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Cultured Stem Cells for Autologous Use: Practice of Medicine or FDA Regulated Drug and Biological Product?

Stem cell research and commercialization offer amazing therapeutic promise since stem cells are adaptable regenerative cells capable of transforming themselves into a variety of body cell types. In the United States, the discussion of stem cell treatment has been largely overshadowed by political debate concerning embryonic stem cells, but research has shown that stem cells can be obtained from numerous sources, including bone marrow, blood vessels, muscle, and fat tissue.[1]

This article explores the legal and regulatory issues raised in a currently pending case that involves the commercialization of a procedure that isolates and expands stem cells taken from a patient's bone marrow that are then returned to the patient's site of injury. The case raises fundamental questions about the practice of medicine and the Food and Drug Administration's ("FDA") authority to regulate new drugs and biological products.

Regulatory Overview

Human stem cell treatment and associated products are regulated by the FDA under the authority of the Federal Food, Drug, and Cosmetic Act ("FDCA") and the Public Health Service Act ("PHSA"). Under the FDCA, an article is a drug if it is "intended for use in the diagnosis, cure, mitigation, or prevention of disease" or is "intended to affect the structure or any function of the body of man or other animals."[2] The FDCA "deems" a drug to be adulterated and misbranded unless it complies with the requirements in 21 U.S.C. §§ 351, 352 and 353(b)(4) and FDA's implementing regulations. For purposes of this discussion, these provisions require that a new drug be the subject of an approved new drug application ("NDA") or an abbreviated new drug application ("ANDA"), be clinically tested pursuant to an investigational new drug application ("IND"), be manufactured in compliance with current good manufacturing practices ("cGMPs"), and bear adequate directions for use.

Under the PHSA, a "biological product" is defined as any "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."[3] A new biological product must be the subject of an approved Biologics License Application ("BLA") before it is introduced into interstate commerce. To obtain a BLA, a manufacturer must show that the proposed product is safe, pure, and potent and that the facility in which the product is manufactured, processed, packed or held meets established quality control standards.

A stem cell-based product can be regulated as a drug and/or a biological product. While a product that has been licensed under the PHSA is not required to also have an approved NDA under the FDCA,

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[1] U.S. Department of Health and Human Services, National Institutes of Health Website. Stem cell basics: what are adult stem cells? Available at http://stemcells.nih.gov/info/basics/basics4.asp.

[2] 21 U.S.C. § 321(g)(1)(B)-(C).

[3] 42 U.S.C. § 262(i).

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FDA's drug regulations otherwise apply to biological products, including the IND requirements and the misbranding and adulteration provisions.

Stem cells intended for therapeutic purposes in humans are subject to FDA's April 2006 regulations governing the use of human cells, tissues, and cellular and tissue-based products ("HCT/Ps") in humans.[4] The regulations define HCT/Ps as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."[5] Examples include bone, ligament, skin, dura mater, stem cells, cartilage cells, and various other cellular and tissue-based products. Among other things, the regulations include provisions governing registration and listing requirements; provisions discussing donor eligibility; recommended current good tissue practices covering all stages of production, including harvesting, processing, manufacture, storage, labeling, packaging, and distribution; and other requirements intended to prevent the introduction, transmission, and spread of communicable diseases in humans.

For general categorical purposes, an HCT/P is considered a biologic just like blood, plasma or tissue. For regulatory purposes, however, an HCT/P can be treated as just that (simply an HCT/P) or something entirely more complex such as a drug or biological requiring an NDA or BLA, respectively. Thus, not every HCT/P necessarily requires an NDA or BLA. That determination is based on a comparison to a set of established factors or criteria found in 21 C.F.R. § 1271.10(a), with products that satisfy the criteria not requiring an NDA or BLA, and products that exceed the criteria needing one.

Factors considered in the regulation of these products include the degree of manipulation exerted on the product (i.e., whether the product has been more than minimally manipulated), whether the product is intended for a homologous function, whether the product has been combined with non-cellular or non-tissue components, and the product's overall effect or dependence on the body's metabolic function.[6] Where an HCT/P is only minimally manipulated, is intended strictly for homologous use, has not been combined with non-cellular or non-tissue substances, and does not depend on or have an effect on the body's metabolism (e.g., blood, plasma, a kidney transplant), such a product will be regulated as simply an HCT/P requiring the manufacturer to register its establishment and list the product with FDA, and adopt and implement procedures for the control of communicable diseases. Where one or more of the factors is exceeded, however, the product will likely be regulated as a drug requiring the filing of an IND and eventual approval of NDA prior to marketing and sale in the U.S.

United States v. Regenerative Sciences, LLC

FDA recently brought an action to permanently enjoin Regenerative Sciences, LLC ("Regenerative") from using the Regenexx™ procedure to process mesenchymal stem cells ("MSC") for the treatment of various orthopedic conditions.[7] This case is still ongoing and we do not intend to focus on all the

[4] 21 C.F.R. Part 1271.

[5] 21 C.F.R. § 1271.3(d).

[6] 21 C.F.R. § 1271.10.

[7] *United States v. Regenerative Sciences, Inc.*, Civil Action No. 1:10-CV-01327-RMC (D.C. Dist. 2010). For more background, *see* FDA "Untitled Letter" to Regenerative Sciences, Inc. (July 25, 2008), FDA News Release, "FDA Seeks Injunction Against Colorado Manufacturer of Cultured Cell Product," dated August 6, 2010, and prior case history *Regenerative Sciences, Inc. v. United States Food and Drug Administration*, Civil Action No. 1:10-cv-01055-RMC (D.C. Dist. 2010).

issues involved in the case or leading up to the case. However, stripped to its very core, the case involves a procedure whereby a patient's own MSC cells are extracted and isolated from the patient's bone marrow, processed at a laboratory on site for two to three weeks to undergo expansion, and then returned to the same patient to treat a medical condition. The fundamental question raised by this case is at what point does a medical procedure become the manufacturing of a drug or biological product regulated by FDA.

Regenerative takes the position that the Regenexx procedure is the practice of medicine and thereby is outside of FDA's jurisdiction. It also contends that the manipulation of the stem cells occurs in the normal course of medical practice which is regulated by Colorado, the state in which the company is located. Because the Regenexx procedure occurs completely within Colorado, Regenerative contends there is no interstate commerce and therefore it is not subject to FDA's authority. The Government argues that FDA is not impinging on the company's ability to practice medicine; instead, it considers the product being reinjected into the patient to be a cultured cell product subject to FDA's regulations governing the use of HCT/Ps. According to FDA's position, the Regenexx procedure involves growth factors, reagents and drug products that cross state lines thereby placing the product in interstate commerce. Moreover, FDA contends that the product is more than "minimally manipulated" and, consequently, does not meet the conditions listed in 21 C.F.R. Part 1271 that exempts HCT/Ps from being regulated as drugs, devices, and/or biological products. As a result, the product is subject to the provisions of the FDCA and PHSA, including the adulteration, misbranding, and IND requirements.

This case is interesting for many reasons. While it does not impact stem cell products involving more than "minimal" manipulation, since those are clearly covered under 21 C.F.R. Part 1271, it raises legal and practical questions as to how much manipulation is "minimal." Is this a floating standard that will be applied on a case-by-case basis? If so, what are the primary determining factors that would distinguish one procedure from another? And, is the HCT/P regulatory scheme itself vulnerable for being unconstitutionally overbroad? The answers to these questions are critical to the growth of stem cell therapies. On the one hand, clinics, laboratories, and industry could be subject to significant regulatory expense and FDA oversight or, on the other hand, the use of autologous stem cells could remain largely unregulated with patient safety monitored through state laws and malpractice lawsuits.

While the outcome of the *Regenerative* case may provide some answers to these critical questions, the court's ruling (or settlement by the parties) is unlikely to settle all of the regulatory issues surrounding the use of autologous stem cells. Whether one is a physician seeking to treat patents with stem cells or a laboratory considering the business potential surrounding the culturing of cells for physicians, the post-*Regenerative* world will likely continue to be a regulatory minefield.

For example, if Regenerative is successful in its attempt to characterize the Regenexx procedure as the "practice of medicine" instead of a biologic under the PHSA, therapeutic use of autologous stem cells will likely move into the individual physician's office under the regulation of each individual state board of medicine. One sees this process beginning to unfold in Texas where the Texas Medical Board recently signaled its intention to regulate stem cell autologous transplant procedures as "investigational" that require review by an Institutional Review Board ("IRB").[8]

This will likely lead to differing regulatory approaches among the various state boards of medicine and individual IRBs. Such an outcome may also lead to further questions as to precisely where the line will be drawn dividing "manufacturing" and the "practice of medicine." FDA is unlikely to cede

[8] *See* "Texas Medical Board seeks to regulate stem cell transplants, like Perry's back treatment," *InvestorStemCell.com* <http://investorstemcell.com/stem-cell-research/texas-medical-board-seeks-to-regulate-stem-transplants-like-perrys-back-treatment/>, Aug. 27, 2011.

ground on this point willingly. If Regenerative wins this case, FDA is likely to scrutinize every future stem cell procedure for any activity that could go outside of the practice of medicine as defined in the court's ruling. A careful analysis of the court's ruling, and a review of any proposed stem cell procedure in light of that ruling, will be necessary to prevent running afoul of the FDA. Even with such a careful review, future litigation may be necessary to precisely define the limits of the "practice of medicine."

On the other hand, if FDA successfully convinces the court that the cultured cells produced using the Regenexx procedure are "biologics" under the PHSA and "drugs" under the FDCA, the regulatory landscape for stem cell products will change dramatically. Requiring BLAs for stem cell procedures would make it very difficult for individual physicians to perform procedures in their offices. However, such a court ruling may also present potential opportunities for the fledgling stem cell industry. If a BLA is required, a company willing to commit the resources towards the clinical studies that will be required to establish the procedure's safety and efficacy for a given indication could set up a centralized center for receiving patient samples and preparing the purified stem cells. Recent changes to the PHSA enacted by the Patient Protection and Affordable Care Act ("PPACA") provide another incentive for industry to pursue a BLA. Under the PPACA, the first company to obtain a BLA for the stem cell procedure could obtain 12 years of market exclusivity protection against the approval of a biosimilar version of the same procedure.[9]

Lastly, the *Regenerative* case has the potential to affect a fundamental aspect of FDA's regulatory activities. A key element of the case goes to whether an autologous stem cell procedure is a "drug" under the FDCA. The court has raised questions as to how the "device" definition in the FDCA, which excludes articles that operate by chemical action or that are dependent on being metabolized to achieve their intended purpose, could affect whether a stem cell procedure falls within the "drug" definition. It is unclear whether these questions may lead to stem cells being regulated as "devices" instead of "drugs." However, if the court were to render such a decision and the ruling were upheld on appeal, it would have far reaching implications for other drug/device determinations in the future.

Regardless of the outcome of the *Regenerative* case, there will be opportunities in the stem cell industry for those who are prepared to operate in the resulting regulatory environment. The court's decision will, to a large degree, dictate the types of legal strategies and business models that will be necessary to successfully perform stem cell procedures in the future.

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[9] *See* 42 U.S.C. § 361(k).

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