UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED STATES OF AMERICA,	)	
Plaintiff,	)	
v.	)	**Civil Action No. 10-1327 (RMC)**
REGENERATIVE SCIENCES, LLC, CHRISTOPHER J. CENTENO, M.D., JOHN R. SCHULTZ, M.D., and MICHELLE R. CHEEVER,	)	
Defendants.	)	

MEMORANDUM OPINION

Drs. Christopher J. Centeno and John R. Schultz developed the Regenexx™ Procedure, by which they use stem cell therapies to aid healing for their orthopedic patients. They formed Regenerative Sciences LLC ("Regenerative") for this endeavor, at which Michelle R. Cheever is the Laboratory Director. They are all now facing an enforcement action by the Food and Drug Administration ("FDA"), which charges them with "causing articles of drug to become adulterated" and "misbranded" within the meaning of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 301 *et seq.* Compl. [Dkt. 1] ¶ 1. Defendants respond that they practice medicine wholly within the State of Colorado and under its oversight and that the Regenexx™ Procedure is not a "drug" subject to regulation by the federal government. Defs.' Opp. to Pl.'s Mot. for Summ. J. [Dkt. 26] ("Defs.' Opp") at 1.

It is a close question but ultimately the Court concludes that the Regenexx™ Procedure is subject to FDA enforcement because it constitutes a "drug" and because a drug that has been shipped in interstate commerce is used in the solution through which the cultured stem cells are administered to patients. This acknowledged connection to interstate commerce renders the Regenexx™ Procedure subject to the FFDCA even though the doctors themselves are practicing medicine under Colorado law. Summary judgment will be granted to the United States and an injunction will be issued precluding the continued use of the Regenexx™ Procedure without compliance with the FFDCA.

I. FACTS

Drs. Centeno and Schultz practice together and jointly own the Centeno-Schultz Clinic in Broomfield, Colorado. Drs. Centeno and Schultz are also the majority shareholders of Regenerative, which owns the Regenexx™ Procedure and exclusively licenses the Clinic to use it. Ms. Sheever serves as Regenerative's Laboratory Director. Regenerative and the Clinic are related companies and operate as one business. The Regenexx™ Procedure is a non-surgical procedure for patients suffering from moderate to severe joint, muscle, tendon or bone pain due to injury or other conditions. Am. Answer Countercls. [Dkt. 16] ("Countercls.") ¶ 3.

> The Regenexx™ Procedure begins with a licensed physician taking a small bone marrow sample from the back of a patient's hip through a needle. Blood samples are also taken from a vein in the patient's arm. These samples are then sent to the Regenerative laboratory which is also in Broomfield, Colorado, just a few miles from the Clinic where the mesenchymal stem cells (MSCs) are isolated from the bone marrow and then grown to greater numbers. This process uses the natural growth factors found in the patient's blood to grow the MSCs.
>
> After approximately 2 weeks, the expanded stem cells are sent to the University of Colorado affiliated Colorado Genetics Laboratory for testing. . . .

> Once the cells pass quality assurance testing, they are placed back into the patient's injured area (i.e. knee, hip, rotator cuff), typically 4-6 weeks after they were removed. The stem cells then begin to repair the patient's degenerated or injured area. The repair process usually takes between 3-6 months but many patients demonstrate marked improvement within 1-3 months.

Countercls. ¶¶ 5-10. In August 2010, when this matter began, the Regenexx™ Procedure constituted about one-third of the procedures performed by the Clinic. Defs.' Opp. at 15.

Of critical importance here is the process by which Regenerative expands the mesenchymal cells taken from a patient's bone marrow and delivers a syringe with the cells in solution to the Clinic.

> 1. A doctor at the Clinic obtains a tissue sample from the patient's bone marrow by inserting a needle into the hip bone and drawing a thick blood like liquid into a syringe; the sample is then sent to the laboratory.
>
> 2. The marrow sample is centrifuged to separate out fractions of the bone marrow and the middle layer ("buffy coat") is taken off with a pipette.
>
> 3. The cells from the buffy coat are placed in a plastic flask and kept in a warm environment to incubate with the patient's own blood platelets that contain growth factors, as well as a nutrient solution. Over a few days, the mesenchymal stem cells adhere to the plastic flask while the rest of the cells do not adhere.
>
> 4. The non-adherent cells are discarded and the mesenchymal stem cells are collected using Trypsin, an enzyme, to detach the cells from the plastic flask.
>
> 5. The process is repeated to grow the cells.
>
> 6. The cells undergo a visual inspection by the Colorado Genetics Laboratory to make sure that there are no genetic mutations or other genetic problems. The treating doctor then approves the cells.

Defs.' Opp., Ex. 7 [Dkt. 26] (Centeno Decl.) ¶¶ 13-24; *see also* Compl. ¶ 11. "[T]he expanded cells, along with a drug product that has been shipped in interstate commerce[1] and other additives, are placed into syringes. Regenerative Sciences [sends] the filled syringes in sterile bags to the Clinic, where they are injected into patients." Compl. ¶ 11; *see* Answer ¶¶ 11 & 13 (admitting this fact).

In a letter dated July 25, 2008, the FDA notified Regenerative that the FDA believed that the cell product used in the Regenexx™ Procedure constituted a drug under the FFDCA and a biological product under the Public Health Service Act, 42 U.S.C. § 262 ("PHSA"). Further, the FDA stated that because Regenerative had not obtained the necessary approvals for the cell product, its actions in this regard were possibly unlawful. Countercls. ¶¶ 20 & 21; Pl.'s Mot. for Summ. J. [Dkt. 19] ("Pl.'s Mot.") at 13.

FDA investigators inspected Regenerative between February 23, 2009 and April 15, 2009. Compl. ¶ 31; Countercls. ¶ 24. That inspection showed that the laboratory did not operate in conformity with current good manufacturing practice ("CGMP").[2] *See* 21 U.S.C. § 351(a)(2)(B) and 21 C.F.R. Parts 210-211; *see also* 21 C.F.R. Parts 600-680. When the 2009 inspection concluded, the FDA investigators issued a list of observations that identified a series of alleged CGMP violations. Compl. ¶ 31.

FDA investigators again inspected Regenerative between June 2, 2010 and June 16, 2010. Countercls. ¶¶ 26, 27. That inspection also revealed alleged CGMP violations, which the investigators catalogued in a list of observations. Compl. ¶ 32.

[1] The "drug product" is not identified except in sealed documents as Defendants claim it is confidential commercial information. *See* Pl.'s Mot. at 12 n.14.

[2] CGMP "assure[s] that [a] drug meets the requirements of [the statute] as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." 21 U.S.C. § 351(a)(2)(B).

While the initial FDA inspection was ongoing, Regenerative filed a complaint against the FDA in United States District Court for the District of Colorado, alleging that the FDA did not have the jurisdiction to regulate autologous[3] use of stem cells. *Regenerative Sciences, Inc. v. FDA*, Civ. No. 1:09-cv-00411-WYD-BNB [Dkt. 1] (D. Colo. Feb. 26, 2009) ("*Regenerative I*"). On March 26, 2010, the district court granted the FDA's motion to dismiss on ripeness grounds. *Regenerative I*, Civ. No. 1:09-cv-00411-WYD-BNB [Dkt. 42] (D. Colo. Mar. 26, 2010). Regenerative then filed a notice of appeal with the United States Court of Appeals for the Tenth Circuit on March 29, 2010.[4] *Regenerative I*, Civ. No. 10-1125 (10th Cir.).

On June 22, 2010, Regenerative filed a complaint in this Court challenging FDA's determination that Regenerative is a drug manufacturer. *Regenerative Sciences, Inc. v. FDA*, Civ. No. 1:10-cv-01055 [Dkt. 1] (D.D.C. June 22, 2010) ("*Regenerative II*"). On July 6, 2010, Regenerative filed a motion for a temporary restraining order in this Court. *Regenerative II*, Civ. No. 1:10-cv-01055 [Dkt. 9] (D.D.C. July 6, 2010). Pursuant to a Stipulated Order, the parties agreed to litigate the entire dispute in this Court. Defs.' Opp. at 19-20. Accordingly, Regenerative agreed to dismiss the pending actions in the District of Colorado and the Tenth Circuit, as well as withdraw its motion for a temporary restraining order in this Court. Stip. Order [Dkt. 10] at ¶ 11. Regenerative also agreed to stop using the Regenexx™ Procedure during the pendency of this litigation. *Id.* at ¶ 6. FDA has filed a motion for summary judgment, as well as a motion to dismiss Defendants' counterclaims.

[3] "Autologous use means the implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered." 21 C.F.R. § 1271.3.

[4] On June 30, 2010, Regenerative filed a motion to stay the Colorado case pending its appeal. *Regenerative I*, Civ. No. 1:09-cv-00411-WYD-BNB [Dkt. 53] (D. Colo. June 30, 2010).

II. LEGAL STANDARDS

A. Summary Judgment

Under Rule 56 of the Federal Rules of Civil Procedure, summary judgment shall be granted "if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a); *accord Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247 (1986); *Talavera v. Shah*, 638 F.3d 303, 308 (D.C. Cir. 2011). Moreover, summary judgment is properly granted against a party who "after adequate time for discovery and upon motion . . . fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986).

In ruling on a motion for summary judgment, the court must draw all justifiable inferences in the nonmoving party's favor and accept the nonmoving party's evidence as true. *Anderson*, 477 U.S. at 255; *Talavera*, 638 F.3d at 308. A nonmoving party, however, must establish more than "[t]he mere existence of a scintilla of evidence" in support of its position. *Anderson*, 477 U.S. at 252. In addition, the nonmoving party may not rely solely on allegations or conclusory statements. *Greene v. Dalton*, 164 F.3d 671, 675 (D.C. Cir. 1999). Rather, the nonmoving party must present specific facts that would enable a reasonable jury to find in its favor. *Id.* If the evidence "is merely colorable, or is not significantly probative, summary judgment may be granted." *Anderson*, 477 U.S. at 249-50 (citations omitted).

B. Motion to Dismiss

A motion to dismiss for failure to state a claim pursuant to Federal Rule of Civil Procedure 12(b)(6) challenges the adequacy of a complaint on its face. Fed. R. Civ. P. 12(b)(6). A complaint must be sufficient "to give the defendant fair notice of what the . . . claim is and the

grounds upon which it rests." *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 555 (2007) (internal quotation marks and citation omitted). Although a complaint does not need detailed factual allegations, a plaintiff's obligation to provide the grounds of his entitlement to relief "requires more than labels and conclusions, and a formulaic recitation of the elements of a cause of action will not do." *Id.* To survive a motion to dismiss, a complaint must contain sufficient factual matter, accepted as true, to state a claim for relief that is "plausible on its face." *Twombly*, 550 U.S. at 570.

A court must treat the complaint's factual allegations as true, "even if doubtful in fact." *Twombly*, 550 U.S. at 555. But a court need not accept as true legal conclusions set forth in a complaint. *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009). In deciding a motion under Rule 12(b)(6), a court may consider the facts alleged in the complaint, documents attached to the complaint as exhibits or incorporated by reference, and matters about which the court may take judicial notice. *Abhe & Svoboda, Inc. v. Chao*, 508 F.3d 1052, 1059 (D.C. Cir. 2007).

III. ANALYSIS

The question presented here is whether the Regenexx™ Procedure constitutes a drug (or biologic product) subject to FDA regulation or whether it is merely an intrastate method of medical practice subject only to the laws of the State of Colorado. FDA asserts that the Regenexx™ Procedure constitutes the manufacturing, holding for sale, and distribution of an unapproved biological drug product. Moreover, FDA claims that Defendants have violated the FFDCA's prohibition on adulteration and misbranding a drug with their Regenexx™ Procedure. On the other hand, Defendants argue that the Regenexx™ Procedure constitutes the practice of medicine as defined by Colorado law and that the FDA lacks jurisdiction to regulate it.

Defendants also assert that the Regenexx™ Procedure occurs entirely intrastate and is not covered by the Commerce Clause or the FFDCA, which limit federal power to interstate commerce.

A. Federalism and the Commerce Clause

Defendants insist that the FDA's complaint must be understood within the constitutional principles of federalism and the limits of the Commerce Clause. They urge the Court to apply the "assumption that the historic police powers of the States were not to be superseded by [a] Federal Act unless that was the clear and manifest purpose of Congress." *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (internal quotation marks and citations omitted). By long tradition, the health and safety of the people is left to the States as matters of local concern. *Id.* at 475. Accordingly, Defendants state that Congress has left the practice of medicine to the States to regulate. FDA does not disagree with these principles but asserts that their exercise of jurisdiction over Defendants' Regenexx™ Procedure is a permissible exercise of federal power under the Commerce Clause.

Congress may regulate the practice of medicine or rather, certain aspects of it, when it does so pursuant to its Commerce Clause powers. Congress has the power "[t]o regulate Commerce . . . among the several states . . . ." U.S. Const. art. I, § 8, cl. 3. The United States Supreme Court has defined three categories of activity that may be regulated by Congress pursuant to its Commerce Clause power: (1) "channels of interstate commerce," (2) "instrumentalities of interstate commerce, or persons or things in interstate commerce," (3) "those activities having a substantial relation to interstate commerce," or "those activities that substantially affect interstate commerce." *United States v. Lopez*, 514 U.S. 549, 558-59 (1995).

> The [FFDCA] rests upon the constitutional power resident in Congress to regulate interstate commerce. To the end that the

> public health and safety might be advanced, it seeks to keep interstate channels free from deleterious, adulterated and misbranded articles of the specified types. It is in that interstate setting that the various sections of the Act must be viewed.

United States v. Walsh, 331 U.S. 432, 434 (1947) (internal citations omitted). The FFDCA provisions at issue in this case require an interstate commerce nexus, ensuring that regulation under the FFDCA is consistent with the Commerce Clause. 21 U.S.C. § 331(k) (applying only if the drug is held for sale "after shipment in interstate commerce"). Thus, the question here is one of statutory interpretation – whether Defendants' cell product is subject to the terms of the FFDCA.

B. The Regenexx™ Procedure is a "Drug" Under the FFDCA

1. Definition of a "Drug"

The best place to start when interpreting a statute is the language of the law itself. *Barnhart v. Sigmon Coal Co.*, 534 U.S. 438, 450 (2002) ("As in all statutory construction cases, we begin with the language of the statute."). The FFDCA defines "drug" to mean "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "articles (other than food) intended to affect the structure or any function of the body of man or other animals." 21 U.S.C. § 321(g)(1)(B)&(C). Based on this definition, whether an "article" is a "drug" depends on its "intended use." *Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004) is binding precedent on this point:[5] under the FFDCA, "classification of a substance as a 'drug' turns on the nature of the claims advanced on its behalf."[6] Further, "it is well established

[5] The Court asked the parties "why the Court should not read the definition of 'device' at 21 U.S.C. § 321(h) as informing and restricting the definition of 'drug' at 21 U.S.C. § 321(g)(1)(B)&(C)" and is now persuaded to adopt the direct language of the statute without interpretation. Order to Show Cause [Dkt. 42].

[6] *See also United States v. Writers & Research, Inc.*, 113 F.3d 8, 11 (2d Cir. 1997) ("Regardless of the classification of a drug, if an article is intended for use in the diagnosis, cure, mitigation,

that the intended use of a product, within the meaning of the [FFDCA], is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source." *Action on Smoking & Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980) (internal quotation marks and citations omitted); *see* 21 C.F.R. § 201.128 ("The words *intended uses* or words of similar import in §§ 201.5, 201.115, 201.117, 201.119, 201.120, and 201.122 refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article . . . ." (emphasis added)); *Estee Lauder, Inc. v. FDA*, 727 F. Supp. 1, 2 (D.D.C. 1989) ("Courts have held that the decision as to whether a product is a drug depends on its 'intended use,' which can be determined from objective evidence such as the product's current and past containers, instructions, and advertisements.").

FDA also regulates biological products under the PHSA, 42 U.S.C. § 262. A "biologic product" is defined by the PHSA 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." 42 U.S.C. § 262(i)(1). A product may be both a drug and a biological product. *See, e.g., CareToLive v. von Eschenbach*, 525 F. Supp. 2d 952, 957 (S.D. Ohio 2007).[7] Except for some licensing distinctions, the FFDCA applies in full to a biologic product licensed under the PHSA. 42 U.S.C. § 262(j); *see*

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treatment, or prevention of disease in man it is defined as a drug."); *Nat'l Nutritional Foods Ass'n v. Mathews*, 557 F.2d 325, 333 (2d Cir. 1977) ("The vendors' intent in selling the product to the public is the key element in this statutory definition.").

[7] *See also United States v. Loran Med. Sys., Inc.*, 25 F. Supp. 2d 1082, 1084-1087 (C.D. Cal. 1997) (holding that a cell product made from neonatal rabbit and human fetal cells was both a drug and a biological product).

CareToLive, 525 F. Supp. 2d at 957 ("Biological products . . . are generally subject to the same statutory and regulatory requirements that apply to drugs.").

Defendants' website and pleadings describe their "intended use" for the Regenexx™ Procedure. Defendants promote the Regenexx™ Procedure to treat a variety of orthopedic conditions and injuries. On the Regenerative Sciences' website, www.regenexx.com, Defendants describe the Regenexx™ Procedure as "an Alternative to Traditional Surgery" that can treat "[f]ractures that have failed to heal, joint cartilage problems, partial tears of tendons, muscles, or ligaments, chronic bursitis, avascular necrosis of the bone, and lumbar disc bulges." *See* Answer ¶ 16.b.

Defendants' pleadings confirm their intentions to use the Regenexx™ Procedure for "mitigation" and "treatment," among others, of disease and injury. They explain how the "stem cells . . . begin to repair the patient's degenerated or injured area," Countercls. ¶ 10; how the Regenexx™ Procedure is "for the treatment of orthopedic injuries and arthritis," *Regenerative II*, Civ. No. 1:10-cv-01055 [Dkt. 1] (D.D.C. June 22, 2010) (Compl. ¶ 14); and how "[t]he Procedure is for the treatment of musculoskeletal and spinal injury." *Regenerative I*, Civ. No. 09-cv-00411-WYD [Dkt. 1] (D. Colo.) (Compl. ¶ 16). These statements of "intended use" fully satisfy the statutory definition for a "drug." Similarly, Defendants' admissions that the Regenexx™ Procedure is based on mesenchymal stem cells derived from the patient's bone marrow (Countercls. ¶ 5) and that it is intended to treat orthopedic conditions fully satisfy the definition of "biological product" under the PHSA because it is a "blood, blood component or derivative, . . . or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i); *see* Pl.'s Mot., Ex. C (Shannon

Dec.) ¶ 9. In sum, the cell product used in the Regenexx™ Procedure meets the statutory definition for both a "drug" under the FFDCA and a "biological product" under the PHSA.

2. The Regulations at 21 C.F.R. Part 1271 Do Not Exempt the Regenexx™ Procedure

The FDA has the authority under the PHSA to enact regulations to prevent the spread of communicable diseases. Section 361 of PHSA, 42 U.S.C. § 264(a), states that

> The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession.

Although this section grants this authority to the Surgeon General, it now rests with the FDA.[8]

The development of research and medical treatments using human cells, tissues, and cellular or tissue-based products (human cell or tissue products or "HCT/Ps") caused the FDA to announce in 1997 a tiered, risk-based approach for their regulation. *See* Proposed Approach to Regulation of Cellular and Tissue-Based Products, FDA Dkt. No. 97N-0068 (Feb. 28, 1997) (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM062601.pdf. In 2001, after notice and comment, the FDA issued the first of a set of regulations pertaining to HCT/Ps pursuant to its authority under section 361 of the PHSA. *See* Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing; Final Rule, 66 Fed. Reg. 5447 (Jan. 19, 2001) ("Registration Rule").[9] The regulations created a new regulatory

[8] *See infra* Section III. E.

[9] *See also* Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products; Final Rule, 69 Fed. Reg. 29,786 (May 25, 2004); Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments;

framework for HCT/Ps "to improve protection of the public health without imposing unnecessary restrictions on research, development, or the availability of new products." *Id.* at 5447. Part 1271.3 defines 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." 21 C.F.R. § 1271.3(d). Those HCT/Ps that meet the set of criteria listed in 21 C.F.R. § 1271.10 are only regulated under section 361 of the PHSA and Part 1271 of the C.F.R. In contrast, those HCT/Ps that do not meet these criteria are regulated as "a drug, device, and/or biological product." 21 C.F.R. § 1271.20.

One of these criteria is that the HCT/Ps be "minimally manipulated." 21 C.F.R. § 1271.10(a)(1). Minimal manipulation is defined as "processing that does not alter the relevant biological characteristics of cells or tissues." 21 C.F.R. § 1271.3(f)(2). Defendants admit that "[t]he processing of the cultured cell product 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." Pl.'s Statement of Material Facts [Dkt. 19] ("Pl.'s SMF") ¶ 10; Defs.' Resp. to Pl.'s SMF [Dkt. 26] ¶ 10. This admission supports the conclusion that the biological characteristics of the cells change during the process employed by Defendants, resulting in more than minimal manipulation of the HCT/Ps originally extracted from the patient. Moreover, the FDA's conclusion that the Regenexx™ Procedure does not meet the regulatory definition of "minimal manipulation" is entitled to "substantial deference." *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994); *see also Petit v. Dep't of Educ.*, 675 F.3d 769, 778 (D.C. Cir.

Inspection and Enforcement; Final Rule, 69 Fed. Reg. 68,612 (Nov. 24, 2004) ("Good Practice Rule").

2012) (citing the deference afforded to an agency's interpretations of its own regulations); *Am. Wildlands v. Kempthorne*, 530 F.3d 991, 1000 (D.C. Cir. 2008) ("The rationale for deference is particularly strong when the [agency] is evaluating scientific data within its technical expertise . . . .") (internal quotations marks and citation omitted) (alteration in original)). As a result, Defendants fail to meet at least one of the criteria listed in 21 C.F.R. § 1271.10, and the HCT/Ps in the Regenexx™ Procedure must be regulated as a "drug" under the FFDCA.

C. Defendants Violated 21 U.S.C. § 331(k)

1. The Regenexx™ Procedure Is Subject to the Commerce Clause

The FFDCA prohibits any act "with respect to, a . . . drug . . . , if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated for misbranded." 21 U.S.C. § 331(k). FDA alleges that Defendants have violated § 331(k) by both adulterating and misbranding a drug. To prevail on this claim, the FDA must first establish that the cell product used in the Regenexx™ Procedure was both (1) "held for sale" and prior to such sale had been (2) "ship[ped] in interstate commerce." The cell product meets both of these requirements.

Concerning the first element, "a doctor who ha[s] held drugs for use in his practice ha[s] held those drugs for sale within the meaning of [§ 331(k)]." *United States v. Evers*, 643 F.2d 1043, 1052 (5th Cir. April 1981); *see also United States v. Sullivan*, 332 U.S. 689, 697 (1948) (interpreting the statute to cover "every article that ha[s] gone through interstate commerce until it finally reache[s] the ultimate consumer."); *United States v. Diapulse Corp. of Am.*, 514 F.2d 1097, 1098 (2d Cir. 1975) (holding that § 331(k) covers medical devices held by practitioners used for the treatment of their patients). Defendants create the cell product, the "drug" in this case, and use it to treat their patients. Such conduct satisfies the "held for sale" requirement of the statute.

Defendants do not contest the "held for sale" requirement but instead argue that the Regenexx™ Procedure does not meet the "interstate commerce" requirement because the entire process takes place intrastate at Defendants' medical facilities in Colorado. The FFDCA defines "drug" to include "articles intended for use as a *component* of any article . . . ." 21 U.S.C. § 321(g)(1)(D)(emphasis added). Courts have held that the "interstate commerce" element is met if any component of that drug moved in interstate commerce. *See Baker v. United States*, 932 F.2d 813, 816 (9th Cir. 1991) ("We hold that wholly intrastate manufacturers and sales of drugs are covered by 21 U.S.C. § 331(k) as long as an ingredient used in the final product travelled in interstate commerce."); *Dianovin Pharmaceuticals, Inc.*, 475 F.2d 100, 103 (1st Cir. 1973) ("The appellants' use of components shipped in interstate commerce to make vitamin K for injection brought their activities within § 331(k) . . .). Defendants combine an antibiotic, doxycycline, with the cell product before the drug is administered to the patients through a syringe. Pl.'s SMF ¶ 23; Def.'s Resp. to Pl.'s SMF ¶ 23. Defendants do not dispute that the doxycycline is shipped from out of state to their facilities in Colorado. *Id*. Therefore, because a component of the drug in this case is shipped through interstate commerce prior to its administration to the patient, the "interstate commerce" requirement is also met.

2. Adulteration

The FDA claims that Defendants have adulterated and misbranded their drug in violation of the FFDCA. Under the terms of the FFDCA, a drug is adulterated "if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice . . . ." 21 U.S.C. § 351(a)(2)(B). "Drugs produced in violation of these CGMP regulations are deemed to be adulterated without the agency having to show that they are

actually contaminated." *John D. Copanos & Sons, Inc. v. FDA*, 854 F.2d 510, 514 (D.C. Cir. 1988). Although Defendants claim that the Regenexx™ Procedure is not subject to the FFDCA, they admit that the procedure does not comply with CGMP. Answer ¶¶ 31, 32. The FDA performed two separate inspections, one in 2009 and the other in 2010, which revealed a number of CGMP violations. *Id.* Having concluded that the cell product used in the Regenexx™ Procedure is a "drug" that is subject to regulation by the FFDCA and that the drug has been "held for sale after shipment in interstate commerce," the fact that the Regenexx™ Procedure does not comply with CGMP renders the drug adulterated in violation of the FFDCA.

3. Misbranding

The FDA also claims that Defendants have violated the FFDCA by misbranding the cultured cell product. The FDA asserts that the cultured cell product is misbranded because it is a prescription drug that does not bear the "Rx only" symbol or carry "adequate directions for use." Under the FFDCA, a prescription drug is one which "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug ." 21 U.S.C. § 353(b)(1)(A). Once Defendants' cell product is ready to be used for treatment, it is administered by injection using a type of x-ray device for guidance. Pl.'s SMF ¶ 13; Def.'s Resp. to Pl.'s SMF ¶ 13. Given the drug's "method of use" and the "collateral measures necessary to its use," administration of the drug can only safely take place under the supervision of a specially-trained practitioner. Thus, the cultured cell product is a prescription drug under the terms of the statute.

A prescription drug is misbranded "if at any time prior to dispensing the label of the drug fails to bear, at a minimum, the symbol "Rx only." 21 U.S.C. § 353(b)(4)(A). It is

undisputed that the label of the cultured cell product does not bear this symbol. Pl's SMF ¶ 17; Def's Resp. to Pl's SMF ¶ 17. On this basis, Defendants misbrand the cultured cell product in violation of the FFDCA.

The FDA further alleges that Defendants have misbranded the cultured cell product because its label does not bear "adequate directions for use," which the FFDCA requires. 21 U.S.C. § 352(f)(1) . The FDA defines "adequate directions for use" as "directions under which the layman can use a drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.5. However, a prescription drug by its very definition cannot bear "adequate directions for use" by a layman. As a result, a prescription drug must qualify for an exemption to avoid violating the FFDCA's misbranding provision. *See United States v. Articles of Drug,* 625 F.2d 665, 673 (5th Cir. 1980) ("Since a prescription drug by definition can be used only under a physician's supervision, and is unsuitable for self-medication, such a drug must qualify for a regulatory exemption created by FDA, pursuant to the authority of section 352(f).").

There are two principal exemptions to the "adequate directions for use" requirement for prescription drugs. The statute provides an exemption to the misbranding provision for prescription drugs if the label contains, *inter alia*, identifying information regarding the dispenser, the prescriber, and the patient, as well as "directions for use and cautionary statements." 21 U.S.C. § 353(b)(2). This exemption, however, applies only when the drug is actually dispensed by filling a prescription of a practitioner. *Id.* The FDA has also created a regulatory exemption to the misbranding provision, which exempts prescription drugs with a label bearing, *inter alia*, information regarding dosage, administration, and ingredients. 21 C.F.R. § 201.100. In contrast to the statutory exemption, the regulatory exemption applies throughout the distribution process. *Id.*

The label for the cultured cell product contains only the "the patient's name, date of birth, laboratory notebook number, cell passage number, day in culture, cell number, number of cells cryo-preserved, and condition of cell suspension." Compl. ¶ 34: Answer ¶ 34. The information on this label does not satisfy the disclosure requirements under either the statutory or the regulatory exemptions.[10] For this reason also, Defendants have violated the misbranding provision of the FFDCA.

D. The Regenexx™ Procedure Does Not Avoid FDA Regulation Because Defendants Are Engaged in the Practice of Medicine

Defendants rely heavily on their argument that the FDA cannot regulate the Regenexx™ Procedure because it constitutes the practice of medicine. However, "[w]hile the [FFDCA] was not intended to regulate the practice of medicine, it was obviously intended to control the availability of drugs for prescribing by physicians." *Evers*, 643 F.2d at 1048; *see also Loran Med. Sys., Inc.*, 25 F. Supp. 2d at 1087 (dismissing defendants' "practice of medicine" argument because the court concluded that the cell product was a drug and that the FDA therefore had the authority to regulate its use). There is a difference between a licensed physician's use of an FDA-approved drug such as doxycycline in an off-label way, which is permissible within the "practice of medicine,"[11] and adding doxycycline to a cell product to be administered to patients, which renders the latter a "drug" that has connections to interstate commerce. The question of interstate commerce is not relevant to the first issue but controls the

[10] The FDA has also created a regulatory exemption for "new drugs." Section 201.115 exempts a "new drug" from the misbranding provision if "such exemption is claimed in an approved application." 21 C.F.R. § 201.115. It is undisputed that Defendants have neither sought nor has the FDA approved a new drug application for Regenexx™ Procedure. Compl. ¶. 20; Answer ¶ 20. This exemption is therefore also inapplicable.

[11] *See Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 56 (D.D.C.1998) ("[O]ff-label use of FDA-approved drugs by physicians is an established aspect of the modern practice of medicine."), *vacated in part on other grounds*, *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).

second. Likewise, the fact that off-label use of an FDA-approved drug is permissible within the practice of medicine does not speak to whether the drug traveled in interstate commerce, which provides the nexus for regulation under the provision of the FFDCA relevant here.

Where, as here, a product meets the definition of "drug" under the FDCA, it comes under the ambit of this law and is thus subject to its provisions. This is true even if its regulation will affect the practice of medicine. Consequently, Defendants' argument that the cell product cannot be regulated by the FDA because the Regenexx™ Procedure constitutes the "practice of medicine" is unavailing.

E. Defendants' Counterclaims Will Be Dismissed

In addition to its motion for summary judgment, FDA has filed a motion to dismiss Defendants' counterclaims. Counterclaims I, II, III, and VII challenge the FDA's authority to regulate the practice of medicine. These claims are dismissed for the reasons stated above. Counterclaims IV, V, and VI concern the following statement in the preamble to 21 C.F.R. § 1271: "We do not agree that the expansion of mesenchymal cells in culture . . . [is] minimal manipulation." Registration Rule, 66 Fed. Reg. at 5447. Counterclaims IV and V allege that this statement is arbitrary and capricious because the underlying science for the statement was never shared with the public and the statement was issued without considering all relevant factors. Counterclaim VI alleges that this statement constitutes a legislative rule that was not issued through notice and comment rulemaking.

Counterclaims IV, V, and VI arise under the Administrative Procedure Act ("APA"). *See* 5 U.S.C. §§ 553, 706(2)(A). Accordingly, Defendants can only bring the challenges in these counterclaims if the statement at issue represents "final agency action." 5 U.S.C. § 704; *see also Trudeau v. FTC*, 456 F.3d 178, 188 (D.C. Cir. 2006) (explaining that

causes of action under the APA are limited to "final agency action"). To constitute final agency action, two conditions must be met: (1) "the action must mark the consummation of the agency's decisionmaking process" and (2) it "must be one by which rights or obligations have been determined, or from which legal consequences will flow." *Bennett v. Spear*, 520 U.S. 154, 177-78 (1997) (internal quotation marks and citations omitted). The challenged statement does not meet at least the latter of these two requirements because FDA's own regulations provide that statements in a preamble do not carry the force of law. *See* 21 C.F.R. § 10.85(d)(1) & (j) (stating that a preamble constitutes an advisory opinion and may be used for illustrative purposes but "not as a legal requirement"). Indeed, the D.C. Circuit recently held that a statement in a preamble did "not express a final agency action." *Am. Petroleum Inst. v. EPA*, Nos. 10-1079, 10-1080, 2012 WL 2894566, at *9 (D.C. Cir. July 17, 2012). Counterclaims IV, V, and VI are therefore dismissed.[12]

Finally, Defendants allege in Counterclaim VIII that the FDA lacks the authority to enact the "entire regulatory scheme governing stem cells" because the autologous use of stem cells carries no risk of spreading communicable diseases. As discussed above, "by delegation from the Surgeon General and the Secretary of Health and Human Services," FDA may enact regulations to prevent the spread of communicable diseases pursuant to section 361 of the PHSA, 42 U.S.C. § 264(a). *See* Good Practice Rule, 69 Fed. Reg. at 68,613. When issuing these

[12] FDA moved to dismiss on statute of limitations grounds pursuant to Fed. R. Civ. P. 12(b)(1) (subject-matter jurisdiction), as well as Fed. R. Civ. P. 12(b)(6) (failure to state a claim). The D.C. Circuit has not resolved whether the statute of limitations in 28 U.S.C. § 2401(a) is jurisdictional. *See Harris v. FAA*, 353 F.3d 1006, 1013 n.7 (D.C. Cir. 2004) (noting uncertainty regarding whether § 2401(a) is jurisdictional in light of *Irwin v. Dep't of Veterans Affairs*, 498 U.S. 89 (1990) but concluding it need not reach the issue). Because the statement in the preamble does not constitute final agency action and the counterclaims regarding the preamble must be dismissed for failure to state a claim, the Court does not reach FDA's arguments that these counterclaims are barred by the statute of limitations.

regulations, FDA carefully explained its determination that the manufacturing of HCT/Ps, including autologous stem cells, presents a risk of spreading communicable disease:

> It is important to recognize that HCT/P manufacturing inevitably has interstate effects . . . Certain diseases, such as those caused by the human immunodeficiency virus (HIV) and the hepatitis B and C viruses (HBV and HCV respectively), may be transmitted through the implantation, transplantation, infusion, or transfer of HCT/Ps derived from infected donors . . . Errors in labeling, mixups of testing records, failure to adequately clean work areas, and faulty packaging are examples of improper practices that could produce a product capable of transmitting disease to its recipient . . . [and] improper handling of an HCT/P can lead to bacterial or other pathogenic contamination of the HCT/P, or to cross-contamination between HCT/Ps, which in turn can endanger recipients.

Id. The FDA has acted within the authority granted by section 361 of the PHSA. Counterclaim VIII will be dismissed.

IV. CONCLUSION

The FDA seeks a statutory injunction to restrain Defendants' violations of the FFDCA. The FFDCA provides this court with the authority "for cause shown to restrain violations of section 331 of [the FFDCA]." 21 U.S.C. § 332(a). In the case of a statutory injunction, once the FDA has established a violation, it need only show that there is some "cognizable danger of recurrent violation." *United States v. W. T. Grant Co.*, 345 U.S. 629, 633 (1953); *see also United States v. Articles of Drug*, 825 F.2d 1238, 1248 (8th Cir. 1987) ("A district court may issue an injunction if it concludes that the injunction is necessary to prevent future violations."). FDA notified Defendants that their Regenexx™ Procedure may be in violation of the FFDCA. It then twice inspected Defendants' laboratories and found a number of CGMP violations. Defendants maintained that the FDA could not regulate their cell product and did not bring their processes into compliance with CGMP. Although Defendants agreed to stop

using their Regenexx™ Procedure during the pendency of this lawsuit, there remains a "cognizable danger of recurrent violation."

Accordingly, FDA's motion for summary judgment [Dkt. 19] and motion to dismiss counterclaims [Dkt. 20] will be granted. In addition, FDA's request for a permanent injunction will be granted.[13] Memorializing orders accompany this Memorandum Opinion.

Date: July 23, 2012

/s/
ROSEMARY M. COLLYER
United States District Judge

[13] Defendants did not assert any opposition to the specific language of FDA's proposed Order of Permanent Injunction.