who have bridged the gap between adult stem cell research and treatment. It has done so despite the fact that it lacks jurisdiction over the practice of medicine, an area that is traditionally within the scope of state law.[19] Prior to 2005, the FDA did not assert regulatory authority over autologous ASC therapies primarily because the patient would receive her own cells back.[20] This all changed in 2005, however, when a subtle modification in a single regulation, implemented without public notice and comment rulemaking, laid the groundwork for a major expansion of FDA oversight of regenerative, ASC therapies using both autologous and allogenic cells. [21]

In an untitled letter dated July 25, 2008, the FDA first asserted its regulatory authority over the ASC therapies advertised and performed by Regenerative Sciences, a Colorado-based medical practice and its physician owners.[22] The FDA specifically

---

[17] *See* NAT'L INST. OF HEALTH, *Stem Cell Information-Executive Summary* (Mar. 24, 2009), http://stemcells.nih.gov/info/scireport/execSum.asp (last visited May 11, 2011) (highlighting that adult stem cells have been extensively studied but are still difficult to identify, isolate, and purify).

[18] *See* Jason Blevins, *Stem-Cell Therapy Feels Food and Drug Administration's Pinch*, DENV. POST, (Aug. 19, 2010), http://www.denverpost.com/news/ci_14871656?source=email (last visited May 11, 2011).

[19] 21 C.F.R. § 1271 (2006); *see also* Dina Gould Halme & David A. Kessler, *FDA Regulations of Stem-Cell-Based Therapies*, 355 NEW ENG. J. MED. 1730, 1730-31 (2006) (describing FDA's authority to regulate "tissue based products").

[20] *See* 21 C.F.R. § 1270.1(c) (2006) (stating that "regulations for this chapter do not apply to autologous human tissue); *see also* FDA WEBSITE-TISSUE & TISSUE PRODUCT QUESTIONS & ANSWERS, http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/Questionsabout Tissues/ucm101559.htm (last visited May 11, 2011) (stating that all tissues recovered prior to May 25, 2005, are regulated under 21 C.F.R. Part 1270).

[21] *See* 21 C.F.R. § 1271; *see also infra* notes 134, 206 and accompanying text.

[22] Letter from Mary A. Malarkey, Dir. of Compliance and Biologics Quality, U.S. Food & Drug

targeted their "Regenexx Procedure," which was promoted as an alternative to invasive orthopedic surgery.[23] The technique involves isolating a patient's own stem cells, culturing them in the lab using growth factors drawn from the patient's own blood, and re-injecting the multiplied autologous ASCs back into the patient's body.[24] Based on its review of the Regenerative Sciences website, the FDA determined that this procedure constituted a "drug" under section 201(g) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and a "biological product" under section 351(i) of the Public Health Service Act ("PHSA"), thereby subjecting Regenerative Sciences to the same requirements that govern commercial manufacturers of mass produced drugs.[25]

In response, Regenerative Sciences filed two lawsuits challenging the FDA's jurisdiction to regulate the use of a patient's own adult stem cells when performed by a medical practice (as opposed to a commercial manufacturer).[26] It first filed suit in the United States District Court for the District of Colorado in February 2009, alleging that the FDA had exceeded its regulatory authority under the FDCA and the PHSA.[27] After this was dismissed for lack of ripeness,[28] Regenerative Sciences filed a second suit against the FDA in June 2010, this time in the United States District Court for the District of Columbia.[29] It sought to enjoin the FDA to either take formal agency action against it or abandon its enforcement activities.[30] In August 2010, the FDA, acting

---

Admin., to Christopher J. Centeno, M.D., Med. Dir., Regenerative Sci., Inc. (July 25, 2008), *available at* http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatory Information/ComplianceActivities/Enforcement/UntitledLetters/ucm091991.htm.

[23] *See id.* The FDA letter quotes the Regenexx site as characterizing the procedure as restorative and as a less disruptive alternative to surgery. *See id.*

[24] REGENEXX, *Procedure Explained*, http://www.regenexx.com/the-regenexx-procedure-explained (last visited May 11, 2011).

[25] *Id.* (noting how the FDA determined the procedure to constitute a drug). *See generally* Food, Drug, and Cosmetic Act § 201(g), 21 U.S.C. 321(g)(1) (2006); Public Health Service Act § 351(i), 42 U.S.C. 262 (2006).

[26] *See* Complaint for Declaratory Judgment Against United States Food & Drug Admin., Regenerative Sci. Inc. v. United States Food & Drug Admin, No. 1:09-CV-00411 (D. Colo. Feb. 26, 2009); Complaint Against United States Food & Drug Admin., Regenerative Sci. Inc. v. United States Food & Drug Admin, No. 1:10-CV-01055 (D. D.C. filed June 22, 2010).

[27] *See* Complaint for Declaratory Judgment Against United States Food & Drug Admin., Regenerative Sci. Inc. v. United States Food & Drug Admin, No. 1:09-CV-00411 (D. Colo. Feb. 26, 2009).

[28] *See* Order of Dismissal, Regenerative Sci. Inc. v. United States Food & Drug Admin, No. 1:09-CV-00411, at *9 (D. Colo. Feb. 26, 2009).

[29] *See* Complaint Against United States Food & Drug Admin., Regenerative Sci. Inc. v. United States Food & Drug Admin, No. 1:10-CV-01055 (D. D.C. filed June 22, 2010).

[30] *See* Complaint Against United States Food & Drug Admin., Regenerative Sci. Inc. v. United States Food & Drug Admin, No. 1:10-CV-01055, at *13 (D. D.C. filed June 22, 2010).

through the United States Department of Justice ("DOJ") filed its own suit against Regenerative Sciences in the U.S. District Court for the District of Columbia.[31] Alleging that the Regenexx Procedure is subject to regulation under the FDCA and PHSA, the FDA is currently attempting permanently to enjoin Regenerative Sciences from treating patients with autologous ASC therapies.[32] Regenerative Sciences agreed to stay its June 2010 lawsuit against the FDA pending the resolution of the FDA's claims.[33]

This article discusses why the FDA's decision to assert jurisdiction over physicians producing autologous ASC therapies sets a dangerous precedent. It begins with an historical overview of the FDCA and the PHSA and explains the FDA's definition of "drug" and "biologic product" in interpreting and applying these laws. Next, it examines the FDA's lawsuit against Regenerative Sciences, with the goal of evaluating whether the FDA *can*, as well as whether it *should*, exert such regulatory authority over independent medical practices.

This article concludes that given the degree of judicial deference accorded to an agency's rule-making discretion to interpret and apply its authorizing statutes, the FDA is likely to prevail in its effort to subject physicians involved in direct patient care to a regulatory scheme designed for mass drug manufacturers. Nevertheless, as explained herein, the FDA should abandon its current stance since it impedes medical advances and therefore undermines the agency's overall purpose of advancing public health. This article recommends that the FDA either revert to its pre-2005 regulation, which acknowledged that autologous and allogenic ASCs carry different risk potentials and treated them accordingly, or follow the European Commission's lead in crafting a flexible regulatory regime to accommodate the interests of physicians and commercial drug manufacturers while promoting *both* safety and innovation.

---

[31] *See* Complaint Against Regenerative Sci. Inc., United States v. Regenerative Sci. Inc., No. 1:10-CV-01327 (D. D.C. filed Aug. 8, 2010).

[32] *See* Complaint Against Regenerative Sci. Inc., United States v. Regenerative Sci. Inc., No. 1:10-CV-01327, at *6, *8 (D. D.C. filed Aug. 8, 2010).

[33] *See* Jennifer B. Davis, *Rulings Issued in Two Unrelated Lawsuits Challenging FDA's Authority Under Section 361 of the PHS Act*, FDA LAW BLOG (Apr. 12, 2010, 2:07 PM), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2010/04/rulings-issued-in-two-unrelated-lawsuits-challenging-fdas-authority-under-section-361-of-the-phs-act.html (last visited May 11, 2011) (discussing the dismissal of Regenerative Science's case in the U.S. District Court for the District Court of Colorado).

## II. Discussion

### A. The Evolution of FDA Regulation of "Biologics" and "Drugs" and its Impact on the Practice of Medicine

That the Commerce Clause empowers Congress to protect the general public from unsafe medical products has been well established for over a century.[34] Moreover, the United States Supreme Court has consistently found federal food and drug statutes, such as the Biologics Act, the Pure Food and Drug Act, and the Food, Drug, and Cosmetic Act, all discussed below, to be a valid exercise of that power.[35] As the agency charged with interpreting and enforcing such laws,[36] the FDA can expect substantial judicial deference toward its actions via *Chevron* analysis.[37] Nevertheless, the Supreme Court has invalidated, albeit infrequently, FDA actions for exceeding the agency's statutory power to define drugs or biologics subject to FDA oversight[38] and has also curtailed its preemption of state law in certain instances, primarily because of conflict, as opposed to complete preemption.[39] The tension between deference to agency discretion

---

[34] *See, e.g.*, Hipolite Egg Co. v. United States, 220 U.S. 45, 57 (1911) (characterizing the 1906 Pure Food and Drug as an appropriate means to execute the power the Constitution conferred upon Congress).

[35] *See, e.g.*, United States v. Sullivan, 332 U.S. 689, 696 (1948) (finding implicitly that the FDCA is a valid exercise of Commerce Clause power). "For the Act as a whole was designed primarily to protect consumers from dangerous products." *Id.*

[36] *See, e.g.*, Medtronic, Inc. v. Lohr, 518 U.S. 470, 482 n.5 (1996). These statutes delegate enforcement authority to the Secretary of Health and Human Services, which in turn, delegates it to the FDA.

[37] FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 132 (2000) (citing Chevron, U.S.A., Inc. v. NRDC, Inc., 467 U.S. 837, 842 (1984)). The Court explained that, as required by *Chevron*, when Congress "has directly spoken to the precise question at issue . . . [the reviewing court] must give effect to the unambiguously expressed intent of Congress." *Id.* Otherwise, a court "must respect the agency's construction of the statute so long as it is permissible." *Id.*

[38] *See id.* at 156 (FDA lacks jurisdiction to regulate tobacco products as drugs and drug delivery devices).

[39] *See, e.g.*, Wyeth v. Levine, 555 U.S. 555 (2009) (finding no conflict preemption by FDA drug labeling regulations, as found in 21 C.F.R. section 314.70, of certain state tort claims for inadequate warnings in the absence of congressional intent); Lohr, 518 U.S. at 503 (holding similarly as *Wyeth* for regulations of Medical Device Amendments to the FDCA, 21 USC § 301 et seq.). Courts should engage a "starting presumption" against federal preemption of state law, especially in areas rationally left to state control. N.Y. Conf. Blue Cross & Blue Shield Plans v. Travelers Ins. Co., 514 U.S. 645, 654-655 (1995). "Complete" or "field" preemption occurs when Congress intends to legislate in an area to the exclusion of any state laws, even compatible ones; whereas, "conflict" preemption permits federal and state laws to co-exist unless the state law conflicts or interferes with the operation of the federal statute. *See generally* Rice v. Santa Fe Elevator Corp., 331 U.S. 218, 230 (1947) (describing the basic legal principles of preemption by

and concern for preserving the operation of state law in areas traditionally subject to state control, such as the practice of medicine, permeates FDA jurisprudence and will undoubtedly continue to do so in the Regenexx litigation. For a better understanding of how this will play out, an overview of the evolution and impact of the Biologics Act, the Pure Food and Drug Act, and the Food, Drug, and Cosmetic Act is essential.

*1. The Biologics Act*

In 1902, after thirteen children died from receiving a contaminated vaccine, Congress enacted the Biologics Act[40] to allow federal regulation of "biologics," such as a "virus, therapeutic serum, toxin, antitoxins . . . or analogous product" that were intended for the "prevention, treatment, or cure of a disease or condition of human beings."[41] The goal of this legislation was to maintain the quality of biologics by focusing on manufacturing activities concerning production, labeling, and interstate movement of biologics,[42] while continuing to abstain from regulating the biologic products themselves.[43] Manufacturers now had to obtain a federal "establishment license" to produce and market a biologic,[44] which tended to favor large manufacturers since smaller firms often lacked the resources to implement stringent quality control measures and comport with other licensing prerequisites.[45]

---

the federal government).

[40] *See* Philip D. Noguchi, *From Jim to Gene and Beyond: An Odyssey of Biologics Regulation*, 51 FOOD & DRUG L.J. 367, 367-68 (1996).

[41] Biologics Act of 1902, 42 U.S.C. § 262(i)(1); *see also* Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, §§ 7001-7003, 124 Stat. 119 (amending 42 U.S.C. § 262(i)) (defining a biological product as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein . . . or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings"). The 2009 Biologics Price Competition and Innovation Act was enacted for the purpose of providing an abbreviated approval pathway for follow-on (i.e., generic) biologics. Biologics Price Competition and Innovation Act of 2009 §§ 7001-7003. Under this legislation, the FDA regulates this approval process. *Id.*

[42] *See* 42 U.S.C. § 262(a)(1)(A); Gary E. Gamerman, *Regulation of Biologics Manufacturing: Questioning the Premise*, 49 FOOD & DRUG L.J. 213, 217-18 (1994).

[43] *See generally* 42 U.S.C. § 262.

[44] *See* Al Ghignone, *The Product License Application* (PLA), *in* BIOLOGICS DEVELOPMENT: A REGULATORY OVERVIEW 146 (Mark Mathieu ed., 1993).

[45] *See* JONATHAN LIEBENAU, MEDICAL SCIENCE & MEDICAL INDUSTRY: THE FORMATION OF THE AMERICAN PHARMACEUTICAL INDUSTRY 51, 79 (1987).

### 2. *The Pure Food and Drug Act*

The eventual overlap of biologics and drug regulation began in 1906, when Congress passed the Pure Food and Drugs Act ("PFDA") to quell public fears about food contamination following the publication of Upton Sinclair's harrowing account of the unsanitary meat industry in *The Jungle*.[46] While the PFDA primarily regulated foods, it also provided limited oversight of drugs that were "adulterated" (by differing from applicable standards regarding their make-up) or "misbranded" (insofar as they deviated from the brand name and ingredients contained on the package label).[47]

### 3. *The Food, Drug, and Cosmetic Act*

In 1938, Congress enacted the PFDA's successor: the Food, Drug, and Cosmetic Act ("FDCA"), which serves as the primary source of the FDA's regulatory power over drugs.[48] It authorizes the FDA to regulate "[t]he introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded," with the aim of protecting the public health.[49] While the FDCA significantly expanded federal regulatory authority, its legislative history shows that Congress never intended the FDA to regulate "the practice of medicine."[50] Senator

---

[46] Pure Food and Drug Act of 1906, Pub. L. No. 59-384, c. 3915, 34 Stat. 768 (1906) (repealed 1938); Sharlene W. Lassiter, *From Hoof to Hamburger: The Fiction of a Safe Meat Supply*, 33 WILLAMETTE L. REV. 411, 446-47 (discussing the impact of the *The Jungle* on the congressional agenda); *see also* FOOD & DRUG ADMIN., FDA HISTORY - PART I, http://www.fda.gov/About FDA/WhatWeDo/History/Origin/ucm054819.htm (last visited May 11, 2011).

[47] *See* Pure Food and Drug Act § 2, 34 Stat. at 768. The PFDA defined a drug as adulterated if it differed from either the USP "standard of strength, quality, or purity" or the product's own "[p]rofessed standard under which it was sold." *Id.* § 7, 34 Stat. at 769-70. A drug was misbranded if it was an imitation sold under the name of another product, if the original contents were removed in whole or part and replaced, or if the article neglected to state the quantity of alcohol, morphine, cocaine, heroin, etc. *See id.* § 8, 34 Stat. at 770.

[48] *See* Food, Drug, and Cosmetic Act, 21 U.S.C. § 331 (2010) (listing actions prohibited under FDCA).

[49] 21 U.S.C. § 331(a).

[50] *See* FOOD DRUG LAW INST., FUNDAMENTALS OF LAW & REGULATION: AN IN-DEPTH LOOK AT FOOD & DRUG ADMINISTRATION MODERNIZATION ACT 423, 424 (David G. Adams & Richard M. Cooper eds., 1997); *see also* Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350 (2001) ("[T]he FDA's mission [is to] . . . regulate . . . without directly interfering with the practice of medicine"); James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 76 (1998) ("[The] FDA never has had authority to regulate the practice of medicine; physicians may use legally marketed drugs or devices in any way that they believe, in their professional judgment, will best serve their patients").

Royal Copeland, the driving force behind the legislation and a physician himself, was determined to preclude FDA interference with the medical profession, explaining:[51]

> [T]he bill is not intended as a medical practices act and will not interfere with the practice of the healing art by chiropractors and others in the States where they are licensed by law to engage in such practice. It is not intended to permit the sale in interstate commerce or otherwise in Federal jurisdiction of adulterated or misbranded drugs or devices under the guise of the practice of a healing art. It is likewise not intended to permit the false advertising of drugs and devices under such guise.[52]

Accordingly, to ensure that the FDA had no role in overseeing the practice of medicine, one bill sought to limit the definition of "drug" by omitting any "medicine prepared and dispensed by a physician in the course of his professional practice."[53] However, the bill was rejected as superfluous since there was "nothing in the [FDCA] which would interfere at all with the ordinary legal practice of medicine."[54]

Despite Congress' clear intent to avoid FDA interference with the practice of medicine, a last-minute modification of the 1938 Act, which created restrictive new drug provisions, provided the basis for indirect agency interference.[55] The modified Act banned the shipment in interstate commerce of drugs that were not generally regarded as safe unless a New Drug Application ("NDA") had been filed with the Secretary of Agriculture.[56] The NDA was required to describe the drug's components and composition, the process by which it was manufactured, and the intended uses of the drug, as well as establish that the drug was safe for its intended use.[57] Although the

---

[51] *See* Peter Barton Hutt, *Regulation of the Practice of Medicine Under the Pure Food and Drug Laws*, 33 Q. BULL. ASS'N OF FOOD & DRUG OFF. 1, 7 (1969).
[52] FOOD DRUG LAW INST., *supra* note 50, at 424.
[53] *See* Hutt, *supra* note 51, at 8.
[54] *See* Hutt, *supra* note 51, at 8.
[55] *See* Hutt, *supra* note 51, at 9. These drug provisions were a direct response to the public health crisis that arose from the Elixir of Sulfanilamide incident, an improperly prepared medicine that was widely distributed and subsequently led to the deaths of one-hundred people. *See* Sharon B. Jacobs, *Crises, Congress, and Cognitive Biases: A Critical Examination of Food and Drug Legislation in the United States*, 64 FOOD & DRUG L.J. 599, 604 (2009).
[56] *See* Jacobs, *supra* note 55, at 604.
[57] Food, Drug, and Cosmetic Act, ch. 675, § 505(b), 52 Stat. 1052 (1938) (current version codified at 21 U.S.C. § 355(b)). These modifications also authorized the Secretary to suspend an existing NDA for just cause and exempt from the NDA requirements drugs intended for investigational purposes, the safety of which was to be tested by qualified experts. *See id.* § 505(h)-(i), 52 Stat.

FDA's power to determine which drugs can enter the market could have potentially circumscribed a physician's discretion in prescribing medications,[58] then section 505(b) of the FDCA was neither interpreted nor enforced to that end from 1938 to 1962.[59]

*4. The FDCA's 1962 Drug Amendments*

When Congress amended the FDCA in 1962 to require new drugs to be proven both safe and effective for their intended uses prior to being shipped in interstate commerce, it again displayed no intent to regulate the practice of medicine.[60] Instead of addressing the medical profession's involvement in disseminating information about drugs, the 1962 Amendments charge pharmaceutical manufacturers with preventing inaccurate drug labeling and advertising, avoiding misuse of drugs, and thwarting ethically questionable drug experimentation.[61]

This reflected fundamental principles of federalism and the longstanding allocation of medical drug and device oversight to the federal government,[62] while leaving intact the states' historical authority to define and regulate the practice of medicine to protect the health and safety of their citizens.[63] However, Article I of the U.S. Constitution gives Congress the authority to regulate interstate commerce, which extends to "commerce among the states," as well as to intrastate activities, "which so affect interstate commerce . . . as to make regulation of them appropriate."[64] Consequently, state oversight of the medical profession does not preclude concurrent and even preemptive federal regulation if the practice of medicine is interpreted as having a substantial effect on interstate commerce.[65] As one court explained:

To the extent that the plaintiffs' claim of unconstitutional interference

---

1053.

[58] *See id.* ch. 675, § 505(b), 52 Stat. 1052 (1938) (current version at 21 U.S.C. § 355(b)) (describing application requirements for a new drug).

[59] *See* Hutt, *supra* note 51, at 9.

[60] *See* Hutt, *supra* note 51, at 9.

[61] Hutt, *supra* note 51, at 9-10.

[62] *See* Linder v. United States, 268 U.S. 5, 18 (1925).

[63] *See, e.g.*, Nat'l Pharmacies, Inc., v. De Melecio, 51 F. Supp. 2d 45, 54-55 (D. P.R. 1999) (citing cases with similar holdings).

[64] United States v. Darby, 312 U.S. 100, 118 (1941); *see also* U.S. CONST. art. I, § 8, cl. 3 ("The Congress shall have Power . . . [t]o regulate Commerce with foreign Nations, and among the several States, and with the Indian tribes").

[65] *See, e.g.*, United States v. Whited, 311 F.3d 259, 267-72 (3d Cir. 2002); Abbott v. Bragdon, 912 F. Supp. 580, 593 (D. Me. 1995).

> with the right to practice medicine is founded on a notion of federalism which reserves all rights over such regulation to the states, it is without merit. It is undisputed that the practice of medicine is subject to the exercise of state police power where such regulation furthers a legitimate state interest. But that assumption does not imply an absence of federal jurisdiction over the same area, where the federal regulation constitutes a reasonable exercise of a power vested in Congress under the Constitution . . . . The fact that the practice of medicine is an area traditionally regulated by the states does not invalidate those provisions of the [FDCA] which may at times impinge on some aspect of a doctor's practice.[66]

To that end, the FDA has not hesitated to regulate physician activities that the FDA has deemed to have had a substantial effect on interstate commerce, such as advertising to both local and out-of-state patients, which is easily accomplished through the internet and occurs particularly where patients have an incentive to cross state lines to obtain an innovative procedure that has not yet become widely available.[67] More typically, however, the FDA targets physician entrepreneurial activities that exceed the mere exercise of professional judgment in selecting a course of treatment for patients. In this context, courts have upheld FDA enforcement actions that subject these physicians to the same regulations as large corporations.[68] Therefore, the broad power accorded to the FDA under the Commerce Clause is unlikely to prevent the agency

---

[66] Pharm. Mfrs. Ass'n v. Food & Drug Admin., 484 F. Supp. 1179, 1187-88 (D. Del. 1980). *See generally* Daniel v. Paul, 395 U.S. 298, 305 (1969) (finding a snack bar that served food to interstate travelers subject to regulation under Commerce Clause); Heart of Atlanta Motel, Inc. v. United States, 379 U.S. 241, 261-62 (1964) (finding a hotel that served interstate travelers subject to regulation under Commerce Clause); United States v. Wilson, 73 F.3d 675, 681-93 (7th Cir. 1995) (finding provision for reproductive health services substantially affects interstate commerce).

[67] *See, e.g.*, Robert J. Davis, *Surgery Money-Back Guarantees*, WALL ST. J., Apr. 16, 2002, at D6 (providing coverage of a urologist that has advertised his money-back guarantee nationally through use of billboards); Randy Kennedy, *Memo to Doctors: Cross the River*, N.Y. TIMES, Sept. 28, 1999, at B1 (reporting that residents of New Jersey often seek medical care in Philadelphia or New York City).

[68] *See, e.g.*, United States v. Burzynski Cancer Research Inst., 819 F.2d 1301, 1304-05, 1313-14 (5th Cir. 1987); Cowan v. United States, 5 F. Supp. 2d 1235, 1240 (N.D. Okla. 1998) (denying a terminally ill patient's attempt to obtain access to an unapproved AIDS drug containing goat neutralizing antibodies since the FDCA does not "permit doctors to test unapproved drugs"); Retkwa v. Orentreich, 579 N.Y.S.2d 577, 578-81 (N.Y. Sup. Ct. 1991); Cabiroy v. Scipione, 767 A.2d 1078, 1081-82 (Pa. 2001) (holding that a doctor who had injected unapproved liquid silicone into a patient was guilty of negligence *per se*).

from regulating the activities of most health care providers.[69]

*5. Defining a "Drug" Under the FDCA*

Given the FDA's perceived Commerce Clause power to affect the practice of medicine, perhaps its most significant impact on physician practice has been the FDCA's and FDA's definition of what constitutes a "drug." Section 321(g) of the FDCA defines a drug as an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease"[70] or that is "intended to affect the structure or any function of the body . . . ."[71] An article's "intended use" denotes "the objective intent of the persons legally responsible for the labeling of drugs," and can be determined by those persons' representations, including "labeling claims, advertising matter, or oral or written statements by such persons or their representatives."[72] Thus, a major point of contention in the FDA and Regenerative Sciences litigation is whether a patient's own cells, i.e., ASCs, qualify as a "drug" when a treating physician harvests and re-injects those cells in a therapeutic setting.

Courts typically give substantial deference to an agency's interpretation of its enabling statute as long as the court is confident that agency rulemaking accords with statutory text and congressional intent.[73] This has certainly been true regarding the FDA's construction of the FDCA and its interpretation of what constitutes a "drug."[74] To determine whether an article is a "drug" under the FDCA, a court will look to both the FDA's interpretation of its own statute and, as required by the statute itself, the product's intended use.[75] In making this determination, reviewing courts do not consider an article's inherent properties.[76] For example, melaleuca oil, a homeopathic

---

[69] *See Abbott*, 912 F. Supp. at 593.
[70] 21 U.S.C. § 321(g)(1)(B) (2009).
[71] *Id.* § 321(g)(1)(C).
[72] 21 C.F.R. § 201.128 (1999).
[73] *See, e.g.*, Chevron U.S.A., Inc. v. NRDC, Inc., 484 U.S. 495, 517 (1988) (explaining that "the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress").
[74] *See, e.g.*, United States v. Article of Drug . . . Bacto-Unidisk . . . , 394 U.S. 784, 799-800 (1969) (upholding FDA's interpretation of the term "drug" to include antibiotic sensitivity disks manufactured by the defendants).
[75] *See supra* text accompanying notes 70-72, (explaining FDCA defines an "article" as a "drug" if it is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or is "intended to affect the structure or any function of the body of man or other animals").
[76] *See* Meza v. S. Cal. Physicians Ins. Exch., 73 Cal. Rptr. 2d 91, 93 (Cal. Ct. App. 1998) ("a substance's actual or intended use or administration may determine whether it is a drug . . . ."); Whitaker v. Thompson, 353 F.3d 947, 953 (D.C. Circ. 2004) (allowing the FDA to use labeling to

remedy for warts, was deemed a drug when a doctor used it to treat or cure a medical condition.[77] The court emphasized that "the federal decisions construing the Act's definition of 'drug' consistently hold that it must be read as widely as possible."[78] Thus, "[the Act's] scope should not be restricted to products commonly called drugs."[79] Consequently, by recommending the melaleuca oil to the patient as a treatment for her wart, the physician effectively conveyed his intent that the oil be used for a medical purpose without regard to the product's inherent properties; and it was this intended use that rendered it an unapproved drug under the FDCA.[80]

In its 1969 decision of *United States v. Article of Drug . . . Bacto-Unidisk . . .*,[81] the U.S. Supreme Court upheld the FDA's determination that antibiotic sensitivity discs, which are used for selecting appropriate antibiotics for a particular patient, were drugs and not devices.[82] This classification subjected the discs to the more rigid regulation of drugs than devices that existed at that time, despite Justice Douglas' insistence that this directly contradicted the FDCA's express terms.[83] The majority stated that it "must give effect to congressional intent in view of the well-accepted principle that remedial legislation such as the [FDCA] is to be given a liberal construction consistent with the Act's overriding purpose to protect the public health."[84]

This broad interpretation of the FDCA, coupled with the judiciary's traditional deference to agency action, makes the normally uphill battle of regulatory challenges especially steep when taking on the FDA.[85] Consequently, overturning the FDA's characterization of a product as a "drug" is particularly difficult. However, it can be

---

infer intent in order to determine whether a marketed product is a drug); Culver v. Nelson, 54 N.W.2d 7, 10 (Minn. 1952) (defining drugs as "substances and preparations intended for external and internal use in the cure, mitigation, treatment, or prevention of disease in man or other animal").

[77] *Meza*, 73 Cal. Rptr. 2d at 94.

[78] *Id.*

[79] *Id.* (quoting United States v. An Article Consisting of 36 Boxes, 284 F. Supp. 107, 111 (D. Del. 1968), *aff'd*, 415 F.2d 369 (3d Cir.1969)).

[80] *Meza*, 73 Cal. Rptr. 2d at 94. *But see* Food & Drug Admin. v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 170 (2000) (noting that intent may also be shown by circumstances surrounding the article's distribution).

[81] 394 U.S. 784 (1969).

[82] *Id.* at 800.

[83] *Id.* at 800-01.

[84] *Id.* at 798.

[85] *See id.* (discussing how the FDCA's definitions were meant to be construed broadly to better protect the public). *See also generally* Chevron, U.S.A., Inc. v. NRDC, Inc., 467 U.S. 837 (1984) (judicial deference given to administrative agency interpretations of ambiguous statutes).

done, as demonstrated by *FDA v. Brown & Williamson Tobacco Corp.*,[86] in which the U.S. Supreme Court rejected the FDA's effort to regulate tobacco products as medical drugs and devices.[87] Even here, though, the Court declined to supplant the FDA's definition of a drug with its own; rather, it premised its decision on Congress' overarching intent to exempt tobacco products from FDA oversight altogether.[88]

Once the FDA defines an article as a drug, the manufacturer must satisfy onerous pre-marketing administrative and clinical requirements, including submitting a NDA[89] or an Investigational New Drug Application ("IND").[90] Further, the agency is statutorily obligated to ensure that investigational drug studies have been critiqued and approved by an Institutional Review Board for the purpose of protecting human subjects.[91] This system obviously requires considerable time and resources to bring a new drug to the market, but it was designed for major pharmaceutical companies capable of meeting these challenges.[92] Not surprisingly, the sizeable costs of bringing a new drug to the market, including the high risk of never gaining FDA approval, have given large manufacturers dominion over new drug development.[93]

The potentially confusing overlap and interplay of drug regulation under the

---

[86] 529 U.S. 120 (2000).

[87] *Id.* at 161.

[88] *Id.* at 126 (finding the FDA's assertion of authority was inconsistent and therefore invalidated by "the intent that Congress has expressed in the FDCA's overall regulatory scheme and in the tobacco-specific legislation that it has enacted subsequent to the FDCA").

[89] *See* 21 U.S.C. §§ 355(a)-(b) (2002), 21 C.F.R. § 312.23 (2002) (requiring a NDA to provide extensive information on its active ingredient(s), the chemical means of delivering this ingredient, the manufacturing and packaging procedures, suggested labeling, and clinical trial data establishing the drug to be both safe and effective).

[90] *See* 21 U.S.C. § 355(i). Under 21 U.S.C. section 355(i), a FDA-approved IND permits a manufacturer to distribute a drug in limited quantities for the sole purpose of performing studies on human subjects. *Id.* The IND application must be supported by detailed information about the drug, the planned course of study, the protocols for such studies, the identity and location of the investigators overseeing the studies, and the action that it will take to ensure the safety of its participating human subjects. *Id.*; *see also* 21 C.F.R. § 312.23.

[91] 21 C.F.R. § 56 (2002); *see* Halme & Kessler, *supra* note 19 (describing the need for stem cell therapies to abide by these FDA Guidelines to protect human subjects while researchers study efficacy).

[92] *FDA Approval of Drugs: Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Commerce*, 104th Cong. (1995) (statement of Kenneth I. Kaitin, Ph. D., Associate Director, Tufts Center for the Study of Drug Development, Tufts University).

[93] Alastair J.J. Wood, M.D., *A Proposal for Radical Changes in the Drug-Approval Process*, 355 NEW ENG. J. MED. 618 (2006) (describing the expense and risk associated with new drug approvals that make the process prohibitive to all but the biggest companies).

FDCA and biologics under the Biologics Act is nothing new.[94] In 1944, Congress conducted hearings on whether to narrow or reconcile the applicability of either law, but in re-codifying the Biologics Act as the Public Health Service Act of 1944 ("PHSA"), Congress opted to maintain a dual yet separate biologics regulatory regime that continues today.[95] Thus, biologics are licensed under the PHSA after they are proven to be "safe, pure, and potent."[96] They are also subject to the FDCA, although biologics manufacturers are not required to file NDAs in addition to obtaining biologics licenses.[97] Consequently, with the exception of new drug provisions, applying the FDCA's dual safety and effectiveness requirements has made the standards for biologics "similar, if not identical" to drugs, meaning that biologics manufacturers also must prove through clinical studies that the biological product is both safe and effective in order to obtain FDA approval.[98] Moreover, under the FDCA, the term "drug" is defined not in terms of its colloquial meaning but as "a term of art for the purposes of the Act, encompassing far more than the strict medical definition of that word."[99] As a result, an article can qualify as both a biologic subject to PHSA licensing criteria and a drug subject to FDCA pre-marketing requirements, thereby exposing that product to extensive regulatory oversight.

### B. FDA Regulation of Human Cells and Tissues: A Three-Tiered Framework

Scientific developments in the field of cellular medicine achieved real traction in the 1990s. In the FDA's view, the products of this innovative research were potentially governed by both the FDCA and the Biologics Act; therefore, problems quickly arose in subjecting cellular products to the conventional Investigational New Drug or Biologic License Application ("BLA") regulatory approval mechanisms.[100] In dealing with new

---

[94] *See* Gamerman, *supra* note 42, at 220 n. 42 (citing *Hearings Before the Subcomm. of the S. Comm. on Educ. & Labor*, 78th Cong., 2d Sess. 48 (1944)).

[95] Public Health Service Act, Pub. L. No. 78-410, ch. 373, 58 Stat. 682, 702 (July 1, 1944) (codified as amended at 42 U.S.C. §§ 262 et seq.); *see* Edward L. Korwek, *Human Biological Regulation: Past, Present, and Beyond the Year 2000*, 50 FOOD & DRUG L.J., 123, 126-27 (1995).

[96] 42 U.S.C. § 262 (a)(2)(C)(i)(I) (2010).

[97] *See* Biologics; Products Subject to License Control, 21 C.F.R. § 310.4(a) (2005).

[98] DONALD O. BEERS, GENERIC AND INNOVATOR DRUGS: A GUIDE TO FDA APPROVAL REQUIREMENTS, BIOLOGIC APPROVAL REQUIREMENTS § 13.02, at 13-4 (Aspen Law & Bus., 6th ed. 2004).

[99] United States v. Article of Drug . . . Bacto-Unidisk . . . , 394 U.S. 784, 793 (1969).

[100] Robert A. Preti, *Bringing Safe and Effective Cell Therapies to the Bedside*, 23 NATURE BIOTECHNOLOGY 801, 803 (2005); *see also* Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1754 (1996); Philip D. Noguchi, *From Jim to Gene and Beyond: An Odyssey of Biologics Regulation*, 51 FOOD & DRUG L.J. 367, 368 (1996) ("Despite

experimental treatments, the FDA's priority has traditionally been to permit only safe and effective cellular therapies to enter the market.[101] However, the PHSA's biologics licensing requirements, as well as the FDCA's drug pre-marketing approval requirements for regulating comparatively simpler chemical (e.g., small molecules and natural products) or biological entities (e.g., monoclonal antibodies or recombinant proteins), were ill suited to regulate these emerging cell and tissue products.[102] In terms of safety, the FDA was especially concerned with preventing transmission of communicable pathogens or agents, but also recognized the value of flexible regulation in accommodating the public health interest of permitting ongoing development of innovative, experimental treatments.[103]

Thus, in 1997, the FDA announced its plans to re-work its regulatory approach to human cells, tissues, and cellular and tissue-based products, and invited public comments.[104] After several years of publishing various proposals and receiving extensive comments, the agency promulgated its human cell and tissue-based products ("HCT/P") regulations in January 2001, codified in 21 C.F.R. section 1271.[105] Section 1271 created a hierarchy that subjected products with greater risks to more stringent oversight than their lower-risk counterparts.[106] It did so by categorizing products into one of three tiers based on their perceived risk potential.[107] At the time, the agency stated that "consolidating the regulation" of HCT/Ps in this way would promote consistency, efficiency, safety, and "encourage[ ] the development of new products."[108]

---

the agency's recent approach to unification toward single product therapeutics, cell and gene therapies continue to challenge existing statutes and regulations").

[101] Preti, *supra* note 100, at 803.

[102] Gregory N. Mandel, *The Generic Biologics Debate: Industry's Unintended Admission That Biotech Patents Fail Enablement*, 11 VA. J.L. & TECH. 8, 31 (2006) (discussing legal hurdles for generic biologics that stem from a regulatory structure "developed long before the modern biologics era"); *see also* Preti, *supra* note 100.

[103] *See* Mandel, *supra* note 102, at 31.

[104] A Proposed Approach to the Regulation of Cellular and Tissue-Based Products, 62 Fed. Reg. 9721 (Mar. 4, 1997).

[105] According to 21 C.F.R. section 1271.1(a), the FDA intended its HCT/P regulations "to create a unified registration and listing system for establishments that manufacture human cells, tissues, and cellular and tissue-based products (HCT/P's) and to establish donor-eligibility, current good tissue practice, and other procedures to prevent the introduction, transmission, and spread of communicable diseases by HCT/P's." *See also* Final Rule, Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 21 C.F.R. pts. 207, 807 and 1271.1 (2001).

[106] 21 C.F.R. § 1271 (2010).

[107] *Id.*

[108] 66 Fed. Reg. 5447-5448 (Jan. 19, 2001).

*1. Category 1 Products–No Oversight*

The first category of products, comprised of human organs for transplantation, whole blood and blood-derived products, and extracted human products such as collagen and bone marrow, are not regarded as human cell or tissue-based products, and therefore, they are not subject to the 21 C.F.R. section 1271 regulations.[109] Products in this category must satisfy two criteria during their manufacture: (1) they must not undergo more than minimal manipulation, or experience any other alteration of biological traits; and (2) their use must be homologous, meaning that the products must be used to perform the same basic biological function in the recipient as in the donor.[110]

*2. Category 2: Section 361 Products–Minimal Oversight*

The second category of HCT/Ps is regulated solely under authority of section 361 of the PHSA; such "361 products" include human cells, tissues, or cellular or tissue based products that, in the FDA's assessment, pose a slightly higher risk.[111] To qualify as a 361 product, and thus be subject to minimal oversight, an HCT/P must meet each of the following four criteria:

> (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 cells or tissues with another article . . . 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 (a) is for autologous use; (b) is for allogenic use in a first-degree or second-degree blood relative; or (c) is for reproductive use.[112]

---

[109] 21 C.F.R. § 1271.3(d).

[110] 21 C.F.R. § 1271.3(c) (defining homologous); 21 C.F.R. § 1271.3(f) (defining minimal manipulation). Minimal manipulation is defined as: "(1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and (2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues." *Id.*

[111] 21 C.F.R. § 1271.3(d). Examples of HCT/P's include, but are not limited to: bone, ligament, skin, dura mater, and cornea. *Id.*

[112] 21 C.F.R. §§ 1271.10(a)(1) – (4)(ii).

Section 361 products, involving "minimally processed tissues transplanted from one person to another for their normal structural functions," are subject to "infectious disease screening and testing and to requirements for good handling procedures" in order to prevent contamination or disease transmission.[113] However, these products are not subject to FDCA pre-market review and approval requirements, need not have an IND, NDA, or BLA, and need not conform to the current Good Manufacturing Practices ("cGMPs") requirements that govern commercial manufacturers of medical drugs and devices.[114]

The FDA has stated that section 361's first criterion of minimal manipulation encompasses such processes as centrifugation, sterilization by ethylene oxide treatment or irradiation, cell separation, lyophilization, and cryopreservation.[115] The agency has made clear that the second criterion of homologous use will be construed broadly; for example, using amniotic membrane in the eye and cartilage in the bladder are non-homologous uses.[116] The FDA has also emphasized that a product's homologous use depends on how its *manufacturer*, which may or may not be the practitioner who uses the product, intended the product to be used.[117] The agency justified the third criterion, that the product may not be combined with a drug or device (save for a sterilizing, preserving, or storage agent), by explaining that "[t]he addition of a drug or device to the cell or tissue component of [the product] may ordinarily be expected to add a therapeutic effect and may also raise safety concerns."[118] Therefore, adding agents that have a therapeutic effect, as well as operating as cryoprotectants, sterilizers, or storage agents, will remove the product from section 361 regulation and expose it to stiffer controls.[119]

The fourth criterion for qualifying for section 361's reduced oversight is that a product cannot have a systemic effect or depend on the metabolic activity of living cells

---

[113] *See generally* Dep't of Health & Human Servs., Food & Drug Admin., Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products, 63 Fed. Reg. 26744-01, 26745 (proposed May 14, 1998) (to be codified at 21 C.F.R. pts. 207, 807, and 1271).

[114] *See supra* notes 89-90 and accompanying text (detailing pre-market approval requirements for articles that are deemed to be drugs).

[115] *See* Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5447, 5449 (Jan. 19, 2001) (to be codified at 21 C.F.R. pts. 207, 807, 1271).

[116] *Id.* at 5458. The intent was to interpret the term "nonhomologous" narrowly. *Id.*

[117] *Id.* at 5458-59.

[118] *Id.*

[119] *See id.*

for its primary function,[120] unless the product is intended for: (a) autologous use;[121] (b) allogenic use in a first- or second-degree blood relative; or (c) reproductive use.[122] Consequently, the cell or tissue product cannot be intended for release to the general population.

### 3. *Category 3: Section 351 Products–Stiff Regulation of Biologic Drugs*

The third and final category classifies products as biologic drugs or medical devices under the FDCA and/or section 351 of the PHSA and subjects them to the highest level of regulatory scrutiny.[123] These products have undergone more than minimal manipulation and/or are intended for non-homologous use. For instance, section 351 governs products that have been manipulated through gene transduction or tissue culture and are used non-homologously, such as treating incontinence by using knee cartilage to supply bladder support.[124] In the FDA's view, there is no biological precedent for such uses and the higher risk of unforeseeable consequences justifies more rigorous oversight.[125] Accordingly, section 351 products are regarded as pharmaceutical products subject to both the FDCA and PHSA that must undergo extensive pre-market review procedures, including the procurement of a BLA.[126] In addition, entities that conduct the recovery, screening, testing, processing, storing, labeling, packaging, or distribution of these products are "manufacturers" and are subject to cGMPs requirements.[127] These entities must also conduct the typically three-phased clinical trials required of pharmaceutical companies to verify the safety, purity, potency, efficacy, and stability of their products.[128]

### 4. *The Impact of the FDA's HCT/P Regulatory Hierarchy on the Practice of Medicine*

The FDA implemented the three-tiered HCT/P system because its conventional regulatory models for enforcing the FDCA and PHSA made little sense

---

[120] 21 C.F.R. § 1271.10(a)(4) (2010).
[121] *Id.*
[122] *Id.*
[123] 42 U.S.C. § 262 (2010); 21 C.F.R. § 1271.20 (stating that HCT/Ps that do not fall under either of the first two tiers are regulated under Section 351 of the PHSA).
[124] *See* 21 C.F.R. § 1271.20.
[125] *See* Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5447, 5449 (Jan. 19, 2001) (to be codified at 21 C.F.R. pts. 207, 807, 1271).
[126] 42 U.S.C. § 262(a).
[127] 21 C.F.R. § 207.3(a)(8) (defining manufacturing).
[128] 42 U.S.C. § 262(k) (outlining the process for licensure of biological products).

when applied to cell and tissue products. Cell and tissue products are produced and used in ways and settings that differ from those of drugs, devices, and standard biologics, thereby requiring separate regulatory standards.[129] The HCT/P hierarchy is laudable in its intent and basic approach, but it often compounds the confusion that it was supposed to resolve.[130] The Regenerative Sciences litigation brings this into sharp contrast by revealing uncertainties regarding: (a) what qualifies as minimal manipulation; (b) what qualifies as homologous use; (c) whether autologous and allogenic uses should be regulated collectively or uncoupled; and (d) whether physician practices should be held to the same "pre-marketing" requirements as commercial manufacturers, especially when doing so may impede innovation and interfere with the practice of medicine.[131]

The FDA's response to these concerns, in terms of the content of its rules, the process by which they were enacted, and the manner in which they will be enforced, is at the core of the Regenerative Sciences litigation.[132] Indeed, before the Regenexx case, little attention was paid to a subtle change in how the FDA defines HCT/Ps and, therefore, whether a particular cell product will qualify for the first tier of no oversight, the second tier of minimal 361 oversight, or the third tier of more burdensome 351 requirements. Specifically, after an extensive and active notice and comment period that extended from 1997 to 2001, the FDA defined HCT/Ps subject to minimal 361 requirements as "any human tissue derived from a human body and intended for transplantation into *another human* . . . ."[133] The use of "another" human signaled that allogenic therapies fell within the second tier of 361 coverage, while physicians would be free to devise and use autologous cells and tissues without having to comply with either section 361 oversight or section 351's pre-marketing new drug application and biologic licensing application requirements.

In 2006, however, the agency departed from its extensive use of notice and comments in establishing and refining its approach to regulating cell and tissue products

---

[129] *Compare* 42 U.S.C. § 262 *and* 66 Fed. Reg. 5447 (Jan. 19, 2001) (setting forth the regulatory framework for HCT/P products), *with* 21 U.S.C. § 360 *and* 21 C.F.R. § 207 (presenting the regulatory framework for drugs, devices, and non-§ 351 biologics).

[130] *See supra* notes 101-103 and accompanying text (displaying the ambiguities in classifying what constitutes a drug); *supra* notes 94-99 (discussing the legislative history leading to the regulation of biologics as a distinct class).

[131] *See* Regenerative Sci., Inc. v. United States Food & Drug Admin., No. 09-CV-00411-WYD-BNB, 2010 WL 1258010 (D. Colo. Mar. 26, 2010); Regenerative Sci., Inc. v. United States Food & Drug Admin., No. 1:10-CV-01055-RMC (D.D.C. June 22, 2010).

[132] *See supra* text pp. 252-54 (outlining FDA's regulatory framework) and *infra* notes 205-207 (analyzing the case).

[133] 21 C.F.R. § 1271.3(d)(1) (2001) (emphasis added); *see also* 21 C.F.R. § 1271.3(d)(1) (2005).

when it quietly, but substantially, changed the basic definition of HCT/Ps that drives the entire three-tiered, risk based framework. With no notice and no opportunity for public comment, and indeed, with no formal announcement beyond its routine, annual publication of regulations, the FDA redefined HCT/Ps by deleting the critical descriptor of "another" human and expanding intended uses. Thus, section 1271.3(d) now states that "[h]uman cells, tissues, or cellular or tissue-based products (HCT/Ps) means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into *a human* recipient."[134] By shifting from "another" to "a" human recipient, this single word change treats autologous and allogenic HCT/Ps as carrying comparable risks, contravening the FDA's prior stance that autologous cells involved "minimal if any risk" at all.[135]

Whether this kind of regulatory change can be effectuated without following notice and comment procedures is a major point of contention in the Regenexx litigation. At a minimum, acting covertly unfairly disadvantages the very actors, practicing surgeons and physicians engaged in the practice of medicine who are most likely to deal with autologous therapies; they are also the least likely to have the legal resources or prior awareness of the need to comb each year's Code of Federal Regulations for minor changes. Compounding this dilemma is the growing irony of the three-tiered approach to regulating HCT/Ps. After all, the agency issued its HCT/P framework because regulating cellular products as if they were standard drugs made no sense. In its pursuit of the Regenexx case, though, the agency stubbornly and ironically refuses to consider whether regulating physicians under sections 361 and especially 351 as if they are large, commercial pharmaceutical manufacturers similarly makes no sense.

### C. The FDA Sues Regenerative Sciences to Enjoin an Autologous Adult Stem Cell Therapy

#### *1. Regenerative Sciences Background*

Two orthopedists operating a small medical clinic in Broomfield, Colorado formed Regenerative Sciences Inc. in 2006.[136] The Regenexx website describes their

---

[134] 21 C.F.R. § 1271.3(d) (emphasis added); *see also*, 21 C.F.R. § 1271.3(d)(1).

[135] *See, e.g.*, 70 Fed. Reg. 29952 (May 25, 2005) ("We have also clarified [section] 1271.90(b)(3), that cells and tissues for autologous use do not require the label 'Advise patient of communicable disease risk' *because the patient's own cells or tissues are being returned, and in this situation, there is minimal, if any, risk*.") (emphasis added).

[136] *See Regenerative Sci., Inc.*, 2010 WL 1258010, at *1 (D. Colo. Mar. 26, 2010); REDORBIT.COM, *New Non-Surgical Stem-Cell Procedure Relieve Degenerative Joint Disease* (Nov. 8, 2007),

"Regenexx Procedure" as an alternative to traditional joint and bone surgery.[137] The procedure begins when a Regenerative Sciences physician extracts bone marrow from the back of a patient's hip and draws blood from the patient's arm.[138] The marrow and blood samples are transported to Regenerative Sciences' laboratory, also located in Broomfield, Colorado, where Mesenchymal Stem Cells ("MSCs")[139] are isolated from the bone marrow and multiplied using the natural growth factors in a patient's blood.[140] After one to two weeks of multiplying in the lab, a now greater number of MSCs are re-injected into the patient's injured area with the goal of regenerating bone and cartilage and ultimately repairing the injury.[141]

Regenerative Sciences has published a large safety study indexed in the National Library of Medicine that, it claims, demonstrates that the Regenexx Procedure is much safer than invasive surgery.[142] Moreover, the procedure follows the International Cellular Medicine Society's ("ICMS") autologous cell processing guidelines.[143] Regenerative has also undergone audits by Reglera, an independent consulting firm specializing in medical device and tissue regulatory compliance.[144]

---

http://www.redorbit.com/news/health/1136294/new_nonsurgical_stemcell_procedure_relieves_degenerative_joint_disease/ (noting Regenerative Sciences founded in 2006) (last visited May 11, 2011).

[137] REGENEXX, *About the Regenexx Procedure*, http://www.regenexx.com (last visited May 11, 2011).

[138] REGENEXX, *Procedure Explained*, http://www.regenexx.com/the-regenexx-procedure-explained/ (last visited May 11, 2011).

[139] *See* Suzanne Kadereit, *Adult Stem Cells*, INT'L SOC'Y FOR STEM CELL RES. (2005), *available at* http://www.isscr.org/public/Adult_SC.pdf. Mesenchymal Stem Cells are multi-potent cells that can differentiate into a number of cell types, fat cells, cartilage, bone, tendon and ligaments, muscles cells, skin cells, and even nerve cells. *Id.*

[140] *Regenerative Sci., Inc.*, 2010 WL 1258010, at *1.

[141] *Id.* (describing the Regenexx Procedure).

[142] STEM CELL PIONEERS, *Regenerative Sciences and the FDA–FAQs* (Aug. 8, 2010), http://www.stemcellpioneers.com/showthread.php?t=3501 (last visited May 11, 2011).

[143] *Id.* The International Cellular Medicine Society ("ICMS") is a global non-profit organization dedicated to enhancing patient safety and peer oversight in adult stem cell research; ICMS publishes guidelines and best practices standards for the conduct of adult stem cell medicine; and ICMS maintains a "Treatment Registry" of patient reports to track patient outcomes and complications. *See generally,* INT'L CELLULAR MED. SOC'Y, http://www.stemcelldocs.org/ (last visited May 11, 2011). In addition, ICMS, together with Regenerative Medicine Institute ("RMI") of Tijuana, Mexico, recently launched a detailed accreditation process for clinics that use ASC therapies. *See* INT'L CELLULAR MED. SOC'Y, *First Clinic Accreditation Participant* (Mar. 15, 2011), http://cellmedicinesociety.org/home/news/latest/338-first-clinic-accreditation-participant (last visited May 11, 2011).

[144] *See* REGLERA, *Reglera Achieves ISO Certifications for Medical Device Production and Quality Management System*, http://www.reglera.com/biomed/fs_biomed.asp (last visited May 11, 2011)

The Regenexx-SD procedure combines extracted cells with "a super platelet mix" to obtain a greater yield of stem cells that can be re-injected in patients within a shorter timeframe than the two weeks needed when using a patient's own growth factor.[145] In this regard, Regenerative Sciences distinguishes itself from other stem cell clinics that simply utilize Platelet Rich Plasmas ("PRP").[146] Regenerative Sciences has also provided background on PRPs, explaining that treatments using these substances involve the injection or addition of blood platelets for growth factor delivery.[147] Nevertheless, Regenerative Sciences acknowledges that the overall effectiveness of using these plasmas has not been confirmed, concluding that, "like most things in medicine, the jury is still out."[148]

According to Christopher Centeno, M.D., the Medical Director and Chief Executive Officer of Regenerative Sciences, approximately seventy percent of the clinic's patients "fly in for treatment," and "[a]bout half of them are coming in from outside the country."[149] As of January 2011, Regenerative Sciences had treated approximately eight hundred individual patients with its Regenexx procedures and had performed well over one thousand orthopedic stem cell re-injections.[150]

*2. Legal Action*

In July of 2008, the FDA informed Regenerative Sciences that after reviewing the Regenexx Procedure website, it determined that the procedure constituted a drug under section 201(g) of the FDCA and a biological product under section 351(i) of the PHSA.[151] The FDA further maintained that the Regenexx MSCs were HCT/Ps, as defined by section 1271.3(d) of the HCT/P regulations, but failed to satisfy the section

---

(providing background on Reglera and its consulting business which specializes in "medical devices and human cellular and tissue products").

[145] REGENEXX.COM, *Super Platelet Mix and Regenexx-SD* (Aug. 9, 2010), http://www.regenexx.com/2010/08/super-platelet-mix-and-regenexx-sd (last visited May 11, 2011).

[146] *Id.* ("Not satisfied with just adding PRP to isolated bone marrow stem cells, we looked for better solutions. Since nobody had ever compared different growth factor (platelet) mixes with human mesenchymal stem cells, we did that in 2009").

[147] REGENEXX.COM, *Is Platelet Rich Plasma the Same Thing as Stem Cell Therapy?* (Mar. 16, 2010), http://www.regenexx.com/2010/03/is-platelet-rich-plasma-the-same-thing-as-stem-cell-therapy (last visited May 11, 2011).

[148] *Id.*

[149] Jeff Thomas, *Clinic Uses Stem Cells to Relieve Joint Pain,* BOULDER COUNTY BUS. REPORT, Jan. 8, 2010, *available at* http://www.bcbr.com/article.asp?id=103673.

[150] *See generally* REGENEXX, http://www.regenexx.com (last visited May 11, 2011).

[151] *See* Letter from Malarkey, *supra* note 22.

1271.10 criteria necessary to avoid obtaining a BLA or filing an IND.[152] Thus, since these autologous ASCs qualified as heavily regulated section 351 products, it warned Regenerative Sciences that "implantation of the [MSCs] for which a valid license or IND is not in effect appears to violate the FDCA and PHSA and may result in FDA seeking relief as provided by law."[153]

Regenerative Sciences challenged the FDA's assertion that its MSCs were drugs or biological products under either statute, arguing that the Regenexx Procedure constituted the practice of medicine; therefore, the agency could not regulate it.[154] The FDA, in turn, sought permanently to enjoin Regenerative Sciences from using adult stem cells to treat patients, claiming that the mesenchymal ASCs are at least one, if not more, of the following: (1) a drug; (2) a new drug; (3) a biological product; (4) a section 351 HCT/P; (5) adulterated; or (6) misbranded.[155] In response, Regenerative Sciences insists that the FDA has no jurisdiction to regulate the practice of medicine and that even if it can regulate, it acted arbitrarily and capriciously when it bypassed notice and comment rulemaking through its 2006 changes to the redefinition and re-categorization of autologous ASCs from a section 361 HCT/p to the more zealously regulated section 351 product.[156] Obviously, this case involves layers of complexity since it turns on a multifaceted regulatory scheme designed to enforce not one, but two intricate statutes against physicians using a complicated and emerging technology.

*a. The Regenexx Procedure as a Drug*

The FDA's most basic argument is that the Regenexx Procedure is a "drug" within the meaning of the FDCA; implicitly, the FDA contends that the Regenexx Procedure's use of autologous stem cells no longer entitles it to less oversight, particularly where the product's "labeling and promotional literature, including

---

[152] *See* Letter from Malarkey, *supra* note 22.
[153] *See* Letter from Malarkey, *supra* note 22.
[154] Davis, *supra* note 33.
[155] *See* Complaint at 1, United States Dep't of Justice v. Regenerative Sci., L.L.C., No. 1:10-CV-01327 (D.D.C. Aug. 6, 2010).
[156] *Id.*; *see* discussion *infra* Part III.A. In 2005, 21 C.F.R. section 1271 went into effect and defined HTC/Ps as "articles containing or consisting of human cells or tissues that are intended for implantation, transportation, infusion, or transfer into a human recipient." 21 C.F.R. § 1271.3(d). Regenerative Sciences argues that this is a new definition of human cells, tissues, or cellular and tissue based products and that the public was not afforded public notice and the opportunity to comment. Regenerative Sci., Inc. v. United States, No. 09-CV-000411, 2010 WL 1258010, at *1 (D. Colo. 2010) (dismissing complaint on other grounds); *see also supra* text pp. 254-56 (identifying the word change).

information contained on Regenerative Sciences' website, establish that their cultured cell product is intended to be used in the cure, mitigation, and treatment of diseases in man and to affect the structure and function of the body."[157] Specific examples of the marketing, or "labeling and promotional literature" include the website's representations that the Regenexx Procedure "prevents the need for surgery," "is an Alternative to Traditional Surgery," and is "shown to be safer than traditional surgery techniques . . . ."[158]

The FDA then argues that the Regenexx Procedure constitutes a prescription drug because, "due to its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, it is not safe for use except under the supervision of a practitioner licensed by law to administer such drug."[159] Although Dr. Centeno has authored publications about the procedure, the FDA claims that no adequate and well-controlled studies have been conducted to demonstrate that the Regenexx Procedure is safe or effective for orthopedic or other uses.[160] The agency has also characterized Regenerative Sciences' product as a "new drug" because experts with scientific training and experience do not generally recognize it as safe and effective for use under each of the conditions prescribed, recommended, or suggested in its labeling.[161] As a result, the FDA claims that Regenerative Sciences was legally obligated to file a NDA or an IND for the Regenexx Procedure when developing this new drug, but Regenerative Sciences failed to fulfill this requirement.[162]

*b. The Regenexx Procedure as a Biological Product*

According to the FDA, the Regenexx Procedure also satisfies the PHSA's definition of a "biological product," which includes a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings."[163] The agency reasons that the Regenexx Procedure is an "analogous product that is applicable

---

[157] Complaint at 6, United States Dep't of Justice v. Regenerative Sci., L.L.C. No. 1:10-CV-01327-RMC (D.D.C. Aug. 6, 2010); *see also supra* text p. 255 (discussing distinction between autologous and allogenic stem cell use).
[158] Complaint at 6, United States Dep't of Justice v. Regenerative Sci., L.L.C, No. 1:10-CV-01327-RMC (D.D.C. Aug. 6, 2010).
[159] *Id.* at 7.
[160] *Id.*
[161] *Id.*
[162] *Id.* at 7-8.
[163] *Id.* at 8 (quoting 42 U.S.C. § 262(i)).

to the treatment or cure of various diseases and conditions of human beings, since it is used to treat, *inter alia*, osteoarthritis, avascular necrosis of the shoulder and hip, chronic bursitis, non-healing bone fractures, and chronic bulging lumbar discs."[164] Consequently, Regenerative Sciences needed to file a BLA as required for biological products under the PHSA, but it never did so.[165]

*c. The Regenexx Procedure as a 351 Product Needing Pre-Market Review*

The agency insists that the Regenexx Procedure does not qualify as a section 361 product that is exempt from pre-market review; as a result, it should have undergone section 351-required pre-market review. Moreover, it should have met all of the filing requirements for INDs, NDAs, and BLAs.[166] A section 361 HCT/P cannot undergo more than minimal manipulation or be processed in a way that alters the relevant biological characteristics of the cells.[167] The Regenexx Procedure, in the FDA's opinion, "involves many steps, including selective culture and expansion of a multitude of different types of blood-forming and rare bone marrow stromal cells using plastic flasks, additives and nutrients, and environmental conditions such as temperature and humidity, to determine the growth and biological characteristics of the resulting cell population."[168] The FDA has thus concluded that the Regenexx Procedure involves more than minimal manipulation and is therefore subject to the more stringent section 351 regulations.[169]

*d. The Regenexx Procedure as an Adulterated Drug*

In support of its adulterated product argument, the FDA argues that the FDCA deems a drug to be adulterated if the methods used in, or the facilities or controls used for its manufacture, processing, packing, or holding, employ cGMPs or satisfy quality and purity standards.[170] The FDA inspected Regenerative Sciences' facilities on two

---

[164] Complaint at 7, United States Dep't of Justice v. Regenerative Sci., L.L.C., No. 1:10-CV-01327-RMC (D.D.C. Aug. 6, 2010).
[165] *See id.* "There has not been, nor has there ever been, an approved biologics license application . . . filed with F.D.A. pursuant to 42 U.S.C. [section] 262 for [Regenerative Science's] cultured cell product." *Id.*
[166] *Id.*
[167] *Id.* at 9-10. "An HCT/P is regulated solely under section 361 of the PHS Act and the regulations in this part if it . . . is minimally manipulated." 21 C.F.R. § 1271.10 (2010).
[168] Complaint at 10, United States Dep't of Justice v. Regenerative Sci., L.L.C., No. 1:10-CV-01327-RMC (D.D.C. Aug. 6, 2010).
[169] *Id.*
[170] *Id.* at 10-11 (citing 21 U.S.C. § 351(a)(2)(B)).

separate occasions in 2009 and alleged various violations of cGMPs. These allegations included: "failure to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity;" "failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile;" and "failure to establish an adequate system for monitoring environmental conditions during product manufacturing."[171]

*e. The Regenexx Procedure as a Misbranded Drug*

Finally, the FDA alleges that the Regenexx Procedure employs misbranding[172] because placing patients' cultivated adult stem cells in a plastic bag "labeled only with the patient's name, date of birth, laboratory notebook number, cell passage number, day in culture, cell number, number of cells cryopreserved, and condition of cell suspension" renders the cells a drug with labeling that fails to bear adequate directions for use.[173] The agency further contends that because this is a prescription drug product, the label improperly failed to denote it as a "Rx only" product.[174]

## III. Analysis

### A. A Court's Likely Holding

If the FDA fails to persuade a court that the Regenexx Procedure meets the FDCA's technical definition of a drug, its argument that it is a prescription drug, a new drug, and/or a misbranded or adulterated drug will also fail. Regarding the FDA's drug arguments, as well as its assertion that the mesenchymal ASCs are not minimally manipulated section 361 HCT/Ps and therefore must be more aggressively regulated under section 351 of the PHSA, much will turn on whether the agency has jurisdiction to act, and if so, whether its regulations and enforcement decisions were arbitrary and capricious. To date, Regenerative Sciences has primarily argued that the FDA impermissibly exceeded its authority by regulating the practice of medicine. However, as explained below, Regenerative Sciences' strongest argument concerns the FDA's decision to forego notice and comment procedures when it expanded the scope of tier

---

[171] *Id.* at 11-12.
[172] *Id.* at 13.
[173] *Id.* at 13-14.
[174] United States Dep't of Justice v. Regenerative Sci., L.L.C., No. 1:10-CV-01327-RMC, at 3 (D. D.C. Aug. 6, 2010).

two and tier three regulated HCT/Ps beyond their former focus on allogenic ASCs (i.e. from a different patient) to include a patient's own, lower-risk autologous ASCs that had previously qualified for tier one's no oversight, or at most, tier two's minimal section 361 oversight.[175]

### 1. *Whether the FDA has Jurisdiction to Regulate*

The FDA's jurisdiction to designate and regulate the Regenexx Procedure's MSCs as a drug is likely to be upheld based on the procedure's a substantial effect on interstate commerce.[176] The Regenerative Sciences website advertises its procedure in a manner that attracts both in and out-of-state patients, with patients regularly crossing state lines to receive treatment.[177] According to Dr. Christopher Centeno, the Medical Director and Chief Executive Officer of Regenerative Sciences, some seventy percent of Regenerative Sciences' patients "fly in" for treatment, indicating a sufficient engagement in interstate commerce to satisfy Commerce Clause requirements.[178]

Moreover, any obstacle to FDA intrusion on the typically state-regulated practice of medicine is somewhat diminished in this case since, although two practicing physicians own and operate Regenerative Sciences, some of its features distinguish it from a conventional physician practice. Operating a separate laboratory with a non-physician director allows the FDA to argue that the entity's primary objective is manufacturing not unlike the activities of commercial pharmaceutical companies.[179] Given Regenerative Science's interstate clientele and the substantial effect of its activities on interstate commerce, a court will recognize the FDA's basic jurisdiction to regulate as a valid exercise of its Commerce Clause power.[180]

---

[175] *See supra* notes 133-134 and accompanying text (comparing language used in the 2001 and 2006 regulations).

[176] *See* United States v. Whited, 311 F.3d 259, 267-72 (3d Cir. 2002) (laying out four criteria for determining whether statute falls within purview of Commerce clause as related to health care theft); *see also* Abbott v. Bragdon, 912 F. Supp. 580, 593 (D. Me. 1995) (recognizing Congress' authority to regulate under the Commerce Clause in dentistry even if particular activity is intrastate, provided that class of actors' aggregate activity substantially affect commerce).

[177] *See* REGENEXX, *About the Regenexx Procedure*, http://www.regenexx.com/about-regenexx (last visited May 11, 2011).

[178] *See* Thomas, *supra* note 149 (referencing direct statements from Dr. Centeno reporting significant out-of-state patients).

[179] *See* Letter from Malarkey, *supra* note 22, at 1 (stating drawn bone marrow sent to separate laboratory for appropriate cultivation).

[180] *See* United States v. Whited, 311 F.3d 259, 267-72 (3d Cir. 2002); Abbott v. Bragdon, 912 F. Supp. 580, 593 (D.Me. 1995).

*2. Whether the FDA Can Regulate Adult Stem Cells as "Drugs" and/or "Biologics"*

In terms of the FDA's power to define and regulate drugs and biologics, it can expect substantial judicial deference to its interpretation and enforcement of its enabling statutes. When evaluating an administrative agency's construction of a statute that it administers, the reviewing court must initially determine whether Congress specifically addressed the issue; if not, the court "must respect the agency's construction . . . so long as it is permissible."[181] Substantial deference is owed to the agency since it is more familiar with the issue or area being regulated, and the agency is better able to choose among competing policy objectives.[182] Accordingly, the FDA is likely to prevail in its determination that the ASCs produced by the Regenexx Procedure qualify as a drug under the FDCA. The FDA's decision that the product also qualifies as a biological product under the PHSA will also likely be upheld, although Regenerative Sciences has a somewhat stronger argument that the agency had no grounds to classify the end-product of the Regenexx Procedure as a heavily regulated section 351 product, given its autologous use.[183]

A court will likely find that the Regenexx Procedure's ASCs constitute a drug under section 201(g) of the FDCA because the procedure and the resulting product fit the plain language of the statute: i.e., it is a procedure that is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases in man and to affect the structure or any function of the body."[184] At a minimum, a court will defer to the FDA's determination given its particular competence to evaluate intended use, which

---

[181] FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 132 (2000) (citing Chevron, U.S.A., Inc. v. NRDC, Inc., 467 U.S. 837 (1984).

[182] *Brown & Williamson Tobacco Corp.*, 529 U.S. at 132.

[183] *See* United States v. Article of Drug . . . Bacto-Unidisk . . ., 394 U.S. 784, 798-801 (1969) (finding by the Supreme Court that the definition of "drug" under 21 U.S.C.A. § 321(g)(1) should be interpreted liberally); *see also* 21 U.S.C. § 321(g)(1) (2009) (defining "drugs" under the Food, Drug, and Cosmetic Act); Public Health Service Act, ch. 373, § 351, 58 Stat. 682, 702 (1944) (codified as amended under 42 U.S.C. § 262(i)(1) (2010)). The statute defines a "biological product" as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide) or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of disease or condition of human beings." *See* Public Health Service Act, ch. 373, § 351, 58 Stat. 682, 702 (codified as amended under 42 U.S.C. § 262(i)(1)). The FDA defines an HCT/P as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." *See* 21 C.F.R. § 1271.3(d) (2007).

[184] *See* Food, Drug, and Cosmetic Act, ch. 675, § 20, 52 Stat. 1041 (1938) (codified as amended under 21 U.S.C. § 321(g)(1)(2009)).

depends on the "objective intent of the persons legally responsible for the labeling of drugs" and may be shown by "labeling claims, advertising matter, or oral or written statements by such persons or their representatives."[185] Regenerative Sciences' website evinces its intent that the Regenexx Procedure affects the structure or functions of the body[186] as a viable alternative to surgery for patients suffering from non-healing bone fractures, osteoarthritis or other injuries of the knee, hip, ankle, shoulder, and hands, chronic bulging lumbar disc or herniated lumbar disc, avascular necrosis of the hip, and chronic bursitis.[187] Patient testimonials on the website also report functional improvement after undergoing the Regenexx Procedure, underscoring that Regenerative Sciences intends the treatment to affect the structure or function of the body.[188]

That the "drugs" at issue in the Regenerative Sciences case are human cells rather than traditional pharmaceuticals does not alter this result.[189] In addition to a court's typical deference to an agency's construction of its statute,[190] the United States Supreme Court in *Bacto-Unidisk* emphasized that the FDCA should be broadly interpreted and applied since "Congress intended to define 'drug' far more broadly than [did] the medical profession . . . 'drug' is a term of art for the purposes of the [FDCA], encompassing far more than the strict medical definition of that word."[191] Regenerative Sciences, nevertheless, argues autologous stem cells cannot be regulated as drugs because they "are not property of the biotech industry" and "nobody invented autologous stem cells . . . ."[192] This might have some appeal if the term "drug" was

---

[185] *See* 21 C.F.R. § 201.128 (2010) (explaining the meaning of "intended uses").

[186] *See* REGENEXX, *Conditions Treated*, http://www.regenexx.com/the-regenexx-procedures (last visited May 11, 2011).

[187] *See id.*

[188] *See* REGENEXX, *Archive for the 'Patient Testimonials' Category*, http://www.regenexx.com/category/patient-testimonials (last visited May 11, 2011).

[189] *See* REGENEXX, *Procedure Explained*, http://www.regenexx.com/the-regenexx-procedure-explained (last visited May 11, 2011). The website explains that a doctor takes samples of bone marrow and blood, which are sent to the lab where the cells are processed and then re-injected in the area in need of repair. *Id.*

[190] *See* United States v. Article of Drug . . . Bacto-Unidisk . . ., 394 U.S. 784, 791-92 (1969) (stating judicial deference to Secretary's decision where regulations are deemed appropriate for public health and such regulations are consistent with the Act).

[191] *Id.* at 793. The Court ruled that in light of the structure, legislative history, and remedial nature of the FDCA, it was clear that Congress intended a broad, sweeping, definition of 'drug.' *Id.* at 798.

[192] Christopher J. Centeno, Our Patients' Autologous Stem Cells Are Drugs: The FDA Moving Down a Dangerous Slippery Slope, Address at the Clinical Applications for Age Management Medicine Conference (Apr. 22, 2010), *available at* http://fapmmed.net/FAPM%20Centeno%20Editorial%20on%20Public%20Health%20Impacts%20of%20FDA%20Regulting%20Practice%20of%20Medicine.pdf.

being used in its colloquial sense, but as the Court explained in *Bacto-Unidisk*, the FDCA employs a technical definition based on an article's intended use, not its inherent properties.[193]

### 3. *Whether the FDA Can Regulate Autologous Adult Stem Cell Therapies under Section 351*

Whether the Regenexx procedure is properly categorized as a section 351 HCT/P is less clear, although it is likely that judicial deference to agency action will result in upholding this claim, too. As explained *supra*, section 351 of the PHSA defines a "biological product" to include any "virus, therapeutic serum, . . . or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings."[194] The FDA views the mesenchymal ASCs produced through the Regenexx Procedure as a section 351 "analogous product," though the courts have yet to define that term.[195] Regenerative Sciences' website suggests that these ASCs do indeed apply to the prevention, treatment, or cure of disease as required by the statute. Specifically, the ASC procedure is touted as an alternative to surgery for the treatment of osteoarthritis, avascular necrosis, and chronic bulging lumbar disks.[196] Further, the Regenexx process multiplies cells by culturing them in a laboratory for as long as two weeks while exposing them to a variety of compounds and techniques. The FDA therefore has a strong argument that these cells are subject to extensive regulation under section 351 since the cells are "highly processed, are used for other than their normal function, are combined with non-tissue components, or are used for metabolic purposes . . . ."[197]

In its pleadings, the FDA insists that its three-tiered, risk based framework is designed to "'provide only the degree of government oversight necessary to protect the public health' [and] 'ensure that innovation and product development in this rapidly growing medical field could proceed unhindered by unnecessary regulation.'"[198] The

---

[193] *Article of Drug . . . Bacto-Unidisk . . .* , 394 U.S. at 798-99 (proclaiming 'drug' should not be deemed as a device nor held to its strict medical definition).
[194] Public Health Service Act § 351, 42 U.S.C. § 262(i) (2010).
[195] *See* United States Dep't of Justice v. Regenerative Sci., L.L.C., No. 1:10-CV-01327-RMC, at *8 (D. D.C. Aug. 6, 2010).
[196] Public Health Service Act § 351, 42 U.S.C. § 261(i)(1).
[197] Halme & Kessler, *supra* note 19, at 1730 (quoting 21 C.F.R. § 1271.10(1-4)).
[198] *See, e.g.*, Memorandum of Law in Support of Plaintiff's Motion for Summary Judgment at pp. 6-7, *available at* http://www.hpm.com/pdf/I%2019%20Plaintiff's%20Motion%20for%20 Summary%20Judgment%20010711.pdf (citing Proposed Approach at 6); *see also* Proposed Registration Rule, 63 Fed. Reg. 26745; Proposed Approach to Regulation of Cellular and Tissue-

FDA has defined the process of culturing stem cells to expand their number and/or facilitate differentiation as involving more than minimal manipulation and therefore, involving more risk than should be regulated accordingly.[199] For instance, the process of cultivation could potentially use non-human fetal calf serum, which the FDA has indicated could contain prion, a protein particle that is believed to cause degenerative diseases of the central nervous system, such as bovine spongiform encephalopathy or "mad cow" disease.[200] Additionally, the self-renewing ability of stem cells that makes them so promising for use in regenerative therapies could also trigger uncontrolled cell growth and produce tumors.[201] Indeed, Regenerative Sciences has acknowledged on its website that the long-term effects of products like Regenexx-SD have not yet been scientifically proven.[202] Although ASC therapies can only be obtained by seeing the physician who will perform the procedure, and thus do not fit the mass manufacturing and marketing model of major pharmaceuticals, health risks remain.[203] Consequently, a court will likely hold that the FDA is authorized to regulate the Regenexx Procedure as a section 351 product.[204]

In its Answer and Counterclaims, Regenerative Sciences argues that judicial deference would be improper here since Congress never authorized the FDA to regulate the use of HCT/Ps for all autologous uses where doing so creates an unwarranted intrusion on the state-regulated practice of medicine.[205] As explained in its initial suit against the FDA and currently asserted as an affirmative defense, Regenerative Sciences maintains that instead of exercising its section 351 power to prevent the spread of communicable diseases from human tissue donors to human tissue recipients, the FDA is now attempting to regulate *all human tissue* by categorizing *both* autologous and allogenic ASC therapies as section 351 products that cannot be used without filing an

---

Based Products, FDA Dkt. No. 97N-0068 (Feb. 28, 1997) at 7; Proposed Approach to Regulation of Cellular and Tissue-Based Products; Availability and Public Meeting, 62 Fed. Reg. 9721 (Mar. 4, 1997).

[199] *See* United States Dep't of Justice v. Regenerative Sci., L.L.C., No. 1:10-CV-01327-RMC, at *10 (D. D.C. Aug. 6, 2010). *See generally supra* note 198.

[200] Halme & Kessler, *supra* note 19, at 1732.

[201] Halme & Kessler, s*upra* note 19, at 1734.

[202] *See* REGENEXX, *Regenexx-SD Orthopedic Stem Cell Injection Results*, http://www.regenexx.com/2010/12/regenexx-sd-orthopedic-stem-cell-injection-results/ (last visited May 11, 2011) (noting the findings presented were for "outcome data to date (all that we were able to obtain)").

[203] *See* Halme & Kessler, *supra* note 19, at 1732, 1734.

[204] *See generally* Plaintiff's Motion, Regenerative Sci., Inc. v. U.S. Food & Drug Admin., No. 09-CV-00411-WYD-BNB (D. Colo. Mar. 26, 2010).

[205] Answer at 47-49, Regenerative Sci., Inc. v. U.S. Food & Drug. Admin, No. 1:10-CV-01327 (D. D.C. Aug. 27, 2010), *available at* http://www.rockysfight.com/files/Centeno_20Answer_1_.pdf.

IND, NDA, and BLA.[206] Regenerative Sciences contends that the FDA's attempted regulatory change is problematic for two reasons. First, erasing the prior regulatory distinction between autologous and allogenic ASC treatments now subjects individual and small physician practices to the same expansive and cumbersome compliance requirements governing large commercial firms that manufacture drugs and biologics for release to the general public.[207] Second, the agency accomplished this dramatic change through a subtle, one word change (i.e., replacing "another human" with "a human") in 2005 without notice and comment rule making.[208] The FDA justifies this as an

---

[206] *Id.* at 9-10; *see also* Plaintiff's Motion, *Regenerative Sci. Inc.*, No. 09-CV-00411-WYD-BNB, at *3-4. In denying Regenerative's request for injunctive relief on grounds that the FDA's action was *ultra vires*, the judge held that Regenerative had not presented sufficient evidence regarding its likelihood of success on the merits. *See id.* He reasoned:

> [A]s a result of the posture of this litigation, such a task would be unduly complex and speculative. The Court would have to assess the likelihood of the transmission of a wide range of diseases, under diverse methods for processing numerous types of HCT/Ps with various autologous uses, to determine at this stage whether FDA's regulation defining HCT/Ps, 21 C.F.R. [section] 1271.3(d), is "ultra vires" in all possible circumstances.

*Id.* It should be noted, however, that a denial of injunctive relief is not necessarily indicative of the eventual outcome of the case. *Id.* It is therefore possible that the district court, after full evidentiary hearings and a trial on the merits, will agree with Regenerative. *Id.* at *8; *see also* Complaint, Regenerative Sci., Inc. v. U.S. Food & Drug. Admin, No. 1:10-CV-01327-RMC (Aug. 6, 2010) (noting the FDA's assertion that "products that are more than minimally manipulated are regulated . . . as biological products under section 351 of the PHSA").

[207] *See* Plaintiff's Motion, *Regenerative Sci. Inc.*, No. 09-CV-00411-WYD-BNB, at *1, *7-8 (describing small size of Regenerative's staff and medical practice, then subsequently and separately outlining Regenerative's hardship argument, focusing upon the detriment Regenerative asserts the regulation will have on its medical practice).

[208] *See supra* text pp. 255-56 (identifying word change). *But see* 66 Fed. Reg. 5447, 5467 (Jan. 19, 2001) (final rule codified at 21 C.F.R. section 1271.3(d) reflecting the relevant parts of the final rule as originally codified). *See also* 66 Fed. Reg. at 5450 (articulating the reasoning for division of the definition of HCT/Ps in the final rule into two sub-parts, the purpose of which was to "stagger[] the effective dates of the registration and listing regulation for different types of HCT/Ps"). In accordance with this goal, the final rule, as originally codified at 21 C.F.R. section 1271.3, included separate paragraphs codified at sections 1271.3(d)(1) and 1271.3(d)(2) respectively. *See* 66 Fed. Reg. at 5467. Paragraph (d)(1) of section 1271.3, as originally codified, composed the HCT/P subgroup whose registration and listing regulation were to go into effect first, while paragraph (d)(2) of 1271.3, as originally codified, included the HCTPs covered by (d)(1), as well as many additional types of HCT/Ps. *Id.* This intent to stagger is further evidenced by the language of the final rule stating that its provisions "[are] effective April 4, 2001, except for . . . [section] 1271.3(d)(2), which [is] to be effective on January 31, 2003." 66 Fed. Reg. at 5447. Delays in the rule making process pushed past this initial effective date for section 1271.3(d)(2), making necessary the further delay of section1271.3(d)(2)'s effective date to January

interpretive rule that simply clarifies existing regulations and is therefore exempt from notice and comment procedures as a procedural (as opposed to a substantive) change.[209]

However, arguing that this word change as merely clarifying and therefore procedural is questionable at best, if not overtly specious. The significant and substantive impact of this change on who and what are subject to zealous section 351 oversight is undeniable, particularly in the case of physicians who typically have the ability to innovate new therapeutic applications but lack the resources to meet compliance obligations that were designed with large pharmaceutical manufacturers in mind.[210] As explained in the oft-quoted case of *Jem Broadcasting Co. v. F.C.C.*,[211] the "'critical feature' of the procedural exception [to notice and comment requirements] 'is that it covers agency actions that do not themselves alter the rights or interests of parties . . . .'"[212] By dropping the role of "transplantation into another human" from its definition of HCT/Ps, the FDA plainly altered how autologous cell therapies would be categorized and regulated by its three-tiered framework and thus, inevitably changed "the rights and interests" of physicians using autologous stem cells. Such a marked change in "substantive outcomes" for stem cell practitioners should prompt the court to reject the agency's procedural characterization of the rule and invalidate it as a substantive rule improperly enacted without notice and comment."[213]

Moreover, the FDA will need to focus on more than minimal manipulation to

---

21, 2004. *See* 68 Fed. Reg. at 2690. The FDA asserts that, "when all of Part 1271's comprehensive framework was in place, the subdivision in the HCT/P definition became superfluous, so (d)(1) was revoked and (d)(2) was renumbered as a conforming amendment." Defendants' Reply to Plaintiff's Opposition to Defendants' Motion to Dismiss Pursuant to Rules 12(b)(1) and 12(b)(6), Regenerative Sci., Inc. v. U.S. Food & Drug Admin., 2009 WL 2956107 (D. Colo. May 26, 2009) (No. 109-CV-00411); *see also* 69 Fed. Reg. at 68,614 (amending paragraph (d)(1) of section 1271.3, as already discussed in this footnote, this amendment had effective date of May 25, 2005).

[209] *See generally* Administrative Procedure Act, 5 U.S.C. § 553(b)(A) (exemptions to notice and comment requirements); Defendants' Reply to Plaintiff's Opposition to Defendants' Motion to Dismiss Pursuant to Rules 12(b)(1) and 12(b)(6), *Regenerative Sci., Inc.*, 2009 WL 2956107 (No. 109-CV-00411); Regenerative Sci., Inc. v. U.S. Food & Drug Admin., No. 09-CV-00411-WYD-BNB (D. Colo. Mar. 26, 2010).

[210] The FDA's aggressive legal maneuverings against Centeno et al. are likely to chill physicians from working in the regenerative sciences field. *See* Letter from Malarkey, *supra* note 22. At a minimum, the FDA needs to clarify how it will treat such therapies, to avoid a lack of research and development in the field.

[211] 22 F.3d 320 (D.C. Cir. 1994).

[212] *Id.* at 326 (quoting Batterton v. Marshall, 648 F.2d 694, 707 (D.C. Cir. 1980)).

[213] *See supra* notes 208-209 and accompanying text.

justify its oversight of autologous ASCs since large concentrations of ASCs can be harvested from adipose tissue and used during the same procedure, obviating the need to expand their number during days, if not weeks, of laboratory culture.[214] At a minimum, the FDA needs to clarify how it will treat such therapies since its aggressive legal maneuverings against Regenerative Sciences is more than likely to chill physicians from working in this area. This result would undercut the FDA's mission to advance the public health by fostering innovation.

### B. A Better Approach to Regulating Large and Small Drug "Manufacturers"

Notwithstanding the weaknesses of the FDA's defense of its re-categorization of autologous therapies, judicial deference to administrative action is likely to result in at least a partial victory for the FDA in its efforts to hold Regenerative Sciences to the same drug pre-marketing and biologics licensing requirements that bind large firms. However, while this may be legally permissible, it is not necessarily legally wise. Rather, imposing a regulatory scheme designed for mass drug manufacturers on small physician practices is problematic in terms of fostering innovation, respecting an individual patient's bodily autonomy, and advancing important public health objectives.[215]

That physicians literally cannot afford to comply with the FDA's pre-marketing approval requirements is unquestioned.[216] In 2003, a trio of economists estimated that

---

[214] *See, e.g.*, Jeanne Adiwinata Pawitan, *Prospect of Adipose Tissue Derived Mesenchymal Stem Cells in Regenerative Medicine*, 2 CELL & TISSUE TRANSPLANTATION & THERAPY 7, 8 (2009). Pawitan states:

> [C]ompared to bone marrow [the most common source of ASCs], adipose tissue can be obtained in larger volumes, at lower risks, less painful, and easier to get as it is the waste product of liposuction. Moreover, in bone . . . the number [of ASCs] is declining with age . . . . Therefore, adipose tissue will be the preferred source of MSCs for future clinical use.

*Id.*

[215] *See* Jeff Morris & L. Stephen Coles, *Will the FDA Kill Adult Stem Cell Medicine*, H+ MAGAZINE, May 1, 2009, *available at* http://www.hplusmagazine.com/articles/bio/will-fda-kill-adult-stem-cell-medicine. Such a regulatory scheme would eventually result in large pharmaceutical companies controlling all of the Regenerative Sciences. *Id.* This would stunt innovation as pharmaceutical companies are bound by the many restrictions of the FDA and other federal agencies. *Id.*

[216] *See* Roger Collier, *Drug Development Cost Estimates Hard to Swallow*, 180 CAN. MED. ASS'N J. 279, 279 (2009). With physicians essentially "priced-out" of the FDA pre-marketing requirements, there is a fear that innovation will be hampered. *See id.* Pharmaceutical companies say that the

pharmaceutical companies spent $802,000,000, on average, to bring a new drug into the market.[217] This considerable expenditure, as well as the time required to conduct three phases of clinical trials, will essentially bar smaller entities from market entry and will allow the market to be entirely controlled by large pharmaceutical companies.[218] In addition, imposing the stringent section 351 regulatory requirements on physicians will prevent individual patients from receiving much-needed new or improved therapies.[219] Insofar as such innovative treatments will not reach the general public, such aggressive oversight also undermines the FDA's core mission of "advancing the public health by helping to speed innovations." This is especially worrisome here since large profit-driven pharmaceutical companies (owing fiduciary duties to shareholders, in contrast to a physician's duty to patients) will emerge with even more market power than they already have.[220]

Consequently, the FDA should continue to refine its underlying objective in designing its current three-tiered structure for regulating HCT/Ps. Physicians must be able to innovate when practicing medicine. Further, a more flexible approach to regulatory oversight will better accommodate the demand for more and better therapies with the need to protect individual patients and the public health from disease transmission and product contamination.[221]

---

high cost of clinical trials in particular is the driving force behind such high pre-marketing requirements. *Id.*

[217] *See id.*; *see also* Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 166 (2003) (explaining the reasons for the high costs of drug development). The lead author of the study that produced this estimate is Joseph DiMasi, director of economic analysis at the Tufts Center of Drug Development in Boston, Massachusetts. Collier, *supra* note 216, at 279. Since the publication of DiMasi's article in 2003, other economists have estimated the current cost of drug development as exceeding DiMasi's estimates and reaching upwards of $1.3 billion. *Id.* However, these estimates have been called into question by those who are skeptical of pharmaceutical industry-supported economists. Donald Light et al., *Extraordinary Claims Require Extraordinary Evidence*, 24 J. HEALTH ECON. 1034, 1035 (2005). Such skeptics accuse the industry of inflating the high cost of drug development to justify the high market price of the drugs. *Id.*

[218] *See* Collier, *supra* note 216, at 279 (describing what goes into the high cost of drug development). Compounding this issue is the fact that the complexity of clinical trials is on a rising trend, which will only further increase the drug development cost. *Id.* While it is known that clinical trials are becoming more complex, it is difficult to estimate how that increased complexity will be translated into the future costs of research and development. *Id.*

[219] *See generally* DiMasi et al., *supra* note 217.

[220] U.S. FOOD & DRUG ADMIN., MISSION STATEMENT (Nov. 18, 2010), http://www.fda.gov/aboutfda/whatwedo/default.htm (last visited May 11, 2011).

[221] *See supra* notes 109-122. The FDA has set up specific criteria that a product must meet to qualify as an HCT/P. 21 C.F.R. § 1271.10(a) (2010).

With regard to the latter two interests, the FDA must remember that even the conventional practice of medicine routinely poses significant risks of disease transmission and contamination. The absence of hand washing, for instance, can transmit infection from one patient to another, as can a failure to sterilize instruments between procedures. However, the FDA is not the contamination police, and therefore, the FDA has no power to intervene in such situations. Rather, practice guidelines, state licensing requirements and duties of care, and other state oversight mechanisms can and should monitor how medicine is practiced.[222] Moreover, the FDA must recognize that physicians and surgeons have always played a leading role in medical innovation. For instance, numerous minimally invasive procedures that have become routine in modern cardiology began with one surgeon's determination to find less traumatic alternatives to vascular surgery.[223] A similar story can be told for coronary artery bypass surgery, a procedure which now saves hundreds of thousands of lives each year.[224] The overall specialty of plastic surgery owes a debt to World War I surgeons whose creative strategies for reconstructing battlefield wounds laid the groundwork for current practice.[225]

From a strictly legal standpoint, perhaps the FDA *can* move aggressively against physicians using emerging ASC therapies. Yet, in determining how it *should* proceed, it would do well to return to treating autologous and allogenic procedures differently. Alternatively, it should look to the European Commission's strategy for permitting small medical groups to produce innovative therapies involving drugs or biologics while

---

[222] *See* Edward P. Richards, *The Police Power and the Regulation of Medical Practice: A Historical Review and Guide for Medical Licensing Board Regulation of Physicians in ERISA-Qualified Managed Care Organizations*, 8 ANNALS OF HEALTH L. 201, 201-02 (1999) (describing the power of states to regulate health care practices).

[223] Thomas J. Fogarty, *Inventor of the Week*, LEMELSON M.I.T. PROGRAM, http://web.mit.edu/invent/iow/fogarty.html (last visited May 11, 2011). Dr. Fogarty built the prototype for the Foley Balloon Embolectomy Catheter in his home attic by "attaching the fingertip of a latex surgical glove to a catheter using fly-tying techniques familiar to him from boyhood fishing expeditions." *Id.*

[224] Valentin Fuster & James T. Willerson, *In Memoriam, Rene G. Favaloro, MD, The Passing of a Pioneer*, AM. HEART ASS'N, http://circ.ahajournals.org/cgi/content/full/103/4/480 (last visited May 11, 2011). In the late 1960's, Rene G. Favolaro, M.D. and his fellow cardiothoracic surgeons at the Cleveland Clinic revolutionized heart surgery by using the saphenous vein from the leg to re-route blood flow to bypass obstructed coronary arteries. *Id.*

[225] *See* THE AM. ACAD. OF FACIAL PLASTIC & RECONSTRUCTIVE SURGERY, http://www.aafprs.org/patient/about_us/h_war.html (last visited May 11, 2011). "They improvised and collaborated to meet each horrific need as it arose, inventing on the spot many of the procedures that comprise the repertoire of the modern facial plastic surgeon." *Id.*

simultaneously promoting safety and effectiveness.[226] The European Commission's "Advanced Therapies" regulations, adopted in 2008 and applicable to gene therapy, somatic cell therapy, and tissue-engineered products, demonstrate a better way to regulate both large and small drug manufacturers.[227] The regulations employ: (a) a centralized marketing authorization procedure; (b) a multidisciplinary committee to advise as to whether a product qualifies as an advanced therapy and to address other scientific concerns; and (c) special incentives for small and medium enterprises ("SMEs") to foster their success.[228]

The European Commission recognizes that SMEs in the biopharmaceutical sector deserve particular attention if patients and society are to reap the benefits of public health advances these companies may achieve.[229] Accordingly, it seeks to create a regulatory environment that enables European Union authorities to provide financial support to SMEs.[230] In this regard, the European Commission has recognized that "the main financial and administrative entry hurdles for SMEs are the various steps involved in pre-marketing authorization procedures . . . such as the seeking of the marketing authorization application . . . ."[231] As such, its regulations offer SMEs a ninety percent reduction on fees related to scientific advice, inspections, and other scientific services, and the regulations defer marketing authorization application fees until the end of the evaluation procedure.[232] Further, it has established an SME office to provide administrative assistance, facilitate communication between SMEs and the government, and address inquiries.[233]

The untenable costs and obstacles that the FDA's current approach poses to regulating cellular medical innovations by practicing physicians directly contravene the agency's obligation to foster innovation for the public health.[234] Consequently, because

---

[226] *See* Commission Regulation 1394/2007, 2007 O.J. (L 324) 121.
[227] *Id.* at 121.
[228] *Id.* at 122-28.
[229] Commission Regulation 2049/2005, 2005 O.J. (L 329) 4. "Such provisions should . . . aim at promoting innovation and the development of new medicinal products by SMEs." *Id.* at 4.
[230] *Id.* "In order to reduce the cost for SMEs of marketing medicinal products authorized via the centrali[z]ed procedure, that Regulation therefore foresees the adoption of specific provisions allowing a reduction of fees, deferring the payment of fees, and providing administrative assistance." *Id.*
[231] Commission Regulation 2049/2005, 2005 O.J. (L 329) 4, 4.
[232] *Id.* at 5-6.
[233] *Id.* at 6-7.
[234] *See generally supra* notes 215-216 and accompanying text (discussing the challenge of cost faced by smaller medical groups).

therapeutic applications for adult stem cells are progressing at a rapid pace,[235] retooling the agency's current HCT/P regulatory framework is nothing short of a public health imperative. The European Commission's support for innovation is one approach, but it does rely heavily on providing financial incentives, something that the FDA is unlikely to match given current economic constraints. Therefore, returning to its bifurcated treatment of autologous and allogenic ASC therapies, especially when developed and/or used by practicing physicians (as opposed to commercial manufacturers) may be the more feasible approach.

## IV. Conclusion

While the FDA lacks jurisdiction specifically to regulate the practice of medicine, its broad Commerce Clause power allows it to affect the activities of individual health care providers. Courts traditionally defer to the FDA's determinations of what constitutes a drug and a biologic product under both the FDCA and the PHSA, and the FDA's suit against Regenerative Sciences promises to be no different. Consequently, the FDA's assertion of jurisdiction over physicians who are using and, therefore, "manufacturing" these products is likely to stand. Less certain is whether the agency can act through *de facto* substantive rule changes that circumvented notice and comment requirements.

Whatever happens in the Regenerative Sciences case, the FDA should recognize that it makes little sense to impose a regulatory framework developed for mass manufacturers on small physician practices. This is especially true where doing so compromises innovative therapies. Instead, the FDA should craft a truly flexible regulatory regime either by refining its current three-tiered framework or following the lead of the European Commission. In this way, the agency can fulfill its statutory charge by properly accommodating the interests of health care providers, commercial manufacturers, and most importantly, patients and the general public.

---

[235] *See generally supra* note 217 and accompanying text (alluding to the rising complexity of clinical trials).