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## Innovative Procedures V. Premarketing Approval

Law360, New York (September 20, 2011, 12:23 PM ET) -- The U.S. Food and Drug Administration is increasingly scrutinizing certain novel stem cell and tissue procedures used by physicians and companies, asserting that such activities do not comply with the Food, Drug and Cosmetic Act ("FDCA") and the Public Health Service Act ("PHSA"). One of the FDA's first test cases is against Regenerative Sciences LLC in the United States District Court for the District of Columbia (1:10-cv-01327-RMC). The decision by the court in this case will likely dictate how this nascent industry develops.

The FDA's position in the Regenerative Sciences case — and others that will likely follow — is that the therapy at issue involves a drug or biologic product that must comply with the extensive premarketing approval requirements set forth by the FDCA and Section 351 of the PHSA (42 U.S.C. § 262). Regenerative's position — as will likely be the position of other innovators — is that the therapy simply constitutes the practice of medicine, which the FDA does not have the authority to regulate, and that the therapy is also a human cell, tissue and cellular- or tissue-based product ("HCT/P") that is only subject to the less cumbersome requirements set forth in Section 361 of the PHSA (42 U.S.C. § 264).

The FDA's attempt to force these types of therapies to comply with the rigorous premarketing approval requirements of the FDCA and Section 351 of the PHSA poses a significant risk to hindering innovation in this field. Because many of these therapies have little, if any, patent protection and are not privy to the marketing exclusivities enjoyed by new chemical entities and new biologic products, many innovators have little incentive or financial ability to complete the extensive application process, including costly and time-consuming clinical trials, that the FDCA and Section 351 of the PHSA require.

### Background of FDA's Case Against Regenerative

An HCT/P is subject only to the regulations set forth in Section 361 of the PHSA and not the premarketing approval requirements specified for drug and biologic products in the FDCA and Section 351 of the PHSA, respectively. But, an HCT/P only qualifies for treatment under Section 361 if it meets all of the criteria set forth in 21 C.F.R. § 1271.10(a). One of these requirements, which is at issue in the Regenerative Sciences case, is that the HCT/P is only "minimally manipulated." 21 C.F.R. § 1271.10(a)(1).

The FDA began targeting Regenerative in July 2008 as a result of a procedure Regenerative's founding physicians were using on patients. This procedure, called the Regenexx™ procedure, is used to treat certain orthopedic conditions, such as osteoarthritis, nonhealing bone fractures, avascular necrosis and bulging lumbar discs. In this procedure, the physician takes bone marrow from the patient's hip or synovial fluid from the patient's knee, as well as blood from the patient, and transports these materials to a nearby laboratory facility.

At this facility, mesenchymal stem cells are isolated from the bone marrow or synovial fluid and expanded in culture for two to three weeks using growth factors from the patient's

blood, as well as other chemical reagents. The cells are then combined with drug products, such as doxycycline, which have been previously approved by the FDA, and are then transported back to the clinic for injection into the patient.

Shortly after learning about the procedure from Regenerative's website in 2008, the FDA advised Regenerative that the FDA considered the procedure to constitute the manufacture of a drug under the FDCA and/or a biologic product under Section 351 of the PHSA. Regenerative countered that its activities fall within the "practice of medicine" and are thus outside the scope of the FDA's regulatory authority. The FDA subsequently conducted two inspections of Regenerative's facilities in 2009 and 2010, and Regenerative brought two lawsuits against the FDA. One of the suits was dismissed, and one was stayed pending the outcome of the present litigation initiated by the FDA. Regenerative also agreed to cease performing the procedure until the lawsuit is resolved.

### **Recent Proceedings Indicative of Broader Dispute**

Earlier this year, the FDA moved for summary judgment that Regenerative violates the FDCA's prohibition on adulterating and misbranding a drug (21 U.S.C. § 331(k)). Specifically, the FDA argued that Regenerative manufactures a drug product that is subject to regulation under the FDCA because the cell culture product used in the procedure involves more than minimal manipulation of the HCT/P. The FDA further argued that Regenerative's drug product is adulterated because it is not manufactured, processed or held in compliance with current good manufacturing practices ("CGMPs"), and that it is misbranded because it is not labeled "Rx only."

The FDA contended that the shipment of doxycycline or other FDA-approved drugs in interstate commerce prior to incorporation into Regenerative's product makes Regenerative's procedure unlawful under 21 U.S.C. § 331(k). The FDA seeks permanent injunctive relief to enjoin Regenerative from "violating the FDCA" and "to protect the public health."

Regenerative countered that summary judgment was not proper because many issues of material fact existed — including whether Regenerative "manufactures" a drug or biologic and is therefore subject to CGMP requirements, whether the procedure meets the criteria for regulation solely under Section 361 of the PHSA, whether the procedure substantially affects interstate commerce, and whether the procedure constitutes the practice of medicine. Two professional organizations, the American Association of Orthopaedic Medicine ("AAOM") and the Association of American Physicians & Surgeons Inc. ("AAPS"), filed amicus briefs in support of Regenerative.

AAOM argued, *inter alia*, that Regenerative does not manufacture a drug product that is offered for sale to the general public and that, because the procedure is accomplished wholly within the state of Colorado and under the regulatory jurisdiction thereof, it has no impact on interstate commerce and is thus outside the scope of authority granted to the FDA by Congress. AAPS similarly argued, *inter alia*, that autologous use of bodily fluids, cells or tissues is within the practice of medicine and outside the jurisdiction of the FDCA, especially where, as here, the therapy does not substantially affect interstate commerce.

Judge Rosemary Collyer, presiding over the case in the U.S. District Court for the District of Columbia, already appears to be giving the issues in this case some serious thought. Last week, she denied the FDA's motion for summary judgment and entered an order to show cause as to why the court should not read the definition of "device" in 21 U.S.C. § 321(h) as informing and restricting the definition of "drug" at 21 U.S.C. § 321(g)(1)(B) and (C).

Judge Collyer noted that the definition of drug under 21 U.S.C. § 321(g)(1)(B) and (C) is broad enough to encompass both drugs and devices, and she suggested that the definition of "device" under 21 U.S.C. § 321(h) should therefore guide and narrow the court's

interpretation of the term "drug." Judge Collyer's proposal would result in the term "drug" including: an article for use in diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals; an article (other than food) intended to affect the structure or function of a patient; and an article that achieves its primary intended purposes through chemical action, and that depends on being metabolized for the achievement of its primary intended purposes.

The court's interpretation of the term "drug" will determine whether the procedure falls within the scope of the FDCA. This determination will in turn govern the decision of whether the procedure must comply with the rigorous premarketing approval requirements set forth in the FDCA. Briefing by the parties on this issue is scheduled to be completed on Oct. 24, 2011.

## **What Will the Future Bring?**

This case addresses an issue of first impression for the court and will likely have a revolutionary impact on a large number of innovators that are involved in developing and/or practicing these novel types of therapies. How will the court define the term "drug" under the FDCA? How will FDA's minimal manipulation criterion for HCT/Ps be defined? Will litigation regarding the interpretation of the other prongs of 21 C.F.R. § 1271.10(a) follow? How will the court define the practice of medicine that is left to regulation by the states alone? How broadly will the court construe "activities that substantially affect interstate commerce"? Will innovators be shut down and left with no ability or motivation to jump through the hoops required for them to continue practicing their products? Stay tuned ...

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