[NOT YET SCHEDULED FOR ORAL ARGUMENT]

No. 12-5254

IN THE UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

UNITED STATES OF AMERICA,

Plaintiff-Appellee,

v.

REGENERATIVE SCIENCES, LLC, A CORPORATION, et al.

Defendants-Appellants.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

FINAL BRIEF FOR APPELLEE

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CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES PURSUANT TO CIR. R. 28(a)(1)

A. Parties and *Amici*

Plaintiff-appellee is the United States of America. Defendants-appellants are Regenerative Sciences, LLC; Christopher J. Centeno, M.D.; John R. Schultz, M.D.; and Michelle R. Cheever. Amici before the District Court were the Association of American Physicians and Surgeons, Inc.; and the American Association of Orthopaedic Medicine. Amici in this Court are the Association of American Physicians and Surgeons, Inc.; the American Association of Orthopaedic Medicine; and Tim Moore.

B. Rulings Under Review

Appellants seek review of the order and permanent injunction entered on July 23, 2012, by the Honorable Rosemary M. Collyer in *United States of America v. Regenerative Sciences, LLC, et al.*, No. 10-1327 (D.D.C. July 23, 2012). The opinion is reported at 878 F. Supp. 2d. 248 (D.D.C. 2012), and available on Westlaw at 2012 WL 2989988 and at page 924 of the Joint Appendix.

C. Related Cases

This case was not previously before this Court. We are not aware of any related cases.

s/ Abby C. Wright
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GLOSSARY

AAOM	American Association of Orthopaedic Medicine
APA	Administrative Procedure Act
DE	Docket Entry
Def. Br.	Defendants' Brief
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
IVF	In-vitro Fertilization
JA	Joint Appendix

STATEMENT OF JURISDICTION

The district court had jurisdiction under 21 U.S.C. § 332(a) and 28 U.S.C. §§ 1331, 1337, and 1345. DE 1: ¶ 2, JA9. The orders under review were issued on July 23, 2012. DE 47; DE 48, JA924, 946. Defendants filed a notice of appeal on August 7, 2012, within the time provided by Fed. R. App. P. 4(a)(1)(B). DE 50; JA958. This Court has jurisdiction under 28 U.S.C. § 1291.

STATEMENT OF THE ISSUES

1. Whether defendants violated the Federal Food, Drug, and Cosmetic Act by causing the adulteration and misbranding of a drug product held for sale after shipment of one or more of its components in interstate commerce.

2. Whether the regulation of defendants' drug product exceeds the bounds of Congress's authority under the Commerce Clause or otherwise violates the Constitution.

3. Whether the district court properly entered a permanent injunction.

PERTINENT STATUTES AND REGULATIONS

Pertinent statutes and regulations are reproduced in the addendum to this brief.

STATEMENT OF THE CASE

Defendants in this case are Regenerative Sciences, LLC, a closely held corporation, the former director of Regenerative Sciences' laboratory, and two physicians, who are employees and part owners of the corporation. DE 47:2, JA925. Defendants perform what they call the "Cultured Regenexx Procedure." Def. Br. 2.

Defendants receive bone marrow or joint fluid that has been extracted from a patient at a clinic owned by the two physician defendants. As described more fully below, defendants attempt to isolate and expand a particular type of stem cell found in the bone marrow or joint fluid. The manufacturing process includes combining the bone marrow or fluid with other substances, and culturing the cells over the course of two to three weeks. The cell product is then provided to the clinic, where it is injected into the patient. *See* DE 19-1: ¶ 8 (Declaration of Karen S. Kreuzer, Acting District Director, Denver District Office, FDA), JA963.[1] Defendants admit that they do not follow the current good manufacturing practices required under the Federal Food, Drug, and Cosmetic Act (FDCA), and that they do not follow the FDCA's labeling requirements. *See* 21 U.S.C. §§ 351(a)(2)(B), 352(f)(1); 353(b)(4).

In August 2010, after twice inspecting Regenerative Sciences, FDA filed suit against defendants, alleging that defendants violated 21 U.S.C. § 331(k) by causing the adulteration and misbranding of a drug while it is held for sale after shipment in interstate commerce. DE 1: ¶¶ 37-39, JA21. Defendants counterclaimed on the ground that they are engaged in the "practice of medicine" and therefore not subject to FDCA requirements. By stipulation, defendants agreed to stop making their cultured cell product during the pendency of this suit.

[1] Unless otherwise noted, all citations in this brief are to the redacted versions of district court filings, which exclude information defendants claimed was confidential commercial information regarding their processing of the cultured cell product.

The district court granted FDA's motion for summary judgment, dismissed defendants' counterclaims, and permanently enjoined defendants from manufacturing their drug product until they comply with the requirements of the FDCA. DE 47:2, JA925; DE 48:2-3, JA947-48. The court held that defendants' cultured cell product is both a "drug" under the FDCA and a "biological product" under the Public Health Service Act. The court further held that defendants' drug product is adulterated and misbranded in violation of section 331(k) of the FDCA and rejected defendants' arguments that FDA's regulation of their drug product exceeded the limits of Congress's Commerce Clause authority. This appeal followed.

STATEMENT OF FACTS

I. STATUTORY AND REGULATORY BACKGROUND

A. The Federal Food, Drug, and Cosmetic Act

The Federal Food, Drug, and Cosmetic Act ("FDCA") imposes substantive restrictions on the distribution of drugs in the United States. *See* 21 U.S.C. § 331. United States district courts have jurisdiction to "restrain violations" of these provisions. 21 U.S.C. § 332(a).

An article is a drug for purposes of the FDCA 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." 21 U.S.C. § 321(g)(1)(B)&(C). Whether a particular article is a drug thus depends on "the nature

of the claims advanced on its behalf." *See Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004).

The FDCA prohibits "[t]he alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other 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 or misbranded." 21 U.S.C. § 331(k).

As relevant here, a drug is adulterated for purposes of this section if "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." *Id.* § 351(a)(2)(B). A drug is misbranded if its labeling does not bear adequate directions for use or, if at any time prior to dispensing, it fails to bear the symbol "Rx only." *Id.* §§ 352(f)(1); 353(b)(4). FDA has defined "adequate directions for use" to mean "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.

As a general matter, drugs manufactured by physicians are subject to the same regulation as other drugs, except that physicians who make drugs need not register with the FDA and need not comply with certain inspection requirements, if specified conditions are met. *See* 21 U.S.C. §§ 360(g)(2), 374(a)(2)(B).

B. The Public Health Service Act

FDA also regulates biological products under the Public Health Service Act, 42 U.S.C. § 262. A "biological product" includes 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).

A product that has been licensed under the Public Health Service Act is not required to have an approved new drug application under the FDCA. In all other respects, however, the requirements of the FDCA apply to products licensed under the Public Health Service Act, including the provisions applicable to adulteration and misbranding of drugs. 42 U.S.C. § 262(j).

A separate provision of the Public Health Service Act grants FDA broad authority to issue regulations to prevent the transmission of communicable diseases. Section 264 provides FDA with authority to "make and enforce such regulations as in [its] 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." 42 U.S.C. § 264(a).[2]

[2] The statute's grant of authority to the Surgeon General has been delegated to FDA. The Office of Surgeon General was abolished by section 3 of the 1966 Reorg. Plan No. 3, eff. June 25, 1966, 80 Stat. 1610, and all of its functions were transferred to the

C. Regulation of Cellular and Tissue Products

In the early 1990s, in response to the development of therapeutic uses for human cells and tissues, FDA began to implement a separate scheme for regulating certain human cells, tissues, and cellular or tissue-based products ("cellular and tissue products"). When intended to treat illness or disease, these products meet the definition of "drug" (or "device") under the FDCA and "biological product" under the Public Health Service Act.[3] Rather than regulating these cellular and tissue products as drugs, devices, or biological products, however, FDA has chosen to adopt a more limited approach to regulating qualifying cellular and tissue products. *See* Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing; Final Rule, 66 Fed. Reg. 5447, 5447 (Jan. 19, 2001) ("2001 Rule").

Relying on its authority to protect the public from communicable diseases under 42 U.S.C. § 264 of the Public Health Service Act, described above, FDA issued

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Secretary of Health, Education, and Welfare (now Secretary of Health and Human Services) by section 1 of 1966 Reorg. Plan No. 3, set out under 42 U.S.C. § 202. The Secretary's authority has been delegated to FDA. *See* FDA Staff Manual Guide 1410.10.1.A.3.

[3] In 1993 FDA issued a Federal Register Notice explaining that cellular products intended for "the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries" are "biological products" under the Public Health Service Act and "drugs" under the FDCA. *See* Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products; Notice, 58 Fed. Reg. 53248, 53249 (Oct. 14, 1993).

three regulations to implement its approach to regulating cellular and tissue products. 2001 Rule, 66 Fed. Reg. 5447; Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, 69 Fed. Reg. 29786 (May 25, 2004); Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement, 69 Fed. Reg. 68612 (Nov. 24, 2004). These regulations are codified in 21 C.F.R. part 1271. FDA's "part 1271" regulations define cellular and tissue products in part 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).

Cellular and tissue products that meet certain criteria are regulated only under FDA's part 1271 regulations and the Public Health Service Act's communicable disease provisions, and not under the FDCA. 21 C.F.R. § 1271.10; 42 U.S.C. § 264. As relevant here, cells and tissues must be not more than "minimally manipulated" from their natural state to qualify for more limited regulation solely under FDA's part 1271 regulations. 21 C.F.R. § 1271.10(a)(1). FDA regulations define "minimal manipulation" as "processing that does not alter the relevant biological characteristics of cells or tissues." 21 C.F.R. § 1271.3(f)(2).[4]

[4] The concept of "minimal manipulation" is at least twenty years old. *See* Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products; Notice, 58 Fed. Reg. 53248, 53249-50 (Oct. 14, 1993). FDA explained that cells intended for therapeutic use would be subject to the Public Health Service Act's licensure requirement when they are "manipulated in a way that changes the biological characteristics of the cell population (e.g., by

In the preamble to its 2001 Rule, FDA provided some examples of "minimal manipulation" in response to public comments. These examples included materials that had been subjected to "selective removal of B-cells, T-cells, malignant cells, red blood cells, or platelets; centrifugation; cutting, grinding, or shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or irradiation; cell separation; lyophilization; cryopreservation; or freezing." 2001 Rule, 66 Fed. Reg. at 5457. With respect to mesenchymal stem cells, the type of cell at issue in this case, FDA further stated: "We do not agree that the expansion of mesenchymal cells in culture . . . [is] minimal manipulation." 2001 Rule, 66 Fed. Reg. at 5457.

II. FACTUAL BACKGROUND

A. Defendants promote their cultured cell product in connection with what they call the "Cultured Regenexx Procedure." *See* Def. Br. 2 n.4. In performing this procedure, the defendant physicians, who jointly own the Centeno-Schultz Clinic in Broomfield, Colorado, inject patients with a cultured cell product, which they claim treats various orthopedic conditions, such as non-healing bone fractures, osteoarthritis, injuries to the meniscus and rotator cuff, avascular necrosis (death of the bone tissue) of the shoulder and hip, and chronic bursitis. *See* DE 19-1: ¶ 6 (Declaration of Karen S. Kreuzer, Acting District Director, Denver District Office,

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expansion, selection, encapsulation, activation, or genetic modification as a part of gene therapy . . . .)." *Id.* at 53249-50.

FDA), JA962; DE 47:2, JA925; DE 26: ¶¶ 11-12, JA101. This cultured cell product has not been approved by FDA. DE 1: ¶ 20, JA14.

To manufacture their drug product, defendants use multiple drug components that have been shipped in interstate commerce in an attempt to isolate, culture, and expand mesenchymal stem cells.[5] Mesenchymal stem cells are adult stem cells found in various tissues, including bone marrow and joint (synovial) fluid. DE 19-3: ¶ 14 (Declaration of Dr. Steven R. Bauer), JA984-85. These cells are "multipotent," meaning that they have the capacity to become many different kinds of cells, including bone cells, cartilage cells, and cells that make tendons. DE 19-3: ¶¶ 12-13, JA984. Mesenchymal stem cells can be grown in large numbers outside the human body through tissue culture. DE 19-3: ¶ 14, JA984-85.

In attempting to isolate these stem cells, defendants first remove bone marrow from the patient's hip or synovial fluid from the patient's knee. They also draw whole blood from the patient. These materials are then sent to Regenerative Sciences where defendants centrifuge the bone marrow or synovial fluid, and certain cells are removed. DE 19-1: ¶ 8, JA963; DE 47:2-3, JA925-26. The removed cells are placed in a flask to incubate, along with the patient's blood platelets, a nutrient solution, and other additives. The mesenchymal stem cells contained in this fluid adhere to the flask, and defendants remove them by applying Trypsin, an enzyme. Defendants

[5] As Dr. Steven R. Bauer explained in his declaration, it is not clear that defendants in fact isolate only mesenchymal stem cells. *See* DE 19-3: ¶¶ 18-23, JA989-95.

harvest the cells and repeat the process, further culturing and expanding the cells over the span of two to three weeks. DE 47:25, JA925-27; Def. Br. 5-7; DE 1: ¶ 11, JA11-12. Defendants engage in this process in an attempt to isolate mesenchymal stem cells and "to determine the growth and biological characteristics of the resulting cell population." DE 16: ¶ 29, JA34 (admitting allegation contained at DE 1: ¶ 29, second sentence, JA17).

The resulting cell population is then combined with doxycycline, an antibiotic, "and other additives" and placed in syringes. *See* DE 1: ¶ 11, JA11-12; Def. Br. 7; DE 19-1: ¶ 17, JA970-71. The syringes are labeled only with personal information about the patient and limited information regarding the manufacture of the product. *See* DE 19-1: ¶ 18, JA971-72. Regenerative Sciences then provides the syringes to the Centeno-Schultz Clinic where physicians inject the cultured cell product. Throughout this manufacturing process, defendants admit that they do not follow current good manufacturing practice as required under the FDCA.

The government's expert, Dr. Bauer, explained in his declaration that defendants' processing alters the original cells' biological characteristics: For example, he explained that "[s]cientists have shown that bone-marrow derived cells that are cultured to manufacture [mesenchymal stem cells] change both in terms of their proteins and in the genes they express." DE 19-3: ¶ 37, JA1007-08.

B. On July 25, 2008, FDA sent a letter to Regenerative Sciences, explaining that the agency had reviewed the company's website and determined that

Regenerative Sciences' cultured cell product was both a drug under the FDCA and a biological product under the Public Health Service Act. DE 19-1: ¶ 10, JA964. Defendants responded to FDA on August 25, 2008, asserting that their activities fell within the "practice of medicine" and were "both lawful and unregulated by the FDA." DE 19-1: ¶ 11, JA964.

FDA conducted its first inspection of Regenerative Sciences' laboratory between February 23 and April 15, 2009. DE 19-1: ¶ 12, JA964-65. This inspection revealed that defendants were not making their cultured cell product consistent with current good manufacturing practice, as the FDCA requires. The inspection found that, among other things, defendants failed to establish and follow procedures to prevent contamination and to assure that their drug product conformed to appropriate standards of identity, strength, quality, and purity. *See* 21 U.S.C. § 351(a)(2)(B); 21 C.F.R. § 211.113(b); § 211.160(b); DE 19-1: ¶ 12, JA964-65.

FDA inspected Regenerative Sciences' laboratory again in June 2010, and again discovered serious deviations from current good manufacturing practice. DE 19-1: ¶ 14, JA 966-70. One government expert described the state of defendants' processing area at the time as an "example[] of the worst possible scenario one would imagine for an area used for the manufacturing of sterile products." DE 19-5: ¶ 21, JA1063 (describing "disgusting contamination"). FDA once more provided defendants with a detailed description of their deficiencies. DE 19-1: ¶ 14, JA966-70.

III. PRIOR PROCEEDINGS

The government filed an enforcement action against defendants on August 6, 2010, in the United States District Court for the District of Columbia. DE 1, JA8. Defendants counterclaimed, asserting that performing their "Cultured Regenexx Procedure" was the "practice of medicine" and not the manufacture of a drug or biological product, and further asserting that application of the regulatory scheme to their products would exceed Congress's Commerce Clause authority. DE 16, JA31. Per a stipulated order, defendants agreed to stop manufacturing and distributing the cultured cell product during the litigation. DE 10, JA26. Defendants also agreed to dismiss two lawsuits they had previously filed that challenged FDA's determination that they were manufacturing drugs under the FDCA and that they are subject to the FDCA's requirements. *See* DE 10, JA26; DE 47:5, JA928.

The district court granted the government's motion for summary judgment and dismissed defendants' counterclaims. DE 47:2, JA925.

The court first determined that defendants' cultured cell product was a "drug" because defendants intend their product to be used for the treatment of disease and injury. DE 47:11, JA934. For the same reason, the court determined that defendants' product was also a "biological product" under the Public Health Service Act. *Ibid.*

Concluding that defendants more than "minimally manipulate" the cells used to make their cultured cell product, the court determined that the defendants' drug product did not qualify for regulation solely under the regulatory framework

established in part 1271. DE 47: 13, JA936. The court explained that the defendants' admissions in the case "support[ed] the conclusion that the biological characteristics of the cells change during the process employed by Defendants," and that "[m]oreover, the FDA's conclusion that the Regenexx™ Procedure does not meet the regulatory definition of 'minimal manipulation' is entitled to 'substantial deference.'" DE 47:13, JA936.

The court held that defendants violated 21 U.S.C. § 331(k) of the FDCA, finding that defendants had failed to comply with current good manufacturing practice and failed to properly label their cultured cell product, thereby causing their product to be adulterated and misbranded in violation of section 331(k). DE 47:15-18, JA938-41.

The court rejected defendants' contention that regulation of their product failed to satisfy the FDCA's interstate commerce requirement, noting that defendants create their cultured cell product using drug components shipped in interstate commerce. The court similarly rejected defendants' contention that the regulation exceeded the bounds of Congress's authority under the Commerce Clause. DE 47:15, JA938.

The court also dismissed defendants' counterclaims, rejecting an Administrative Procedure Act ("APA") challenge to preamble language in FDA's 2001 Rule concerning "minimal manipulation." The court explained that the preamble language

did not represent final agency action subject to an APA challenge. DE 47:19-20, JA942-43.

In a separate order, the court entered a permanent injunction, requiring that defendants refrain from future violations of section 331(k) and cease manufacturing their cultured cell product unless and until, *inter alia,* they follow current good manufacturing practice in their laboratory and retain an expert to inspect their facilities. DE 48:2-3, JA947-48. The court found that there was a "cognizable danger of recurrent violation" on the part of defendants given that FDA "twice inspected Defendants' laboratories" and yet defendants continued to maintain "that the FDA could not regulate their cell product" and refused to "bring their processes into compliance with [current good manufacturing practice.]" DE 47:21-22, JA944-45.

SUMMARY OF ARGUMENT

Defendants remove a patient's bone marrow or synovial fluid and combine the cells with other ingredients to create a drug product that they promote as an effective treatment for a wide range of orthopedic conditions and injuries. That drug product is then injected into the patient. FDA has never approved this drug product, and defendants maintain that the manufacture of their drug product is beyond the reach of FDA and freely admit that they do not comply with manufacturing and labeling requirements designed to protect the health of the patients who receive the drug product. The district court correctly rejected defendants' position and held that in

order to make the cultured cell product, defendants must comply with the FDCA and the Public Service Health Act.

I. In violation of 21 U.S.C. § 331(k), defendants manufacture a cultured cell product without complying with current good manufacturing practice or providing proper labeling. Defendants' cultured cell product is plainly a "drug" as defined in the FDCA, and defendants hold this drug for sale. Defendants' assertion that FDA cannot regulate their drug product because to do so would infringe on the "practice of medicine" is unavailing. Through its review of applications for drugs and biological products, FDA regulates the availability of therapeutic drugs; although this affects the treatment options available to a physician, it does not impermissibly regulate the "practice of medicine."

Defendants freely admit that they do not follow either the current good manufacturing practice requirements designed to ensure patient safety or the FDCA's requirements for drug labels. Defendants also admit that their drug product is made using components that have traveled in interstate commerce. Defendants' drug product is thus adulterated and misbranded in violation of 21 U.S.C. § 331(k).

II. Equally unavailing are defendants' arguments that their drug product should be regulated solely under FDA's part 1271 regulations and the communicable disease provisions of the Public Health Service Act. As the district court recognized, defendants more than "minimally manipulate" the cells used to make their drug product and are therefore ineligible for more limited regulation. Moreover, FDA is

entitled to substantial deference in interpreting its own regulations regarding what cellular and tissue products are subject to regulation solely under part 1271.

Defendants' APA challenges to FDA's part 1271 regulations are also meritless. Any attack on the preamble language to the 2001 Rule fails because it does not challenge final agency action, and is, in any event, time-barred. Moreover, the part 1271 regulations are squarely within FDA's authority to protect the public from communicable disease. Defendants are also not saved from FDA regulation on the baseless assertion that they are "compounding," rather than manufacturing, their drug product.

III. FDA may regulate the manufacture of drugs containing one or more components that were shipped in interstate commerce without exceeding the bounds of either section 331(k) or the Commerce Clause. The Supreme Court has previously rejected a constitutional challenge to the application of section 331(k) to intrastate sales that followed interstate shipment of the product. *United States v. Sullivan*, 332 U.S. 689, 697-98 (1948). Moreover, defendants engage in a commercial business that manufactures a drug for sale to patients. In conducting that business, defendants receive and use multiple drug components that have traveled in interstate commerce.

Amici's contention—not raised by defendants—that regulation of the drug product violates a fundamental right is equally meritless. This Court has expressly held that individuals do not have a fundamental right to access unapproved medical treatments.

IV. In light of the history of violations, and defendants' continued insistence that they operate outside the bounds of FDA regulation, the district court was fully justified in entering permanent injunctive relief.

STANDARD OF REVIEW

This Court reviews the district court's grant of a motion to dismiss and grant of summary judgment de novo. *Piersall v. Winter*, 435 F.3d 319, 321 (D.C. Cir. 2006); *Sherley v. Sebelius*, 689 F.3d 776, 780 (D.C. Cir. 2012). This Court reviews the district court's grant of an injunction for an abuse of discretion, and its fact findings for clear error. *United States v. Philip Morris,* 566 F.3d 1095, 1110 (D.C. Cir. 2009).

ARGUMENT

I. DEFENDANTS VIOLATED THE FDCA.

A. Defendants' Cultured Cell Product Is a "Drug" and "Biological Product" Subject to the FDCA and the Public Health Service Act.

1. The district court correctly held that defendants' cultured cell product is a "drug" within the meaning of the FDCA. Under the FDCA, an "article" is 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." 21 U.S.C. § 321(g)(1)(B)&(C). Thus, as this Court has explained, whether any particular article is a drug depends on "the nature of the claims advanced on its behalf." *See Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004). "That principle, in turn, rests on the idea that claims about a product by its manufacturer

and vendors, including product labeling, serve as evidence of the sellers' intent that consumers will purchase and use the product for a particular purpose—and, therefore, as evidence whether the product is or is not a drug." *Ibid.* (citing *Action on Smoking and Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980)); *see also 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.").

Similarly, a "biological product" includes 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).

Nowhere in their brief do defendants dispute that their cultured cell product is intended to treat disease. Indeed, they expressly claim that their cultured cell product repairs a patient's injuries. Def. Br. 7. Defendants' cultured cell product is therefore both a "drug" under the FDCA and a "biological product" under the Public Health Service Act.

2. Defendants do not argue that their cultured cell product falls outside the definition of "drug" contained in the FDCA. They argue, instead, that the district court erred in looking "no further than the federal definition of drugs." Def. Br. 12. Defendants argue that their procedure falls within Colorado's definition of the

"practice of medicine" and therefore should be held to fall outside the scope of the federal statute.

Defendants' reliance on Colorado law casts no doubt on the applicability of the federal regulatory scheme. The district court correctly held that the definitions of "drug" and "biological product" are clear and unambiguous, and defendants' brief does not appear to contend that the definitions in the federal statutes are ambiguous or that any other provision of federal law casts doubt on the definitions. *See* Def. Br. 14 (urging that the statutory language is "not so unambiguous"). Application of the federal statute does not turn on a state by state analysis of local definitions of the practice of medicine.

Indeed, the FDCA contains the phrase the "practice of medicine" in only one provision, as the title of 21 U.S.C. § 396 ("Practice of Medicine"). That provision concerns physician prescriptions of an FDA-approved or cleared device for uses not approved or cleared by the agency, *see* 21 U.S.C. §§ 360(k), 360e—so-called "off label" prescriptions—and states that "[n]othing in this [Act] shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship." *See also* 21 C.F.R. § 312.2(d) ("the practice of medicine for an unlabeled indication of a new drug product . . ."). This provision does not apply to defendants' manufacture and use of a drug that FDA has not approved for *any use*.

Defendants likewise do not advance their argument by noting that the FDCA was not intended to "interfere with medical practice." *See Chaney v. Heckler*, 718 F.2d 1174, 1180 n.16 (D.C. Cir. 1983), *overruled on other grounds*, *Heckler v. Chaney*, 470 U.S. 821 (1985); *see also* FDA, Legal Status of Approved Labeling for Prescription Drugs, 37 Fed. Reg. 16503, 16503 (Aug. 15, 1972) ("Throughout the debate leading to enactment [of the FDCA and 1962 amendments], there were repeated statements that Congress did not intend the Food and Drug Administration to interfere with medical practice and references to the understanding that the bill did not purport to regulate the practice of medicine as between the physician and the patient.").

FDA regulates defendants' cultured cell product, not the procedure by which physicians inject this drug into their patients or the way in which Colorado licenses medical professionals. As courts in other circuits have explained, FDA's role in determining the availability of therapeutic drugs and biological products inevitably affects the options available to physicians who seek to use or prescribe those products; this does not mean that FDA is impermissibly regulating the practice of medicine. *See United States v. 9/1 Kg. Containers*, 854 F.2d 173, 176-77 (7th Cir. 1988) (the "practice of medicine" has "never meant more than that medical licensure and discipline would continue to be the states' business. . . . Nothing in the history or structure of the Act permits drugs deemed ineffective or dangerous by the FDA to be available for use") (rejecting contentions of sellers of bulk products used by veterinarians to manufacture unapproved drug products); *United States v. Evers*, 643

F.2d 1043, 1048 (5th Cir. 1981) ("[W]hile the [FDCA] was not intended to regulate the practice of medicine, it was obviously intended to control the availability of drugs for prescribing by physicians.").

To hold that FDA may not regulate drugs made by physicians because doing so might infringe the practice of medicine would, in effect, exempt physicians from the requirements of the FDCA. Nothing in the language or history of the FDCA countenances that result.[6] In 1962, Congress established a requirement that drug manufacturers register with FDA, 21 U.S.C. § 360(b), but exempted from that requirement licensed practitioners "who manufacture, prepare, propagate, compound, or process drugs or devices solely for use in the course of their professional practice." 21 U.S.C. § 360(g)(2). Using similar language, Congress narrowed FDA's ability to review records when inspecting licensed practitioners "who manufacture, prepare, propagate, compound, or process drugs . . . solely for use in the course of their professional practice." *Id.* § 374(a)(2)(B). If Congress had considered drugs made by physicians to fall outside the scope of the FDCA because manufacturing by physicians was the "practice of medicine," there would have been no reason for it to enact these special exceptions for physician-manufactured drugs.

3. Defendants miss the point when they urge that the FDA's interpretation of the term "practice of medicine" should not be afforded deference. FDA has

[6] Moreover, the corporate defendant could not rely on any assertion that it is practicing medicine or licensed by the State of Colorado to do so.

interpreted and applied the federal definitions of the terms "drug" and "biological product" in this case, not the generalized concept of the "practice of medicine." For similar reasons, defendants' reliance on the presumption against federal preemption in fields traditionally occupied by state regulation and the Supreme Court's decision in *Gonzales v. Oregon*, 546 U.S. 243 (2006), is also misplaced. Def. Br. 26-30; *see also* Amicus Brief of Association of American Physicians 11-14. Drug manufacturing and labeling are not activities traditionally regulated by the States, and defendants identify no authority to the contrary.[7]

B. Defendants Violate Section 331(k) When They Cause the Adulteration and Misbranding of Their Drug Product While It Is Held for Sale After Shipment in Interstate Commerce.

1. Defendants' cultured cell product is held for sale after shipment of one or more of its components in interstate commerce.

The FDCA prohibits doing 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

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[7] *Gonzales* turned on the Attorney General's interpretation of the phrase "legitimate medical practice" in the context of the Controlled Substances Act. The Supreme Court did not accord deference to that interpretation because Congress had delegated authority to decide issues of medical policy under the Act to the Department of Health and Human Services, not the Attorney General. *Gonzales*, 546 U.S. at 274. Thus not only did the case not concern the phrase "practice of medicine," it also concerned a more limited delegation of authority than the broad rulemaking authority accorded to FDA under the FDCA. *See* 21 U.S.C. § 371.

in interstate commerce and results in such article being adulterated or misbranded." 21 U.S.C. § 331(k).

Defendants hold their drug product for sale to the patients of the Centeno-Schultz Clinic. *See* DE 19-1:¶ 8, JA963. This is true even though two of the defendants are physicians: "A practicing physician may also fall within the bounds of [331(k)]. A serious gap would be left in the statute if doctors who had received drugs in an intrastate transaction from a party who had in turn received them from interstate commerce were allowed to misbrand the drugs and then distribute them to their patients. Doctors holding drugs for use in their practice are clearly one part of the distribution process, and doctors may therefore hold drugs for sale within the meaning of [21 U.S.C. § 331(k)]." *United States v. Evers*, 643 F.2d 1043, 1050 (5th Cir. 1981); *see also United States v. Sullivan*, 332 U.S. 689 (1948) (pharmacists); *United States v. Diapulse Corp. of Am.*, 514 F.2d 1097, 1098 (2d Cir. 1975).

Defendants' cultured cell product also satisfies section 331(k)'s "after shipment in interstate commerce" requirement. Defendants stress that the final cultured cell product is not shipped in interstate commerce. But the FDCA defines "drug" to include components of a drug, 21 U.S.C. § 321(g)(1)(D), and courts applying section 331(k) have consistently held that the final drug product need not have been shipped in interstate commerce in completed form to satisfy the requirement of prior

shipment in interstate commerce.[8] *See Baker v. United States*, 932 F.2d 813, 814-15 (9th Cir. 1991) (defendant violated section 331(k) when he misbranded synthetic heroin that was made from components that had been shipped in interstate commerce, even though the final product was not shipped in interstate commerce); *United States v. Dianovin Pharmaceuticals, Inc.*, 475 F.2d 100, 102-03 (1st Cir. 1973) (defendant violated section 331(k) when it used raw vitamin K that had traveled in interstate commerce).[9]

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[8] Courts have reached the same conclusion with respect to section 334(a), which permits seizure of misbranded and adulterated food and drugs "while held for sale (whether or not the first sale) after shipment in interstate commerce." 21 U.S.C. § 334(a); *see United States v. An Article of Food,* 752 F.2d 11, 14 (1st Cir. 1985) (holding that interstate shipment requirement was satisfied for seizure under section 334 of the FDCA when food additive was shipped in interstate commerce, but final product was sold only in Puerto Rico); *United States v. Articles of Drug*, 625 F.2d 665, 669 (5th Cir. 1980) ("[S]ection 334(a)(1) permits the seizure and condemnation of a misbranded drug which either has been introduced into interstate commerce or is held for sale after it or its component parts have been shipped in interstate commerce."); *United States v. Articles of Drug*, 585 F.2d 575, 585 (3d Cir. 1978); *United States v. Detroit Vital Foods Inc.*, 330 F.2d 78, 80-82 (6th Cir. 1964) (finished drug product held for sale after shipment in interstate commerce under 21 U.S.C. § 334(a) when made from ingredients that were not themselves misbranded when shipped in interstate commerce).

[9] Amicus American Association of Orthopaedic Medicine ("AAOM") suggests that *Baker* and *Dianovin* apply only when the drug components shipped in interstate commerce are "active contributors" to the finished drug product. AAOM Br. 12. No court has adopted this unworkable distinction. On the contrary, the court in *Baker,* after rejecting the defendant's attempt to "unravel the factual basis of the government's conviction," explained that "whether the ingredient is a main one or a minor one, or whether it is identifiable or unidentifiable after combination is inconsequential." *Baker*, 932 F.2d at 815-16; *see also United States v. Generix Drug Corp.*, 460 U.S. 453, 460 (1983) ("drug" does not mean "only the active ingredient in a

Defendants acknowledge that they mix multiple drugs that have traveled in interstate commerce with the cells used to make their cultured cell product. *See* Def. Br. 31. In addition to the antibiotic doxycycline, defendants use heparin and other ingredients in their cell culture that have been shipped in interstate commerce. *See* DE 26-7: ¶¶ 13, 114(b), JA448, 505 (Declaration of Dr. Christopher Centeno); DE 19-1: ¶ 17, JA 970-71; DE 22-7; ¶ 41.c, Sealed JA 1011-12; DE 34-2: ¶ 6 (Sealed Declaration of Paul J. Teitell), Sealed JA1237; DE 34-3 (Sealed Declaration), Sealed JA1303; DE 39-5 (Declaration of John Skousen), J 859.

Defendants mistake the relevant inquiry when they insist that their drug escapes federal regulation because it involves "the use of a patient's own cells to heal the patient's own injuries." Def. Br. 32. This claim does not alter the undisputed fact that the other components of the drug that they manufacture for injection into patients have traveled in interstate commerce.

The suggestion of amicus Association of American Physicians that the interstate components mixed with the cultured cells do not "constitute any part of the cells that the Regenerative group returns to the patient's body" is flatly inconsistent with defendants' description of the procedure. *Compare* Amicus Brief of Association

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product"). Moreover, even assuming the validity of the premise, AAOM's argument fails. Doxycycline, heparin, and trypsin—all shipped in interstate commerce—are critical to defendants' manufacture of the cultured cell product. *See* DE 19-1: ¶¶ 17-18, JA970-72; DE 22-7; ¶ 32.b-.c, Sealed JA1000-02; DE 34-3, Sealed JA1303; DE 39-5, JA859.

of American Physicians 22, *with* Def. Br. 7 (explaining that after the patients' cells are removed from cryopreservation, they are combined with doxycycline and other additives and placed in syringes). Moreover, FDA has defined "component" quite broadly. *See* 21 C.F.R. § 210.3(b)(3) ("Component means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.").

2. Defendants adulterate and misbrand their cultured cell product.

Defendants rely on the assertion that their product is not subject to regulation as a drug. They do not claim that they comply with current good manufacturing practice. *See* Def. Br. 35-36 (arguing that current good manufacturing practice regulations are not applicable to defendants because they are engaging in the practice of medicine, not manufacturing a drug); DE 16: ¶¶ 31-32, JA35-36. When drugs are not manufactured or held in conformance with current good manufacturing practice, they are "deemed" adulterated as a matter of law. 21 U.S.C. § 351(a)(2)(B); *John D. Copanos & Sons, Inc. v. FDA*, 854 F.2d 510, 514 (D.C. Cir. 1988) ("Drugs produced in violation of these [] regulations are deemed to be adulterated without the agency having to show that they are actually contaminated."). It is thus uncontroverted that defendants' product is adulterated.

Defendants have also caused their drug product to be misbranded. The FDCA provides that a prescription drug will be misbranded if it fails to contain information

labeling it as such. 21 U.S.C. § 353(b)(4). The FDCA provides that a drug is a "prescription drug" if due to "its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, [the drug] 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). Because it is intended to be injected into the patient's joint or spine and that injection is safe only under physician supervision, defendants' drug product is a prescription drug. *See* DE 19-6: ¶ 24, JA1113-15 (Declaration of George F. Muschler, M.D.).

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). The label for defendants' cultured cell product does not contain the statement "Rx only." *See* DE 19-1:¶ 18, JA971-72; DE 26: ¶ 17, JA102.

The FDCA also deems a drug misbranded if its labeling fails to bear "adequate directions for use" and the drug does not fall within a regulatory exemption from that requirement. 21 U.S.C. § 352(f)(1). FDA has defined "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.

Because prescription drugs cannot, by definition, "bear adequate directions for use by a layperson," they must meet FDA's requirements for properly labeled prescription drugs, which are contained in 21 C.F.R. Part 201, Subpart D. Those regulations provide "exemptions" to the requirement that a drug must be labeled with

adequate instruction for use by a lay person. 21 C.F.R. § 201.5; *see United States v. Articles of Drug (Rucker Pharmacal),* 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).").

For example, section 201.100 provides that a prescription drug is properly labeled if it is in the possession of certain businesses or licensed physicians and its label and labeling include, *inter alia*, "(b)(1) The statement 'Rx only' and (2) The recommended or usual dosage and (3) The route of administration, if it is not for oral use; and (4) The quantity or proportion of each active ingredient, as well as the information required by section 502(d) and (e); and . . . (c)(1) . . . adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented . . . ." 21 C.F.R. § 201.100. Other exceptions apply, for example, to veterinary drugs and drugs having commonly understood instructions. *Id.* §§ 201.105, 201.116.

Defendants' cultured cell product is labeled only with information about the patient and information regarding some details of manufacture like laboratory notebook number, cell passage number, days in culture, and similar information. *See*

DE 19-1: ¶ 18, JA971-72. Defendants' cultured cell product fails to bear *any* directions for use, and defendants do not claim that their product meets the requirements of 21 C.F.R. § 201.100, or falls within any other exemption to the "adequate directions for use" requirement. Defendants instead argue incorrectly that they need not provide any directions for use, invoking the reasoning of the Fifth Circuit's decision in *United States v. Evers*, 643 F.2d 1043 (5th Cir. 1981). *See* Def. Br. 36-37.

In *Evers*, a physician, Dr. Evers, advertised and prescribed an FDA-approved chelating drug for treating heart disease, a use FDA had not approved. It was not disputed that Dr. Evers could legally prescribe this approved drug to his own patients for an unapproved use. The question, instead, was whether Dr. Evers misbranded the chelating drug in advertising designed to promote prescriptions by other physicians. 643 F.2d at 1049. The Fifth Circuit court of appeals explained that Dr. Evers' alleged misbranding violation was failing to provide adequate directions for a prescribing doctor who might prescribe the drug based on his advertisements. *Id.* at 1051-52. The court thus noted a mismatch: Dr. Evers' misbranding occurred with respect to other physicians who might see his advertisements, while his sale of the product was to his patients, not to other physicians. The court stated: "We believe, therefore, that a doctor who merely advocates to other doctors *a lawful prescription drug* for a use not approved by the FDA, and does not distribute that drug to other doctors, is not holding that drug for sale within the meaning of the statute and therefore is not in violation of section [331(k)] of the Act." *Id.* at 1053 n.16 (emphasis added); *see also*

Chaney v. Heckler, 718 F.2d 1174, 1182 n.20 (D.C. Cir. 1983), *overruled on other grounds*, *Heckler v. Chaney*, 470 U.S. 821 (1985).

Defendants in this case are not recommending an off-label use of an approved drug for prescription by other physicians. Their drug product has not been approved for any use and they hold their drug product for sale to their patients. Because their drug is misbranded (as well as adulterated) as to these patients, the holding of *Evers* has no application in this case.

II. DEFENDANTS' DRUG PRODUCT DOES NOT QUALIFY FOR REGULATION SOLELY UNDER FDA'S PART 1271 REGULATIONS OR 21 U.S.C. § 353A.

A. Defendants' Drug Product Does Not Qualify for Regulation Solely Under Part 1271 Because Defendants More Than "Minimally Manipulate" the Cells in the Cultured Cell Product.

As explained, FDA has established a separate regulatory framework for regulating certain cellular and tissue products—as defined in 21 C.F.R. § 1271.3(d)—solely under 21 C.F.R. Part 1271 and the communicable disease provisions of the Public Health Service Act. The district court correctly concluded that defendants' cultured cell product did not qualify for regulation only under this regulatory framework. FDA is furthermore due deference for its interpretation of its regulation and the scientific evidence upon which it relied. Defendants' arguments to the contrary are without merit. *See* Def. Br. 19.

1. To qualify for regulation solely under 21 C.F.R. Part 1271 and the communicable disease provisions of the Public Health Service Act, a cellular and

tissue product may be only "minimally manipulated." 21 C.F.R. § 1271.10(a)(1). For cells, 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). FDA has explained that if information does not exist to show that the processing of the cells meets the definition of minimal manipulation, then the processing is considered "more than minimal manipulation" and the product cannot qualify for regulation solely under Part 1271. *See* Proposed Registration Rule, 63 Fed. Reg. 26744, 26748 (May 14, 1998) ("FDA considers the processing of cells and tissues to be 'more than minimal manipulation' if information does not exist to show that the process meets the definition of minimal manipulation."); *see also, e.g., FTC v. Morton Salt Co.,* 334 U.S. 37, 44-45 (1948) (providing that "the general rule of statutory construction that the burden of proving justification or exemption under a special exception to the prohibitions of a statute generally rests on one who claims its benefits").

There is no dispute regarding defendants' processing of the cells used to make the cultured cell product. In their district court answer, defendants agreed that the 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*." DE 1: ¶ 29, JA17, admitted at DE 16: ¶ 29, JA34 (emphasis added); *see also* Def. Br. 5-7 (describing the process); DE 39-

9:12, JA892 (questions and answers from Regenerative Sciences' website) ("How do the stem cells know what type of tissue to grow into? Based on the research in this area, local cell type, pressure, and chemical environment also help the cells to determine which type of cells will be formed.").

There is also no genuine dispute regarding the effects of defendants' processing on the bone marrow and synovial fluid used to make the cultured cell product. The declaration of Dr. Steven R. Bauer, Ph.D., Chief of FDA's Cellular and Tissue Therapies Branch, explains that when defendants culture the cells removed from the patient's bone marrow or synovial fluid they alter the original bone marrow or synovial cells, whether or not such changes are intended, because cells grow and respond to the conditions under which they are grown. *See* DE 19-3: ¶ 37 (Declaration of Dr. Steven R. Bauer), JA1007-08. Under the conditions defendants use to culture the cells, most of the cells from the original bone marrow or synovial fluid die. *Id.* ¶¶ 37, 39-40, JA1007-1010. The remaining cells expand in number and change so they are different from the original cells in the bone marrow or synovial fluid. As demonstrated in published scientific literature, these changes include changes in the proteins and the genes expressed by the cells, as well as changes in the shape of the cells. *Id.* ¶ 37, JA1007-08. Moreover, in his sealed declaration, Dr. Bauer explained that a particular step that defendants sometimes use in their manufacturing process is more than minimal manipulation. DE 22-7: ¶ 41.c, Sealed JA1011-12; *see also* DE 34-1: ¶ 8, Sealed JA1215.

The district court had before it the government's detailed declarations and scientific evidence and correctly concluded that defendants' culture and expansion of the cells used to create their drug product alters the biological characteristics of those cells and is therefore more than "minimal manipulation." Although the district court did not recite the government's evidence in detail, it plainly stated that defendants' admission regarding their manufacturing process supported its conclusion that "the biological characteristics of the cells change during the process employed by Defendants." DE 47:13, JA936. It did not make this determination based "upon nothing more than the naked claims of the Government" as defendants contend, or based merely on the fact that the procedure involved "many steps." Def. Br. 21. Rather, it relied on the undisputed facts regarding how defendants handle the cells they extract from their patients.

Defendants do not directly attack the scientific evidence demonstrating that their culture and expansion of bone marrow and synovial cells changes the biological characteristics of those cells. Defendants instead rely on conclusory statements regarding whether they more than minimally manipulate the cells, and statements that the process they employ is similar to other processes that are not regulated as drugs under the FDCA. *See* Def. Br. 19-20 (relying on an affidavit, e.g., "[c]omparing the Procedure to in-vitro fertilization and platelet based wound care . . . neither of which are regulated as drugs or biological products").

Defendants miss the mark in comparing their product to in-vitro fertilization ("IVF") and platelet based wound care. Reproductive tissue and semen are specifically listed as examples of cellular and tissue products under 21 C.F.R. § 1271.3(d). As a result, reproductive tissues must meet the criteria in 21 C.F.R. § 1271.10 to qualify for regulation solely under 21 C.F.R. Part 1271 and the communicable disease provisions of the Public Service Health Act. If an IVF clinic subjects tissues or cells to more than minimal manipulation, then those tissues or cells would not qualify for regulation solely under Part 1271. *See* 21 C.F.R. § 1271.10(a)(1). "Platelet rich plasma," like other blood products, is excluded from the definition of a cellular and tissue product. *See* 21 C.F.R. § 1271.3.

In their statement of disputed facts submitted to the district court, DE 26:64 ¶¶ 9-10, JA105, defendants stated only that "The Regenexx® Procedure does not constitute the more-than-minimal-manipulation of [cellular and tissue products]. Centeno Affidavit, at ¶ 57," and "The Regenexx® Procedure does not change the relevant biological characteristics of the patient's stem cells. Centeno Affidavit, at ¶ 57." The paragraph of the affidavit upon which defendants relied states, "[i]n conclusion, the Regenexx procedure includes no more manipulation of cells than occurs in the body itself or with other medical culture that are not regulated as drugs. In addition, at no time did the agency or its experts actually show that any of the cells produced by this procedure have altered biologic characteristics and as a result are 'more than' minimally manipulated." DE 26-7: ¶ 57, JA476-77.

These statements fail to demonstrate the existence of any material fact dispute. They do not challenge the scientific research on which FDA experts relied to demonstrate that cells subjected to culture and expansion of the sort at issue here change their biological characteristics and are thus more than minimally manipulated. That Dr. Bauer did not examine an example of defendants' cellular product is of no moment. He reviewed defendants' manufacturing practices and laboratory notebooks, along with published scientific literature concerning the effects of cell culture and expansion. *See* DE 19-3: ¶¶ 37-41, JA1007-1012; DE 32-4: ¶ 9, JA1215-16. In addition, as noted, defendants admit that their process is designed "to determine the growth and biological characteristics of the resulting cell population." DE 1: ¶ 29, JA17, admitted at DE 16: ¶ 29, JA34; *see also* DE 39-9:12, JA892.

2. Moreover, the district court correctly deferred to FDA's interpretation of its own regulation. Courts must give "substantial deference to an agency's interpretation of its own regulations." *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994). And, as this Court has explained, "[t]he rationale for deference is particularly strong when the [agency] is evaluating scientific data within its technical expertise," especially "[i]n an area characterized by scientific and technological uncertainty." *Am. Wildlands v. Kempthorne*, 530 F.3d 991, 1000 (D.C. Cir. 2008) (quoting *Int'l Fabricare Inst. v. EPA*, 972 F.2d 384, 389 (D.C. Cir. 1992) and *Envtl. Def. Fund v. Costle*, 578 F.2d 337, 339 (D.C. Cir. 1978)) (internal quotation marks omitted). In its part 1271 regulations, FDA carved out a particular set of requirements for what it determined to be

"minimally manipulated" cellular and tissue products. Its interpretation of those regulations and its evaluation of scientific data regarding changes in cell biology are due substantial deference.

Defendants' arguments against deference betray a fundamental misunderstanding of how FDA determined that defendants' cultured cell product was more than "minimally manipulated." Def. Br. 21-22. FDA did not rely on the number of steps defendants employ; nor did FDA determine that defendants' drug product was more than minimally manipulated by relying on language in the preamble to the 2001 Rule discussing mesenchymal cells. Def. Br. 23. Nor has FDA created any "per se" rule that expansion of stem cells is more than minimal manipulation or taken a position that is contrary to the position taken in public hearings regarding the FDA's proposed approach to regulating cellular tissue products issued in 1997.[10] *See* Def. Br. 22-23.[11] FDA applied the regulatory definition of "minimal manipulation" to

[10] *See* Proposed Approach to Regulation of Cellular and Tissue-Based Products, FDA Dkt. No. 97N-0068 (Feb. 28, 1997), at 17 (available at http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM062601.pdf).

[11] The statement defendants quote is from a discussion leading up to adoption of the proposed rule and is entirely consistent with FDA's position that the minimal manipulation inquiry focuses on whether and how the cells have changed, not on how much processing has been done to the cells. The doctor quoted in defendants' brief is explaining that in a situation in which cells are separated, not expanded, the cells have not been more than minimally manipulated if the cells' functioning has not been

defendants' cultured cell product and determined—based on the scientific evidence before it—that the cells' biological characteristics were altered by defendants' processing and, therefore, that the cultured cell product was more than "minimally manipulated."

B. Defendants' APA Challenges to the Preamble Language in the 2001 Rule and to the Part 1271 Regulations Are Without Merit.

1. As explained, FDA did not rely on language in the preamble of the 2001 Rule to determine that defendants' product was more than minimally manipulated. In addition, defendants' APA challenge to that language is without merit and time-barred. In the preamble to its 2001 Rule, FDA provided some examples of "minimal manipulation" in response to public comments. It also stated that, with respect to mesenchymal stem cells: "We do not agree that the expansion of mesenchymal cells in culture . . . [is] minimal manipulation." 2001 Rule, 66 Fed. Reg. at 5457. Defendants claim that this language in the preamble created a per se legislative rule that was required to have been adopted by notice and comment rulemaking. DE 16:25, ¶¶ 73-77, JA55; Def. Br 44-48; DE 16:28-29, ¶¶ 93-96, JA58-59.

The district court correctly rejected defendants' argument, recognizing that the language in the preamble was not "final agency action" subject to challenge under the APA. DE 47:20, JA943. As this Court recently explained, "[a]lthough 'there is [no]

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changed. This is wholly consistent with the part 1271 regulations and FDA's position in this case.

categorical bar to judicial review of a preamble,' it 'is not the norm.' The operative question when faced with such a challenge is 'whether the [preambular statement] has independent legal effect, which in turn is a function of the agency's intention to bind either itself or regulated parties.'" *American Petroleum Institute v. EPA.*, 684 F.3d 1342, 1353-54 (D.C. Cir. 2012) (internal citations omitted) (quoting *Kennecott Utah Copper Corp. v. U.S. Dep't of Interior*, 88 F.3d 1191, 1222, 1223 (D.C. Cir. 1996), and *Natural Res. Def. Council v. EPA*, 559 F.3d 561, 565 (D.C. Cir. 2009)).

The language in the preamble provided examples of the agency's current thinking regarding what might fit within "minimal manipulation"; those statements did not determine the rights or obligations of regulated parties, or bind regulated parties or the agency. *See Bennett v. Spear*, 520 U.S. 154, 177-78 (1997); *see also* 21 C.F.R. § 10.85(d)(1) & (j) (providing that preamble statements do not create legal requirements). FDA has consistently recognized that it must consider available scientific evidence on a case-by-case basis to determine whether a particular process alters cells' relevant biological characteristics. *See* Proposed Approach to Regulation of Cellular and Tissue-Based Products, FDA Dkt. No. 97N-0068 (Feb. 28, 1997), at 17, available at http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM062601.pdf ("As additional information is generated about procedures in the 'more-than-minimal-manipulation' category, the agency intends to consider them to be in the 'minimal-manipulation' category when clinical data and experience show that the procedure

does not alter the biological characteristics of the cells or non-structural tissue, or the relevant structure-related characteristics of structural tissue."); *see also* 63 Fed. Reg. at 26748-49.

For the same reason, the preamble statements did not require notice and comment rulemaking under the APA. Notice and comment rulemaking is necessary for "legislative" or "substantive" rules, but not for "interpretive rules" or "general statements of policy." 5 U.S.C. § 553(b)(3)(A) & (d). A rule is "legislative" only when the "agency intends to create new law, rights, or duties." *Gen. Motors Corp. v. Ruckelshaus*, 742 F.2d 1561, 1565 (D.C. Cir. 1984). As explained, FDA's statement in the preamble did not create any new legal obligations or requirements and, therefore, is not a "legislative" or "substantive" rule requiring notice and comment rulemaking.

Defendants' attempt to liken the terms "minimal manipulation" and "relevant biological characteristics" to broad terms like "fair and equitable" fails. *See* Def. Br. 47-48 (relying on *Catholic Health Initiatives v. Sebelius*, 617 F.3d 490 (D.C. Cir. 2010)). It is not the case that "but for the preamble statement, nobody—FDA included—would have any idea as to what constituted a 'more than minimally manipulated'" cellular product. Def. Br. 46-47. FDA defined, through notice and comment rulemaking, the term "minimal manipulation" for "cells or nonstructural tissues" as "processing that does not alter the relevant biological characteristics of cells or tissues." 21 C.F.R. § 1271.3(f)(2). Whether there has been a change in relevant biological characteristics is a scientific and empirical question plainly within FDA's

expertise. The language of the regulation is thus hardly the kind of "vague" and "vacuous" term this Court cited in *Catholic Health Initiatives*. *See* 617 F.3d at 495.

Even assuming that defendants could mount an APA challenge to FDA's statements in the preamble, any challenge is time-barred under the six-year statute of limitations in 28 U.S.C. § 2401(a); *see Harris v. FAA*, 353 F.3d 1006, 1009 (D.C. Cir. 2004) ("Unless another statute prescribes otherwise, a suit challenging final agency action pursuant to section 704 must be commenced within six years after the right of action first accrues."). In the case of claimed procedural error in the promulgation of a regulation, final agency action occurs when the regulation is issued, and parties cannot bring procedural challenges outside the statute of limitations. As this Court has explained in the Hobbs Act context, in *JEM Broadcasting Co. v. FCC*, 22 F.3d 320, 325 (D.C. Cir. 1994), "challenges to the procedural lineage of agency regulations, whether raised by direct appeal, by petition for amendment or rescission of the regulation or as a defense to an agency enforcement proceeding, will not be entertained outside the 60-day period provided by statute." *See also id.* at 326 ("We have held unequivocally that when a party complains of an agency's failure to provide notice and comment prior to acting, it is that failure which causes 'injury'; and interested parties are 'aggrieved' by the order promulgating the rules.") (internal citation omitted).

Defendants' APA challenges concern the definition of "minimal manipulation" promulgated in FDA's 2001 Rule. *See* DE 16: ¶¶ 63-97, JA54-59. The rule complained

of was issued in 2001, and defendants' attack on it is therefore outside the six-year statute of limitations.

2. Defendants' broad attack on FDA's part 1271 regulations governing cellular and tissue products similarly fails to advance their argument. Defendants claim that FDA has exceeded its authority under the Public Health Service Act. *See* Def. Br. 49-53; DE 16:30-32, JA60-62. Defendants allege that the regulations are arbitrary and capricious, claiming that FDA did not adequately respond to comments regarding whether such regulations would regulate the practice of medicine. Def. Br. 41-44; DE 16:29-30, JA55-56.

As an initial matter, defendants are attacking the very regulations under which they claim they should be regulated. Defendants argue elsewhere that their cultured cell product is only "minimally manipulated" and therefore subject only to the part 1271 regulations. Assuming a court were to invalidate the part 1271 regulations, defendants' cultured cell product would still be regulated under the FDCA as a "drug" and under the Public Health Service Act as a "biological product." As explained, FDA issued its part 1271 regulations to establish a more limited approach to regulating qualifying cellular and tissue products. FDA's 2001 rulemaking did not enlarge the scope of its authority over cellular products like defendants'. Just as the FDCA and the Public Health Service Act do not impermissibly regulate the practice of medicine, neither do the part 1271 regulations. For the same reason, defendants' reliance on executive orders concerning federalism is misplaced. Def. Br. 43-44. The regulations,

like the FDCA and the Public Health Service Act, do not intrude upon any area of regulation traditionally reserved to the states.

In any event, the regulations are well within FDA's authority to prevent the spread of communicable disease even if the cellular and tissue products regulated are intended for use in the patient who provided the original cells or tissues. 42 U.S.C. § 264.[12] Defendants' processing of their patients' cells involves multiple steps and opportunities for contamination. Defendants remove the cells from the patient, provide the cells to Regenerative Sciences, process the cells using multiple chemicals and equipment, store the cells in freezers and other containers, and provide the finished drug product to the Centeno-Schultz Clinic, where it is injected into the patient. During all of these steps, regardless of whether the cells or tissues are for use in the same patient or a different one, samples may be improperly labeled, mixed up with other cells, and contaminated or exposed to communicable disease agents. *See, e.g.,* 21 C.F.R. § 1271.190(c). As a government expert explained, "A single drip from an over filled syringe could deposit thousands of infectious agents within the work environment. These inadvertent drops of patients' tissue or cells may become a source of contamination for the next cultured cell preparation for a different patient." DE

[12] Defendants' suggestion, Def. Br. 50, that section 264 bars preemption of state laws is without basis. Even assuming the existence of conflicting Colorado state laws dealing with the subject matter of the part 1271 regulations, Section 264(e) expressly provides that state laws that conflict with "an exercise of federal authority under" section 264 are preempted.

19-5: ¶ 42, JA1080. Disease may also be spread when defendants' patients return to their home state following treatment.

To argue that their actions pose no risk of spreading communicable disease, defendants rely on a rule that exempts from mandatory donor screening cells taken from a patient and later "donated" to the individual or a sexually intimate partner. *See* 64 Fed. Reg. 52,696, 52,715 (Sep. 30, 1999); Def. Br. 51. Although FDA determined that the benefit to be gained from donor screening in such a circumstance was minimal, it reached a much different conclusion regarding the risks posed by the manufacturing process. On that issue, FDA has consistently explained that cells and tissues for use in the same patient and cells or tissues for use in a different patient have equal potential to transmit communicable disease.

C. Defendants Are Not "Compounding" Their Drug Product Under 21 U.S.C. § 353a.

Defendants also cannot escape the requirements of the FDCA by relying on 21 U.S.C. § 353a and claiming they are "compounding" their cultured cell product. *See* Def. Br. 38-40. Defendants claim that they "compound" their cultured cell product using an FDA-approved drug product known as Carticel, even though they do not use Carticel in creating their cultured cell product.

Compounded drugs are made by "a process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient. Compounding is typically used to prepare medications that are

not commercially available, such as medication for a patient who is allergic to an ingredient in a mass-produced product." *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 360-61 (2002).

21 U.S.C. § 353a, enacted in 1997, through the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296, addresses "Pharmacy compounding" of human drugs.[13] Under section 353a, when certain statutory conditions are met, compounded drugs are explicitly exempt from three requirements of the FDCA: (i) "current good manufacturing practice," 21 U.S.C. § 351(a)(2)(B); (ii) "adequate directions for use" in labeling, *id.* § 352(f)(1); and (iii) premarket approval for human use, *id.* § 355. Compounded drugs are *not* exempt from 21 U.S.C. § 353(b)(4), which requires that drugs bear the "Rx only" symbol. Thus, even accepting defendants' arguments with respect to compounding, defendants still violate the requirement that their drug bear the label "Rx only."

[13] The status of section 353a is the subject of a split in the circuit courts. This provision codified aspects of FDA's practice of exercising enforcement discretion for traditional pharmacy compounding. The criteria in section 353a include restrictions on the advertising and promotion of compounded drugs, *see id.* § 353a(a), (c), and in 1998, seven pharmacies challenged those restrictions as an impermissible regulation of commercial speech. The Supreme Court agreed that the restrictions were unconstitutional, but did not rule on the severability of those restrictions. *W. States*, 535 U.S. at 360. Two circuit courts have reached different conclusions on this issue. *Compare W. States Med. Ctr. v. Shalala,* 238 F.3d 1090 (9th Cir. 2001), *with Med. Ctr. Pharma. v. Mukasey,* 536 F.3d 383, 394 (5th Cir. 2008). It is thus unclear to what extent section 353a remains viable. In any event, as explained, defendants do not come within the terms of section 353a.

To be exempt under section 353a, compounding must be done by a licensed physician or pharmacist who compounds the drug "using" bulk drug products that comply with certain requirements. *Id.* § 353a(b)(1)(A). Defendants bear the burden of demonstrating that they come within the statutory exemption. *See, e.g., United States v. Kanasco, Ltd.*, 123 F.3d 209, 211 (4th Cir. 1997) (holding that party seeking to invoke the "intended for export" exemption to the FDCA's adulteration requirements must prove that it satisfies each element of the exemption).

Defendants claim that they "compound" their cultured cell product using an FDA-approved drug product known as Carticel.[14] *See* DE 16:9-10, JA39-40; Def. Br. 39-40; DE 39-8, JA861. Carticel is a biological drug product that is the subject of an FDA-approved Biologics License Application. To make the product, Carticel's manufacturer, Genzyme, harvests cartilage cells (chondrocytes) by taking a biopsy from the patient's femoral cartilage, and then isolates and expands the cells through cell culture. The finished product is shipped back to the patient's physician, who implants the product into the patient. *See* DE 39-8, JA861.

Despite the fact that defendants begin their process by removing bone marrow or synovial fluid and do not use cartilage cells in creating their cultured cell product,

[14] Amicus AAOM suggests that defendants' activities are "analogous to that of traditional compounding" because the products are made on a customized basis, AAOM Br. 23, but does not explain how those activities would fit within section 353a.

defendants continue to claim that Carticel is the bulk drug product they use to manufacture their cultured cell product, citing Dr. Centeno's Affidavit. *See* Def. Br. 39. But Dr. Centeno's affidavit merely notes that the Carticel product may include some mesenchymal stem cells. This by no means demonstrates that defendants make their drug product by combining Carticel with other ingredients.

III. DEFENDANTS' CONSTITUTIONAL ARGUMENTS ARE WITHOUT MERIT.

A. Regulation of Defendants' Cultured Cell Product Does Not Exceed Congress's Authority Under the Commerce Clause.

Defendants engage in a commercial business that manufactures a drug for sale to patients. As discussed, in conducting that business, defendants receive and use multiple drug components that have traveled in interstate commerce, and they attract patients from out-of-state to purchase their drug product. *See* DE 26-7 (Declaration of Dr. Christopher Centeno), ¶ 13, 114(b), JA448, 505; DE 19-1: ¶ 17, JA970-71; DE 34-2: ¶ 7, Sealed JA1237-38.

Defendants' contention that they are outside the reach of the federal government's Commerce Clause authority is without foundation. *See* Def. Br. 30. The Constitution grants Congress broad power to "regulate Commerce . . . among the several States," U.S. Const., art. I, § 8, cl. 3. Congress may "regulate the channels of interstate commerce"; it may "regulate and protect the instrumentalities of interstate commerce, and persons or things in interstate commerce"; and it may "regulate activities that substantially affect interstate commerce." *Gonzales v. Raich*, 545 U.S. 1,

16-17 (2005). The Supreme Court has instructed that courts "need not determine whether [defendants'] activities, taken in the aggregate, substantially affect interstate commerce in fact, but only whether a 'rational basis' exists for so concluding." *Id.* at 22. "[W]hen a general regulatory statute bears a substantial relation to commerce, the *de minimis* character of individual instances arising under that statute is of no consequence." *Id.* at 17 (internal quotations and citations omitted).

In *Raich,* the Court sustained Congress's authority to prohibit the possession of home-grown marijuana intended solely for personal use, 545 U.S. at 32-33, relying on the fact that the Controlled Substances Act "regulates the production, distribution, and consumption of commodities for which there is an established, and lucrative, interstate market." *Id.* at 26. Reaffirming its holding in *Wickard v. Filburn*, 317 U.S. 111, 125 (1942), the Supreme Court reiterated that Congress can reach purely local activity, as long as there is a rational basis for concluding that the class of activities being regulated could have a substantial economic effect on interstate commerce. 545 U.S. at 17-18.

Section 331(k) provides an express link to interstate activity, prohibiting the adulterating or misbranding of products "held for sale (whether or not the first sale) after shipment in interstate commerce." 21 U.S.C. § 331(k). Section 331(k) therefore regulates "persons or things in interstate commerce." As explained above, *supra* 23-26, defendants hold their drug product for sale after its components have been shipped in interstate commerce and their actions therefore come within the terms of section

331(k). No further analysis is required. *See United States v. Sullivan*, 332 U.S. 689, 697-98 (1948) (rejecting constitutional challenge to the provision).

Even if one ignores the express link to interstate commerce provided by section 331(k), defendants' conduct substantially affects interstate commerce.[15] Def. Br. Defendants' actions are indisputably commercial and connected to interstate commerce. Defendants receive many of the components of their drug product, including doxycycline and heparin, from out-of-state locations, *see* Def. Br. 31; DE 26-7: ¶¶ 13, 114(b), JA448, 505; DE 22-7: ¶ 32.b, 32.c, 41.c. (Sealed Declaration of Dr. Bauer), Sealed JA1000-02, 1011-12; DE 19-1:¶ 17, JA970-71; DE 34-2: ¶ 6, Sealed JA1237. One drug component that travels in interstate commerce, doxycycline, was directly linked to one of defendants' violations of current good manufacturing practice. DE 19-5: ¶ 48, JA1084-85 (explaining that presence of doxycycline in product rendered defendants' "sterility tests" unreliable and meaningless). Moreover, defendants' conduct affects the market for out-of-state products that are approved by FDA to treat the same orthopedic conditions defendants treat. Amicus AAOM's argument to the contrary, AAOM Br. 15, ignores the fact that the *availability* of

[15] Amicus AAOM state that "FDA's expressed authority only reaches those articles that travel in interstate commerce," and FDA may not argue that it is regulating conduct that substantially affects interstate commerce. AAOM Br. 9. As explained, defendants' actions come within section 331(k) and defendants' drug product has therefore moved in interstate commerce in the relevant sense.

defendants' drug product—even though it is customized for each patient—will affect patient treatment choices and thus the interstate market.

Confirming this understanding, courts have recently applied *Raich* to uphold statutes similar to section 331(k). *See, e.g., United States v. Paige*, 604 F.3d 1268, 1274 (11th Cir. 2010) (sustaining federal statutes criminalizing the intrastate production and possession of child pornography linked to interstate commerce by the equipment used to produce the illegal images); *United States v. Bowers*, 594 F.3d 522, 528 (6th Cir. 2010) (same).

B. Regulation of Defendants' Drug Product Does Not Violate a Fundamental Right.

Amici further contend that FDA's regulation of defendants' cultured cell product violates a fundamental right to medical treatment and bodily integrity. As an initial matter, this issue has not been raised in defendants' brief, nor was it raised by defendants in the district court, and this Court will ordinarily not consider arguments raised only in amicus briefs. *Michel v. Anderson*, 14 F.3d 623, 625 (D.C. Cir. 1994).

The argument is also without merit. As this Court explained in *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 495 F.3d 695, 711 (D.C. Cir. 2007) (en banc), *cert. denied*, 552 U.S. 1159 (2008), there is no fundamental right to "procure and use experimental drugs." There is likewise no fundamental right to access defendants' cultured cell product. Amici's grounds for distinguishing *Abigail Alliance*, *see* Amicus Brief of Tim Moore 8-11, amount to bald assertions that because

the cultured cell product contains in part the patient's own cells, it is inherently safer than the drugs discussed in *Abigail Alliance*. But even assuming this assertion were true, *Abigail Alliance* did not turn on whether the drugs in question were or were not safe; the plaintiffs' claim failed because they could not demonstrate "a tradition of access to drugs that have not yet been proven safe." *Abigail Alliance*, 495 F.3d at 703. Defendants' drug product has not been approved by FDA and has not been "proven safe." Patients may access, and defendants may provide, their cultured cell product once defendants have complied with the requirements of the FDCA and the Public Health Service Act.

Amici also hit wide of the mark in comparing defendants' procedure to the removal and return of a body part. *See* AAOM Br. 26, 28 n.4. Defendants do not simply remove bone marrow and return it to the patient's body. [16] As explained, cells from the bone marrow are cultured and expanded over the span of two or three weeks and combined with other drugs to create a new drug product, which defendants market as an effective treatment for a wide range of orthopedic conditions and injuries. FDA may lawfully regulate the creation of a new drug product even if it contains some of a patient's cells.

[16] In any event, the part 1271 regulations specifically address the situation in which cellular and tissue products are removed and implanted into the same individual during the same surgical procedure. *See* 21 C.F.R. § 1271.15(b).

IV. THE DISTRICT COURT PROPERLY ENTERED A PERMANENT INJUNCTION.

In order to "obtain equitable remedies, the government must demonstrate a 'reasonable likelihood of further violation[s] in the future.'" *United States v. Philip Morris,* 566 F.3d 1095, 1132 (D.C. Cir. 2009) (quoting *SEC v. Savoy Indus., Inc.*, 587 F.2d 1149, 1168 (D.C. Cir. 1978)). This Court has set forth three factors for evaluating whether a reasonable likelihood exists: "'whether a defendant's violation was isolated or part of a pattern, whether the violation was flagrant and deliberate or merely technical in nature, and whether the defendant's business will present opportunities to violate the law in the future.'" *Philip Morris*, 566 F.3d at 1132 (quoting *SEC v. First City Fin. Corp.*, 890 F.2d 1215, 1228 (D.C. Cir. 1989)).

This Court reviews the district court's grant of an injunction for an abuse of discretion, and its fact findings for clear error. *Philip Morris,* 566 F.3d at 1110. Defendants argue that because the district court used the language of the government's proposed permanent injunction, its decision is subject to more searching review, relying on *Berger v. Iron Workers Reinforced Rodmen Local 201*, 843 F.2d 1395, 1407 (D.C. Cir. 1988). That case involved the district court's wholesale adoption of a party's findings of fact and not the adoption of the terms of a proposed injunction: terms that the defendants have not challenged in this Court or the district court. *See* DE 26:43-46, JA95-98. Any objections to particular terms of the injunction are therefore waived. *United States ex rel. Totten v. Bombardier Corp.*, 380 F.3d 488, 497 (D.C. Cir. 2004). Moreover, in *Berger* this Court did not modify the standard it applied,

but noted that it would review the findings with "special care." The usual standard of review thus applies in this case, and defendants have failed to demonstrate any abuse of discretion or clear error with respect to the determination that there is a reasonable likelihood that they will continue to violate the FDCA.

The district court applied the appropriate standard for granting a permanent injunction, and found that there remained "a 'cognizable danger of recurrent violation.'" DE 47:21, JA944 (quoting *United States v. W.T. Grant Co.*, 345 U.S. 629, 633 (1953)). It explained that FDA had notified defendants that their conduct violated the FDCA and twice inspected defendants' laboratories, finding multiple violations of current good manufacturing practice. DE 47:21, JA 944. These violations were most certainly not "technical in nature"; as FDA's experts explained, for example, defendants failed to perform critical tests necessary to ensure the safety of patients who receive the drug. DE 19-1: ¶¶ 12, 14, JA964-70. Defendants also had a grossly inadequate environmental monitoring program and failed to use proper aseptic technique. DE 19-5: ¶¶ 26, 28, 32-35, JA1067-70, 1074-76. Dr. Dennis Guilfoyle, International Expert for the United States Food and Drug Administration in the field of pharmaceutical microbiology, characterized the scene observed during an inspection of defendants' laboratory as an "example[] of the worst possible scenario one would imagine for an area used for the manufacturing of sterile products." DE 19-5: ¶ 21, JA1063. He further described defendants' failure to test for endotoxins as "unimaginable" and "present[ing] a significant risk to patients." *Id.* at ¶ 52, JA1087; *see*

also DE 19-3: ¶¶ 54-55, JA1021-22. FDA informed defendants of these improper and dangerous practices. Nonetheless, defendants continued to manufacture an adulterated and misbranded drug in violation of the FDCA. DE 47:21, JA944.

Defendants have not asserted in their brief that they will conform their manufacturing to the requirements of the FDCA and Public Health Service Act if this Court determines those statutes to be applicable. Indeed, in the district court, defendants argued that the Colorado Board of Medicine might regulate them, not that they would abide by FDA's regulation. *See* DE 26:45, JA97 ("Thus, should the Court rule that the Regenexx® Procedure constitutes something other than the practice of medicine, and should the Defendants continue to treat their patients using it, the Defendants would risk sanction by the Colorado Board of Medicine, which would ultimately have far greater repercussions than any injunction order the Government asks the Court to enter."). None of defendants' equivocal statements on the question of whether they will comply with the FDCA demonstrates any error on the part of the district court—let alone clear error—when it found that there remained "a 'cognizable danger of recurrent violation.'" DE 47:22, JA945.

CONCLUSION

The judgment of the district court should be affirmed.

Respectfully submitted,

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MARCH 2013

CERTIFICATE OF COMPLIANCE WITH
FEDERAL RULE OF APPELLATE PROCEDURE 32(A)

I hereby certify that this brief complies with the requirements of Fed. R. App. P. 32(a)(5) and (6) because it has been prepared in 14-point Garamond, a proportionally spaced font.

I further certify that this brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because it contains 13,573 words, excluding the parts of the brief exempted under Rule 32(a)(7)(B)(iii), according to the count of Microsoft Word.

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CERTIFICATE OF SERVICE

I hereby certify that on this 13th day of March 2013, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the D.C. Circuit by using the appellate CM/ECF system. I further certify that I will cause nine paper copies to be delivered to the Court by hand delivery within two business days.

The participants in the case are registered CM/ECF users and service will be accomplished by the appellate CM/ECF system.

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ADDENDUM

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21 U.S.C. § 321(g)(1)

The term "drug" means (A) articles recognized in the official United States Pharmacopœia, official Homœopathic Pharmacopœia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 343(r)(1)(B) and 343(r)(3) of this title or sections 343(r)(1)(B) and 343(r)(5)(D) of this title, is made in accordance with the requirements of section 343(r) of this title is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 343(r)(6) of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement.

21 U.S.C. § 331(a)-(k)

The following acts and the causing thereof are prohibited:
(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.
(b) The adulteration or misbranding of any food, drug, device, tobacco product, or cosmetic in interstate commerce.
(c) The receipt in interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.
(d) The introduction or delivery for introduction into interstate commerce of any article in violation of section 344, 350d, 355, or 360bbb-3 of this title.
(e) The refusal to permit access to or copying of any record as required by section 350a, 350c, 350f(j), 350e, 354, 360bbb-3, 373, 374(a), 379aa, or 379aa-1 of this title; or the failure to establish or maintain any record, or make any report, required under section 350a, 350c(b), 350f, 350e, 354, 355(i) or (k), 360b(a)(4)(C), 360b(j), (l), or (m), 360ccc-1(i), 360e(f), 360i, 360bbb-3, 379aa, 379aa-1, 387i, or 387t of this title or the refusal to permit access to or verification or copying of any such required record; or the violation of any recordkeeping requirement under section 2223 of this title (except when such violation is committed by a farm).
(f) The refusal to permit entry or inspection as authorized by section 374 of this title.
(g) The manufacture within any Territory of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.
(h) The giving of a guaranty or undertaking referred to in section 333(c)(2) of this title, which guaranty or undertaking is false, except by a person who relied upon a guaranty or undertaking to the same effect signed by, and containing the name and address of, the person residing in the United States from whom he received in good faith the food, drug, device, tobacco product, or cosmetic; or the giving of a guaranty or undertaking referred to in section 333(c)(3) of this title, which guaranty or undertaking is false.
(i)(1) Forging, counterfeiting, simulating, or falsely representing, or without proper authority using any mark, stamp, tag, label, or other identification device authorized or required by regulations promulgated under the provisions of section 344 or 379e of this title.

(2) Making, selling, disposing of, or keeping in possession, control, or custody, or concealing any punch, die, plate, stone, or other thing designed to print, imprint, or reproduce the trademark, trade name, or other identifying mark, imprint, or device of another or any likeness of

> any of the foregoing upon any drug or container or labeling thereof so as to render such drug a counterfeit drug.
> (3) The doing of any act which causes a drug to be a counterfeit drug, or the sale or dispensing, or the holding for sale or dispensing, of a counterfeit drug.

. . .

(k) The alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, tobacco product, or cosmetic, 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 or misbranded.

21 U.S.C. § 332

(a) Jurisdiction of courts
The district courts of the United States and the United States courts of the Territories shall have jurisdiction, for cause shown [FN1] to restrain violations of section 331 of this title, except paragraphs (h), (i), and (j).

(b) Violation of injunction
In case of violation of an injunction or restraining order issued under this section, which also constitutes a violation of this chapter, trial shall be by the court, or, upon demand of the accused, by a jury.

21 U.S.C. § 353a

(a) In general

Sections 351(a)(2)(B), 352(f)(1), and 355 of this title shall not apply to a drug product if the drug product is compounded for an identified individual patient based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient, if the drug product meets the requirements of this section, and if the compounding--

(1) is by--

(A) a licensed pharmacist in a State licensed pharmacy or a Federal facility, or (B) a licensed physician,

on the prescription order for such individual patient made by a licensed physician or other licensed practitioner authorized by State law to prescribe drugs; or

(2)(A) is by a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient; and

(B) is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the drug product, which orders have been generated solely within an established relationship between--

(i) the licensed pharmacist or licensed physician; and

(ii)(I) such individual patient for whom the prescription order will be provided; or

(II) the physician or other licensed practitioner who will write such prescription order.

(b) Compounded drug

(1) Licensed pharmacist and licensed physician

A drug product may be compounded under subsection (a) of this section if the licensed pharmacist or licensed physician--

(A) compounds the drug product using bulk drug substances, as defined in regulations of the Secretary published at section 207.3(a)(4) of title 21 of the Code of Federal Regulations--

(i) that--

(I) comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;

(II) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or

(III) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (d) of this section;

(ii) that are manufactured by an establishment that is registered under section 360 of this title (including a foreign establishment that is registered under section 360(i) of this title); and

(iii) that are accompanied by valid certificates of analysis for each bulk drug substance;

(B) compounds the drug product using ingredients (other than bulk drug substances) that comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;

(C) does not compound a drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective; and

(D) does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product.

(2) Definition

For purposes of paragraph (1)(D), the term "essentially a copy of a commercially available drug product" does not include a drug product in which there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug product.

(3) Drug product

A drug product may be compounded under subsection (a) only if--

(A) such drug product is not a drug product identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product; and

(B) such drug product is compounded in a State--

(i) that has entered into a memorandum of understanding with the Secretary which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or

(ii) that has not entered into the memorandum of understanding described in clause (i) and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.

The Secretary shall, in consultation with the National Association of Boards of Pharmacy, develop a standard memorandum of understanding for use by the States in complying with subparagraph (B)(i).

(c) Advertising and promotion

A drug may be compounded under subsection (a) of this section only if the pharmacy, licensed pharmacist, or licensed physician does not advertise or promote the compounding of any particular drug, class of drug, or type of drug. The pharmacy, licensed pharmacist, or licensed physician may advertise and promote the compounding service provided by the licensed pharmacist or licensed physician.

(d) Regulations

(1) In general

The Secretary shall issue regulations to implement this section. Before issuing regulations to implement subsections (b)(1)(A)(i)(III), (b)(1)(C), or (b)(3)(A) of this section, the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health. The advisory committee shall include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopoeia, pharmacy, physician, and consumer organizations, and other experts selected by the Secretary.

(2) Limiting compounding

The Secretary, in consultation with the United States Pharmacopoeia Convention, Incorporated, shall promulgate regulations identifying drug substances that may be used in compounding under subsection (b)(1)(A)(i)(III) of this section for which a monograph does not exist or which are not components of drug products approved by the Secretary. The Secretary shall include in the regulation the criteria for such substances, which shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify.

. . . .

(f) "Compounding" defined

As used in this section, the term "compounding" does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling.

42 U.S.C. § 262(a)-(g)

(a) Biologics license

(1) No person shall introduce or deliver for introduction into interstate commerce any biological product unless--

(A) a biologics license under this subsection or subsection (k) is in effect for the biological product; and

(B) each package of the biological product is plainly marked with--

(i) the proper name of the biological product contained in the package;

(ii) the name, address, and applicable license number of the manufacturer of the biological product; and

(iii) the expiration date of the biological product.

(2)(A) The Secretary shall establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses.

(B) Pediatric studies

A person that submits an application for a license under this paragraph shall submit to the Secretary as part of the application any assessments required under section 505B of the Federal Food, Drug, and Cosmetic Act.

(C) The Secretary shall approve a biologics license application—

(i) on the basis of a demonstration that--

(I) the biological product that is the subject of the application is safe, pure, and potent; and

(II) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent; and

(ii) if the applicant (or other appropriate person) consents to the inspection of the facility that is the subject of the application, in accordance with subsection (c) of this section.

(D) Postmarket studies and clinical trials; labeling; risk evaluation and mitigation strategy

A person that submits an application for a license under this paragraph is subject to sections 505(o), 505(p), and 505-1 of the Federal Food, Drug, and Cosmetic Act.

(3) The Secretary shall prescribe requirements under which a biological product undergoing investigation shall be exempt from the requirements of paragraph (1).

(b) Falsely labeling or marking package or container; altering label or mark

No person shall falsely label or mark any package or container of any biological product or alter any label or mark on the package or container of the biological product so as to falsify the label or mark.

(c) Inspection of establishment for propagation and preparation

Any officer, agent, or employee of the Department of Health and Human Services, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any biological product.

(d) Recall of product presenting imminent hazard; violations

(1) Upon a determination that a batch, lot, or other quantity of a product licensed under this section presents an imminent or substantial hazard to the public health, the Secretary shall issue an order immediately ordering the recall of such batch, lot, or other quantity of such product. An order under this paragraph shall be issued in accordance with section 554 of Title 5.

(2) Any violation of paragraph (1) shall subject the violator to a civil penalty of up to $100,000 per day of violation. The amount of a civil penalty under this paragraph shall, effective December 1 of each year beginning 1 year after the effective date of this paragraph, be increased by the percent change in the Consumer Price Index for the base quarter of such year over the Consumer Price Index for the base quarter of the preceding year, adjusted to the nearest 1/10 of 1 percent. For purposes of this paragraph, the term "base quarter", as used with respect to a year, means the calendar quarter ending on September 30 of such year and the price index for a base quarter is the arithmetical mean of such index for the 3 months comprising such quarter.

(e) Interference with officers

No person shall interfere with any officer, agent, or employee of the Service in the performance of any duty imposed upon him by this section or by regulations made by authority thereof.

(f) Penalties for offenses

Any person who shall violate, or aid or abet in violating, any of the provisions of this section shall be punished upon conviction by a fine not exceeding $500 or by imprisonment not exceeding one year, or by both such fine and imprisonment, in the discretion of the court.

(g) Construction with other laws

Nothing contained in this chapter shall be construed as in any way affecting, modifying, repealing, or superseding the provisions of the Federal Food, Drug, and Cosmetic Act [21 U.S.C.A. § 301 et seq.].

. . . .

42 U.S.C. § 264

(a) Promulgation and enforcement by Surgeon General

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. For purposes of carrying out and enforcing such regulations, the Surgeon General may provide for such inspection, fumigation, disinfection, sanitation, pest extermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, as in his judgment may be necessary.

(b) Apprehension, detention, or conditional release of individuals

Regulations prescribed under this section shall not provide for the apprehension, detention, or conditional release of individuals except for the purpose of preventing the introduction, transmission, or spread of such communicable diseases as may be specified from time to time in Executive orders of the President upon the recommendation of the Secretary, in consultation with the Surgeon General,

(c) Application of regulations to persons entering from foreign countries

Except as provided in subsection (d) of this section, regulations prescribed under this section, insofar as they provide for the apprehension, detention, examination, or conditional release of individuals, shall be applicable only to individuals coming into a State or possession from a foreign country or a possession.

(d) Apprehension and examination of persons reasonably believed to be infected

(1) Regulations prescribed under this section may provide for the apprehension and examination of any individual reasonably believed to be infected with a communicable disease in a qualifying stage and (A) to be moving or about to move from a State to another State; or (B) to be a probable source of infection to individuals who, while infected with such disease in a qualifying stage, will be moving from a State to another State. Such regulations may provide that if upon examination any such individual is found to be infected, he may be detained for such time and in such manner as may be reasonably necessary. For purposes of this subsection, the term "State" includes, in addition to the several States, only the District of Columbia.

(2) For purposes of this subsection, the term "qualifying stage', with respect to a communicable disease, means that such disease

(A) is in a communicable stage; or

(B) is in a precommunicable stage, if the disease would be likely to cause a public health emergency if transmitted to other individuals.

(e) Preemption

Nothing in this section or section 266 of this title, or the regulations promulgated under such sections, may be construed as superseding any provision under State law (including regulations and including provisions established by political subdivisions of States), except to the extent that such a provision conflicts with an exercise of Federal authority under this section or section 266 of this title.

21 C.F.R. § 1271.3(a)-(g)

(a) 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.
(b) Establishment means a place of business under one management, at one general physical location, that engages in the manufacture of human cells, tissues, and cellular and tissue-based products. "Establishment" includes:

(1) Any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of human cells, tissues, and cellular and tissue-based products; and

(2) Facilities that engage in contract manufacturing services for a manufacturer of human cells, tissues, and cellular and tissue-based products.

(c) Homologous use means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.
(d) Human 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. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue. The following articles are not considered HCT/Ps:

(1) Vascularized human organs for transplantation;

(2) Whole blood or blood components or blood derivative products subject to listing under parts 607 and 207 of this chapter, respectively;

(3) Secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered an HCT/P;

(4) Minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow);

(5) Ancillary products used in the manufacture of HCT/P;

(6) Cells, tissues, and organs derived from animals other than humans; and

(7) In vitro diagnostic products as defined in § 809.3(a) of this chapter.

(8) Blood vessels recovered with an organ, as defined in 42 CFR 121.2, that are intended for use in organ transplantation and labeled "For use in organ transplantation only."

(e) Manufacture means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor.

(f) Minimal manipulation means:

(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.

(g) Transfer means the placement of human reproductive cells or tissues into a human recipient.

21 C.F.R. § 1271.10

(a) An HCT/P is regulated solely under section 361 of the PHS Act and the regulations in this part if it meets all of the following 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, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; 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 allogeneic use in a first-degree or second-degree blood relative; or

(c) Is for reproductive use.

(b) If you are a domestic or foreign establishment that manufactures an HCT/P described in paragraph (a) of this section:

(1) You must register with FDA;

(2) You must submit to FDA a list of each HCT/P manufactured; and

(3) You must comply with the other requirements contained in this part.