United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued October 21, 2013 Decided February 4, 2014

No. 12-5254

UNITED STATES OF AMERICA,
APPELLEE

v.

REGENERATIVE SCIENCES, LLC, A CORPORATION, ET AL.,
APPELLANTS

Appeal from the United States District Court
for the District of Columbia
(No. 1:10-cv-01327)

Andrew S. Ittleman argued the cause for appellants. With him on the briefs was *Mitchell S. Fuerst*.

Jonathan W. Emord was on the brief for *amicus curiae* American Association of Orthopaedic Medicine in support of appellants.

Lawrence J. Joseph was on the brief for *amicus curiae* Association of American Physicians and Surgeons, Inc., in support of appellants.

James S. Turner was on the brief for *amicus curiae* Tim Moore in support of appellants.

Abby C. Wright, Attorney, U.S. Department of Justice, argued the cause for appellee. With her on the brief were *Stuart F. Delery*, Principal Deputy Assistant Attorney General, *Ronald C. Machen, Jr.*, U.S. Attorney, *Mark B. Stern*, Attorney, *William B. Shultz*, Acting General Counsel, Food and Drug Administration, and *Eric M. Blumberg*, Deputy Chief Counsel. *Alisa B. Klein*, Attorney, U.S. Department of Justice, entered an appearance.

Before: GRIFFITH and SRINIVASAN, *Circuit Judges*, and EDWARDS, *Senior Circuit Judge*.

Opinion for the court filed by *Circuit Judge* GRIFFITH.

GRIFFITH, *Circuit Judge*: In this civil enforcement action, we must decide whether the appellants—three individuals and a related corporate entity—violated federal laws regulating the manufacture and labeling of drugs and biological products by producing, as part of their medical practice, a substance consisting of a mixture of a patient's stem cells and the antibiotic doxycycline. Because we conclude that they did, we affirm the district court's judgment and the permanent injunction it entered against appellants.

I

A

This case involves two statutes under which the Food and Drug Administration (FDA) regulates the healthcare industry: the Federal Food, Drug & Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.*, and the Public Health Service Act (PHSA), 42 U.S.C. § 201 *et seq.* Those statutes promote the safety of drugs and biological products, respectively, by setting forth detailed requirements for how such substances are to be

manufactured and labeled. *See* 21 U.S.C. §§ 351 (FDCA manufacturing requirements), 352 (FDCA labeling requirements); 42 U.S.C. § 262(j) (incorporating by reference most of the FDCA's provisions, including its manufacturing and labeling requirements, into the PHSA). Drugs and biological products not satisfying those requirements are deemed "adulterated" or "misbranded," *see* 21 U.S.C. §§ 351, 352, 353(b)(4); 42 U.S.C. § 262(j), and doing any act that causes a drug or biological product to be adulterated or misbranded is a violation of federal law, 21 U.S.C. § 331(k); 42 U.S.C. § 262(j). The FDA may seek an injunction to prohibit such violations. 21 U.S.C. § 332(a); 42 U.S.C. § 262(j).

B

The substance at issue in this case is produced by appellants Dr. Christopher Centeno, Dr. John Schultz, Michelle Cheever, and Regenerative Sciences, LLC, as part of a medical therapy that they market as the "Cultured Regenexx Procedure" (the Procedure). Drs. Centeno and Schultz, who practice medicine together at the Centeno-Schultz Clinic in Colorado, jointly developed the Procedure to treat patients' orthopedic conditions. They are the majority shareholders of Regenerative Sciences, which they founded and which, in turn, owns the Procedure and licenses it exclusively to the Centeno-Schultz Clinic. Michelle Cheever is the laboratory director for Regenerative Sciences.

The Procedure begins with the extraction of a sample of a patient's bone marrow or synovial fluid. From that sample, Regenerative Sciences isolates mesenchymal stem cells (MSCs), which are capable of differentiating into bone and cartilage cells. The MSCs are then placed in a solution to culture them—that is, to cause them to divide and proliferate.

Other substances are sometimes added to the solution that affect the MSCs' differentiation. The culturing process determines the growth and biological characteristics of the resulting cell population. When the MSCs are sufficiently numerous for re-injection, they are combined with doxycycline, an antibiotic obtained in interstate commerce and used to prevent bacterial contamination of the MSCs. The resulting mixture (the Mixture) is injected into the patient from whom the stem cell sample was initially taken, at the site of the damaged tissue.

Appellants promote the Procedure as an alternative to surgery for various orthopedic conditions and diseases. In court filings, they have described the Procedure as a "treatment [for] orthopedic injuries and arthritis" and for "musculoskeletal and spinal injury." Their promotional materials recommend the Procedure for treatment of osteoarthritis, non-healing bone fractures, chronic bulging lumbar discs, and soft tissue injuries.

In August 2010, the government filed this action for a permanent injunction against appellants, alleging that the Mixture is both a drug and a biological product that is adulterated and misbranded in violation of § 331(k) of the FDCA and § 262(j) of the PHSA, which incorporates § 331(k) by reference. Appellants counterclaimed, asserting that the Mixture is not subject to federal regulation and that, even if it is, the FDA's effort to regulate the Mixture is defective under both the PHSA and the Administrative Procedure Act (APA), 5 U.S.C. § 706(2).

The district court granted the government's motion for summary judgment and dismissed appellants' counterclaims, holding that they had violated the FDCA and the PHSA. *United States v. Regenerative Scis., LLC*, 878 F. Supp. 2d

248, 263 (D.D.C. 2012). Then, finding a "cognizable danger of a recurrent violation," the district court entered a permanent injunction prohibiting appellants from committing further violations of the FDCA's adulteration and misbranding restrictions. *Id.* at 262-63 (internal quotation marks omitted). Appellants timely appealed both orders.

We have jurisdiction to review the district court's orders under 28 U.S.C. § 1291. We review the grant of summary judgment and dismissal of appellants' counterclaims de novo, "drawing all reasonable inferences from the evidence in the light most favorable to the nonmoving party," *Geleta v. Gray*, 645 F.3d 408, 410 (D.C. Cir. 2011), and affirming only if "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law," FED. R. CIV. P. 56(a). We review the district court's entry of a permanent injunction for abuse of discretion and its factual findings for clear error. *United States v. Philip Morris USA Inc.*, 566 F.3d 1095, 1110 (D.C. Cir. 2009) (per curiam).

II

Appellants' principal argument is that the Mixture is not subject to regulation under the FDCA or PHSA because it is neither a drug nor a biological product but is, rather, a medical procedure. The text of those statutes forecloses this argument.

The FDCA defines a "drug" as any "article[] intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "intended to affect the structure or any function of the body." 21 U.S.C. § 321(g)(1); *see also* 21 C.F.R. § 201.128 (providing that a drug's intended use is shown by "the objective intent of the persons legally responsible for the labeling of [the] drug[]," which "may . . . be shown by

labeling claims, advertising matter, or oral or written statements by such persons or their representatives"). The PHSA defines "biological product" in similarly broad terms as any "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative . . . or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i)(1). Both of these wide-ranging definitions clearly apply to the Mixture, an article derived mainly from human tissue and intended to treat orthopedic diseases and to affect musculoskeletal function. Indeed, appellants do not actually dispute that the plain language of the statutes compels this conclusion.

Rather, appellants urge us to construe the FDCA in light of purported federalism concerns.[1] But appellants' concerns lack merit. They boil down to the following syllogism: the FDCA was not intended to infringe on states' traditional role in regulating the practice of medicine; the Procedure fits Colorado's statutory definition of the "practice of medicine"; therefore, the FDA's regulation of the Procedure exceeds the FDA's authority under the FDCA. This syllogism is flawed twice over.

First, it misapprehends what this case is about. Notwithstanding appellants' attempt to characterize this case

[1] Because the PHSA simply incorporates the FDCA's substantive provisions by reference, the scope of the FDCA's provisions is determinative of the reach of the PHSA's provisions as well. Thus, the parties' arguments and our discussion focus on the scope and application of the FDCA—keeping in mind that to adulterate and misbrand a substance that is both a drug and a biological product violates the PHSA as well as the FDCA.

as an effort by the FDA to "restrict[] the use of an autologous stem cell *procedure*,"[2] Appellants' Br. 8 (emphasis added), the focus of the FDA's regulation is the *Mixture*. That is, the FDA does not claim that the procedures used to administer the Mixture are unsafe; it claims that the Mixture itself is unsafe. Appellants' arguments about the practice-of-medicine exemption are therefore wide of the mark.

Second, appellants are wrong to suggest that the scope of the FDCA depends on state-by-state definitions of the "practice of medicine." The FDCA enacts a comprehensive, uniform regulatory scheme for the distribution of drugs. The scheme's breadth—and, more specifically, its applicability to doctors—is evident in the fact that the FDCA *carves out* certain exceptions from its requirements for doctors who manufacture and administer drugs in the course of their professional practice. *See, e.g.*, 21 U.S.C. § 360(g)(2) (exempting licensed healthcare practitioners engaged in certain activities from the FDCA's registration requirements); *id.* § 374(a)(2)(B) (narrowing the FDA's ability to review the records of licensed healthcare practitioners "who manufacture, prepare, propagate, compound, or process drugs . . . solely for use in the course of their professional practice"). Those exceptions would be unnecessary if the FDCA did not otherwise regulate the distribution of drugs by licensed physicians. *See 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."). Appellants' construction of the FDCA, by contrast, would allow states to gut the FDCA's regulation of

[2] An "autologous" stem cell procedure is one in which cells are implanted back into the individual from whom they were initially taken. *See* 21 C.F.R. § 1271.3(a).

doctors, and thereby create an enormous gap in the FDCA's coverage, by classifying the distribution of drugs by doctors as the practice of medicine. Given Congress's intent that the FDCA's "coverage be as broad as its literal language indicates," *United States v. An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 798 (1969), such a construction is not tenable.

Equally untenable is appellants' contention that because the Procedure occurs entirely within the state of Colorado, the Mixture lacks a sufficient connection to interstate commerce to permit federal regulation under the Commerce Clause. It is simply impossible to square this argument with the last seventy years of Commerce Clause jurisprudence, which, in recognition of Congress's authority to regulate even "purely local activities that are part of an economic 'class of activities' that have a substantial effect on interstate commerce," *Gonzales v. Raich*, 545 U.S. 1, 17 (2005), has upheld federal laws prohibiting the possession of home-grown marijuana intended solely for personal use, *id.* at 32-33, and restricting the amount of wheat a farmer can grow purely for his farm's consumption, *Wickard v. Filburn*, 317 U.S. 111, 128-29 (1942). Here, not only does the Mixture undoubtedly have effects on interstate markets for orthopedic care, but it actually includes an article shipped in interstate commerce, namely, doxycycline. *Cf. Raich*, 545 U.S. at 17 (noting that when Congress concludes that a class of activities substantially affects interstate commerce, "the *de minimis* character of individual instances [of those activities] is of no consequence" (internal quotation marks omitted)). The Commerce Clause poses no obstacle to regulating the Mixture under the FDCA.

Nor can appellants prevail on their argument that even if the Mixture may be federally regulated in principle, it falls

outside the scope of the statute appellants are charged with violating, 21 U.S.C. § 331(k). That provision prohibits "the doing of any . . . act with respect to[] a . . . drug . . . if such act is done while such [drug] is held for sale . . . *after shipment in interstate commerce* and results in such [drug] being adulterated or misbranded." *Id.* (emphasis added). Appellants read § 331(k) to require that the entire Mixture have been shipped in interstate commerce. They contend that merely using an ingredient that travelled in interstate commerce—here, doxycycline—is insufficient to trigger the bar. We disagree. Not only does the FDCA define the term "drug" to include a drug's components, but to interpret § 331(k) as appellants suggest would severely narrow a statutory scheme designed to regulate the safety of drugs at every stage of their distribution. *See Evers*, 643 F.2d at 1049 (explaining that § 331 is "designed to prevent misbranding at each stage of the distribution process"); *id.* at 1050 ("Doctors holding drugs for use in their practice are clearly one part of the distribution process . . . ."). The two circuits to have considered this issue have reached the same conclusion. In *United States v. Dianovin Pharmaceuticals, Inc.*, which involved a pharmaceutical company that used raw vitamin K purchased in interstate commerce to manufacture injectable vitamin K, the First Circuit held that the company's "use of components shipped in interstate commerce . . . brought their activities within § 331(k)." 475 F.2d 100, 102-03 (1st Cir. 1973); *see also United States v. Cassaro, Inc.*, 443 F.2d 153, 156 (1st Cir. 1971) (explaining that, under the Supreme Court's decision in *United States v. Sullivan*, 332 U.S. 689 (1948), "interstate commerce in drugs continue[s] even after the first purely intrastate sale"). Similarly, in *Baker v. United States*, the Ninth Circuit held that § 331(k)'s "'shipment in interstate commerce' requirement is satisfied even when only an ingredient is transported interstate." 932 F.2d 813, 814 (9th Cir. 1991). We therefore hold that, by virtue of its use of

doxycycline, the Mixture is within the scope of drugs—and, by extension, biological products, *see* 42 U.S.C. § 262(j)—regulated by § 331(k).

III

Appellants next advance two arguments why the Mixture is exempt from the FDCA's manufacturing and labeling requirements even if it is otherwise subject to federal regulation. Each argument fails.

A

In addition to regulating biological products directly, the PHSA gives the FDA authority to issue regulations to prevent the interstate spread of communicable disease. *See* 42 U.S.C. § 264(a). Pursuant to that authority, in 2001 the FDA promulgated regulations to ensure the safety of human cells, tissues, and cellular or tissue-based products (HCT/Ps) used for therapeutic purposes. Those regulations, which appear at 21 C.F.R. part 1271, define HCT/Ps, in relevant 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). HCT/Ps may qualify as drugs or biological products, and when they do, the FDA generally regulates them accordingly under the FDCA, PHSA, and corresponding regulations. *See id.* § 1271.20; *see also* Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, 58 Fed. Reg. 53,248, 53,249 (Oct. 14, 1993) ("Cellular products intended for use as somatic cell therapy are biological products subject to regulation pursuant to the [PHSA] and also fall within the definition of drugs in the [FDCA]."). The Part 1271 Regulations, however, create a regulatory exemption from the manufacturing and labeling

requirements that normally apply to drugs and biological products for any HCT/P that is no more than "minimally manipulated."[3] *See* 21 C.F.R. § 1271.10(a). "Minimal manipulation" of cells means "processing that does not alter the relevant biological characteristics." *Id.* § 1271.3(f)(2). Appellants claim this exemption applies to the Mixture, but the government offers several reasons why appellants' culturing process alters the MSCs' relevant biological characteristics and is therefore more than minimal manipulation. As to some of those reasons, such as the government's claim that culturing MSCs alters the genes and proteins they express, appellants have created genuine issues of fact by submitting expert affidavits arguing that the government's views are based on scientific studies that are inapplicable to appellants' culturing process. But appellants give no response to other reasons offered by the government. For example, appellants admit that the culturing process is designed to "determine the growth and biological characteristics of the resulting cell population." It is also undisputed that, in at least some cases, appellants add substances to the cell culture that affect the differentiation of bone marrow cells.

These concessions are fatal to appellants' attempt to claim refuge under § 1271.10(a). Given that § 1271.10(a) is an exemption from the otherwise applicable provisions of the FDCA, appellants ultimately bear the burden of establishing that it applies to the Mixture. *See United States v. First City Nat'l Bank of Houston*, 386 U.S. 361, 366 (1967) (stating the

[3] To qualify for this regulatory exemption, an HCT/P must meet several other criteria as well, pertaining to its method of manufacture and intended use. *See* 21 C.F.R. § 1271.10(a). The government does not claim, however, that the Mixture fails to meet any of those additional criteria.

"general rule" of statutory construction that the party who "claims the benefits of an exception to the prohibition of a statute" carries the burden of establishing that the exception applies); *FTC v. Morton Salt Co.*, 334 U.S. 37, 44-45 (1948). Because appellants concede that culturing MSCs affects their characteristics and offer no evidence that those effects constitute only minimal manipulation, they fail to carry that burden as a matter of law.

We emphasize that we reach this conclusion based on the evidence in the record, and not merely by deferring to the FDA's statement in the preamble to the Part 1271 Regulations that expansion of MSCs in culture automatically constitutes more than minimal manipulation. *See* Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5447, 5457 (Jan. 19, 2001) ("We do not agree that the expansion of mesenchymal cells in culture . . . [is] minimal manipulation."). Appellants devote considerable energy to challenging that statement as an invalid legislative rule that the FDA now seeks to enforce against them. That is, they claim that the FDA seeks to give legal effect to a statement that was not promulgated through formal rule-making procedures, which the APA forbids. Our decision, however, is based on, and gives effect to, the Part 1271 Regulations, not the preamble. Appellants' procedural challenge to the preamble is therefore irrelevant.

Surprisingly, appellants also challenge the Part 1271 Regulations as *ultra vires* if applied to autologous stem cell procedures because, they argue, such procedures do not carry the risk of spreading communicable disease and thus are not subject to regulation under 42 U.S.C. § 264. It is unclear what appellants hope to achieve with this claim; to prevail would only mean invalidating the very exemption from the FDCA in which they hope to take refuge. In any case, the FDA's

findings, which appellants do not challenge, undercut appellants' argument. In promulgating the Part 1271 Regulations, the FDA noted that any procedure involving HCT/Ps risks spreading disease through, for example, "[e]rrors in labeling, mixups of testing records, failure to adequately clean work areas, and faulty packaging." Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement, 69 Fed. Reg. 68,612, 68,613 (Nov. 24, 2004). Indeed, Regenerative Sciences' own standard operating procedure takes a similar view, recognizing the risk of "[c]ontamination" as a "major problem in tissue culture" and stressing the need for "good tissue practices" to "prevent the introduction, transmission, or spread of communicable diseases." Appellants thus offer no basis to conclude that the Part 1271 Regulations exceed the FDA's authority to issue regulations "to prevent the introduction, transmission, or spread of communicable diseases" between states. 42 U.S.C. § 264(a).

B

Alternatively, appellants contend that the Mixture is exempt from the FDCA's manufacturing and labeling requirements because it is a compounded drug. *See* 21 U.S.C. § 353a(a). A compounded drug must be produced using certain types of "bulk drug substances," one of which is "bulk drug substances . . . that . . . are components of drugs approved by the [government]." *Id.* § 353a(b)(1)(A). Appellants assert that the Mixture meets this definition because cultured MSCs are a component of the FDA-approved drug Carticel. But even if that were the case—and the affidavits appellants cite only suggest that it might be—it would not be enough to bring the Mixture within § 353a. To qualify as a "bulk drug substance," an item must be

"represented for use in a drug," 21 C.F.R. § 207.3(a)(4), and appellants point to no evidence in the record even suggesting that MSCs are held out for use in Carticel, or any other drug for that matter. Appellants therefore fail to establish that the Mixture is exempt from the FDCA's manufacturing and labeling requirements, and we proceed to consider whether the Mixture violated them.

IV

A

The FDCA provides that a drug "*shall be deemed to be adulterated* . . . 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." 21 U.S.C. § 351(a) (emphasis added). The FDA has established the specific elements of current good manufacturing practice at 21 C.F.R. parts 210-211. Here, it is undisputed that appellants' facilities, methods, and controls for processing the Mixture violated federal manufacturing standards in numerous respects. Therefore, the Mixture is *per se* adulterated, regardless of any other safety protocols appellants happen to use. *See John D. Copanos & Sons, Inc. v. FDA*, 854 F.2d 510, 514 (D.C. Cir. 1988) ("Drugs produced in violation of [federal manufacturing] regulations are deemed to be adulterated without the agency having to show that they are actually contaminated.").

B

The FDCA also provides that a drug "shall be deemed to be misbranded" if its label omits certain information. As relevant here, the FDCA requires that a drug's label provide

"adequate directions for use," 21 U.S.C. § 352(f)(1), and, in the case of prescription drugs, bear the symbol "Rx only," *id.* § 353(b)(4)(A). Appellants admit that the Mixture's labeling satisfies neither of these requirements.[4]

Appellants nevertheless argue that it is inappropriate to hold them liable for not providing adequate directions because they produced the Mixture only for their own use. This argument, however, misunderstands how the FDCA's labeling scheme applies to prescription drugs. To satisfy § 352(f)'s requirement of providing "adequate directions for use," a drug's label must provide "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 (emphasis added). A prescription drug, however, is by definition "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) (emphasis added). It is thus impossible to provide "adequate directions for use" for prescription drugs. As the Seventh Circuit has observed, this means that prescription drugs are "presumptively misbranded." *United States v. An Article of Device*, 731 F.2d 1253, 1261 (7th Cir. 1984); *see United States v. Articles of Drug*, 625 F.2d 665, 673 (5th Cir. 1980) (holding that § 352(f)(1) requires a drug's labeling to "contain adequate directions for a consumer to engage in self-medication" and noting that a "prescription drug by definition . . . is unsuitable for self-medication"). A prescription drug can avoid being actually misbranded only by qualifying for

[4] The Mixture's label would have to bear the symbol "Rx only" even if the Mixture were a compounded drug. *See* 21 U.S.C. § 353a(a) (exempting compounded drugs from the labeling requirements of § 352(f)(1) but not § 353(b)(4)). Thus, even if we were to accept appellants' compounding argument, the Mixture still would be misbranded. *See id.* § 353(b)(4).

either of two exemptions from § 352(f): the statutory exemption, which applies when licensed practitioners distribute drugs to patients via prescriptions, *see* 21 U.S.C. § 353(b)(2), or the regulatory exemption, which applies to prescription drugs at any stage of distribution, *see* 21 C.F.R. § 201.100; *Articles of Drug*, 625 F.2d at 673. A prescription drug's label must contain specific information in order for either exemption to apply. If the label does not contain every piece of required information, the prescription drug will remain subject to the impossible mandate of § 352(f) and will be misbranded.

Here, there is no doubt that the Mixture qualifies as a prescription drug. Before the Mixture can be injected into a patient, a physician must review the cultured MSCs to ensure that there are no visible signs of bacterial contamination or genetic mutation. Then, if the MSCs are safe, appellants inject the Mixture using sophisticated imaging devices to ensure that it reaches the right spot on a patient's bone or tissue so that it has the intended therapeutic effect. Because the Mixture can be safely administered only under a physician's supervision, the question for us is whether the Mixture qualifies for either § 352(f) exemption. The answer is clear. Both exemptions require that the label bear the symbol "Rx only," *see* 21 U.S.C. § 353(b)(4)(A); 21 C.F.R. § 201.l00(b)(1), and it is undisputed that the Mixture's label does not. Because its label fails to provide the minimum information necessary to qualify for either exemption from § 352(f), the Mixture is misbranded.

In reaching this conclusion, we reject appellants' broad reading of *United States v. Evers*, in which the Fifth Circuit held that a doctor was not liable for violating § 352(f)(1) by advertising his off-label use of a prescription drug without providing adequate directions for that use. *See Evers*, 643

F.2d at 1053-54. Appellants read *Evers* for the proposition that doctors need not comply with the FDCA's labeling requirements when they prescribe drugs only within their own practices. But *Evers* cannot bear the weight of this interpretation, which is inconsistent with the fact that the FDCA does not exempt doctors in such a categorical manner. As the Fifth Circuit made clear, the "object of the government's case" in *Evers* was not the off-label "*prescription*" of the drug at issue, but rather the "*promotion and advertising*" of such off-label use. *Id.* at 1049 (emphases added). *Evers* thus differs from this case in two important ways: the drug at issue in *Evers* was FDA approved, and the FDA did not question Evers's right to prescribe that drug to his patients. Neither of those circumstances is present here. The FDA has not approved the Mixture as safe for any use and hence challenges appellants' right to prescribe the Mixture at all. We will not broaden *Evers* to vitiate the FDCA's labeling requirements in these circumstances. The strict exemption criteria presumably reflect the judgment of both Congress and the FDA about the minimum information necessary to safely distribute prescription drugs. Because appellants did not meet those criteria, they misbranded their drug.

V

Having found that the government is entitled to summary judgment that appellants adulterated and misbranded the Mixture, we review the district court's entry of a permanent injunction. Appellants attack the injunction on two fronts. They contend that in entering the injunction, the district court failed to make the necessary findings and that, in any event, the facts do not warrant injunctive relief.

The FDCA gives courts jurisdiction to enjoin violations of 21 U.S.C. § 331(k). *See* 21 U.S.C. § 332(a). To obtain injunctive relief, the government "must demonstrate a 'reasonable likelihood of further violation[s] in the future.'" *United States v. Philip Morris USA Inc.*, 566 F.3d 1095, 1132 (D.C. Cir. 2009) (per curiam) (quoting *SEC v. Savoy Indus., Inc.*, 587 F.2d 1149, 1168 (D.C. Cir. 1978)) (alteration in original). A district court should consider three factors in determining whether a reasonable likelihood exists: "'[1] whether a defendant's violation was isolated or part of a pattern, [2] whether the violation was flagrant and deliberate or merely technical in nature, and [3] whether the defendant's business will present opportunities to violate the law in the future.'" *Id.* (quoting *SEC v. First City Fin. Corp.*, 890 F.2d 1215, 1228 (D.C. Cir. 1989)).

Appellants argue that the district court failed to make findings regarding these three factors. Though it is true that the district court did not explicitly list the factors, there can be no serious dispute that its factual findings implicate them. In justifying the injunction, the district court stated:

> [The] FDA notified [appellants] that their Regenexx™ Procedure may be in violation of the [FDCA]. It then twice inspected [appellants'] laboratories and found a number of [current good manufacturing practice] violations. [Appellants] maintained that the FDA could not regulate their cell product and did not bring their processes into compliance with [current good manufacturing practice]. Although [appellants] agreed to stop using their Regenexx™ Procedure during the pendency of this lawsuit, there remains a "cognizable danger of recurrent violation."

Regenerative Scis., 878 F. Supp. 2d at 262-63. These findings speak to the existence of each relevant factor. The fact that the FDA found violations on two separate occasions and that appellants refused to take corrective action even after multiple FDA notices suggests a pattern of deliberate, even flagrant violations. And, of course, these violations were inextricably linked to the operation of appellants' business.

Even so, appellants maintain that the district court abused its discretion. They insist that they have shown "the utmost respect for the judicial system" by discontinuing use of the Procedure during the pendency of this litigation and that the Procedure employed robust safety protocols, albeit not those federal regulations required. These facts, however, do not establish an abuse of discretion. That appellants suspended use of the Procedure does not in itself preclude injunctive relief. *See United States v. Article of Drug Designated B-Complex Cholinos Capsules*, 362 F.2d 923, 928 (3d Cir. 1966) ("It is well settled that the cessation of activities, either before or after suit is begun, does not in itself bar issuance of the injunction."). Furthermore, appellants have admitted to over a dozen violations of federal manufacturing regulations, and evidence in the record supports the serious nature of those violations. Appellants also admit that they did not improve their manufacturing process even after receiving FDA warnings. Such conduct is sufficient to warrant the permanent injunction.

VI

For the foregoing reasons, we affirm the district court's orders granting summary judgment to the government, dismissing appellants' counterclaims, and permanently enjoining appellants from committing future violations of the FDCA's manufacturing and labeling provisions.