IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED STATES OF AMERICA,	)	Civil Action No. 1:10-CV-01327-RMC
	)	
Plaintiff,	)	
	)	
v.	)	
	)	
REGENERATIVE SCIENCES, LLC, et al.,	)	
	)	
Defendants.	)	

REPLY BRIEF IN SUPPORT OF
PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT

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HISTORY

Despite the voluminous amount of paper that has been filed in support of and in opposition to the government's motion for summary judgment, the facts material to resolving this case have either been admitted or are beyond genuine dispute. The evidence presented in this case establishes that Defendants: (1) receive samples of bone marrow or synovial fluid that are harvested from patients and process them outside of the body for [redacted] using plastic flasks, additives and nutrients (including components that have been shipped in interstate commerce), and environmental conditions in a manner that is designed to determine the growth and biological characteristics of the resulting cell population; (2) place the cells, [redacted], and other additives into syringes that they intend to be injected into patients to treat a variety of orthopedic conditions and injuries; (3) promote this cultured cell product as a safe and effective alternative to surgery even though it has not been approved by the U.S. Food and Drug Administration (FDA) for any purpose, and is not labeled with anything approximating adequate directions for use[1] or the "Rx only" symbol; and (4) manufacture the cultured cell product, by Defendants' own admission, in violation of FDA's current good manufacturing practice requirements, by, among other things, failing to perform basic safety tests before releasing the product, despite the fact that their own procedure admits "Contamination by microorganisms is a major problem in tissue culture." Ex. A (Kreuzer Dec.) Ex. 38 at 1. Defendants' violations of the law are serious, and injunctive relief is necessary to prevent their recurrence.

Defendants' opposition brief attempts to defeat the government's entitlement to summary judgment by raising non-meritorious legal arguments, including challenges to the scope of FDA's authority to regulate Defendants' cultured cell product under the Federal Food, Drug, and

[1]Although the FDCA permits unapproved new drugs to be studied under investigational new drug applications (INDs) to determine whether they are safe and effective, *see* 21 U.S.C. § 355(i); 21 C.F.R. § 201.115(b), Defendants have not availed themselves of this procedure.

Cosmetic Act (FDCA) and the Commerce Clause, and the legal conclusions to be drawn from undisputed facts. As we show below, the FDCA contains no "practice of medicine" exception that excuses Defendants' conduct, and FDA's exercise of jurisdiction over Defendants' conduct is a permissible exercise of federal power under the Commerce Clause. Defendants' remaining arguments are likewise without merit. As a result, this case can and should be resolved on summary judgment.

I. DEFENDANTS' "PRACTICE OF MEDICINE" DEFENSE IS WITHOUT MERIT

Defendants' chief defense to this enforcement action is the claim that the FDA lacks the authority to regulate Defendants' conduct because they are engaged in the "practice of medicine," as that term is defined by Colorado state law. Indeed, this contention underpins nearly every argument in the briefs filed by Defendants and *amici* Association of American Physicians & Surgeons, Inc. (AAPS) and the American Association of Orthopaedic Medicine (AAOM). Federal law controls here, however, and the scope of FDA's authority turns on a straightforward issue of statutory interpretation: is the Defendants' cultured cell product a drug within the meaning of the FDCA? As demonstrated below, based on the statutory text and structure, the answer to this question is plainly "yes." Below we first briefly explain that FDA's interpretation of the FDCA should prevail under either step one or step two of the *Chevron* analysis. We then address Defendants' arguments, not one of which is rooted in – or, for that matter, even considers – the text or structure of the FDCA.

1. To determine whether the cultured cell product falls within the scope of the FDCA, the Court must begin with the statutory language. *Hardt v. Reliance Standard Ins. Co.*, 130 S. Ct. 2149, 2156 (2010). If the statutory language is unambiguous, it must be "enforce[d] . . . according

to its terms." *Id.* The FDCA's definition of drug includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals"; "articles (other than food) intended to affect the structure or function of the body of man or other animals"; and "articles intended for use as a component of" any such articles. 21 U.S.C. § 321(g)(1)(B)-(D). The parties agree that, at the end of Regenerative Sciences LLC's (RS LLC) production process, its employees place what they describe as mesenchymal stem cells (MSCs) and [redacted] into a syringe, and the contents of that syringe are intended to be and are injected into a patient to treat orthopedic conditions and injuries. Pl.'s SMF ¶¶ 9, 11-13; Defs.' Resp. to Pl.'s SMF (Dkt. 26) ¶¶ 9-13; Counterclaims ¶¶ 3, 10 (explaining how the "stem cells . . . begin to repair the patient's degenerated or injured area."). Although Defendants cast their conduct as a medical procedure, the substance in that syringe – and the raison d'être for the "procedure" – is unquestionably an "article" that is intended to treat, cure, and mitigate diseases and to affect the structure and function of the patient's body. Pl.'s MSJ at 4, 19-20. Defendants' cultured cell product therefore fits squarely within the FDCA's definition of "drug."

Consistent with the statute's remedial purpose to protect the public health, the FDCA's definition of "drug" does not turn in any way on *who* makes the drug, how the drug is made, or whether it is made for *one patient at a time* or mass produced.[2] 21 U.S.C. § 321(g)(1)(B)&(C); *cf.*

[2]Defendants adamantly deny that they "manufacture" a drug. *See, e.g.*, Defs.' MSJ Opp. at 14. But their disagreement should be quickly rejected as merely one of semantics. *See* Pl.'s Ex. B (Bauer Dec.) ¶ 32 (describing Defendants' manufacturing process); Pl.'s SMF ¶¶ 9-10; Defs.' Resp. to Pl.'s SMF ¶¶ 9-10. In any event, the FDCA's definition of "drug" does not refer to a product being "manufactured"; rather, as discussed above, an article falls within the FDCA's drug definition based on its "intended use." 21 U.S.C. § 321(g)(1)(B)&(C). Moreover, 21 U.S.C. § 331(k) broadly encompasses the doing of *any act* that causes a drug to be adulterated or misbranded. *See* 21 U.S.C. § 331(k).

Med. Ctr. Pharmacy v. Mukasey, 536 F.3d 383, 395 (5th Cir. 2008) (rejecting the argument that drugs compounded by licensed pharmacists are not "new drugs" under 21 U.S.C. § 321(p)(1), "it does not matter that the substance has been created through compounding rather than manufacturing - whether it be through rigorous research and development by a pharmaceutical company, through individualized compounding by a pharmacist or through cut-rate production by a rogue manufacturer."); *see also United States v. Urbuteit*, 335 U.S. 355, 357-358 (1948) (Jurisdiction is to be analyzed in terms of "consumer protection, not dialectics").

The FDCA's application to all drugs, even when made by physicians, already evident in the broad definition of "drug," was reinforced in 1962. In the Drug Amendments of 1962, Pub. L. 87-781, 76 Stat. 780, 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 considered drugs made by physicians (even if solely for use in their professional practice) to fall outside the scope of the FDCA, there would have been no reason for it to enact 21 U.S.C. §§ 360(g)(2) and 374(a)(2)(B). Defendants' contrary position impermissibly renders both of these sections superfluous. *See TRW Inc. v. Andrews*, 534 U.S. 19, 31 (2001) (a "cardinal principle of statutory construction" is that statutes should be construed to avoid rendering any "clause, sentence, or word [to] be superfluous, void, or insignificant") (internal

quotation marks omitted). Moreover, sections 360(g)(2) and 374(a)(2)(B) reflect Congress' decision to limit the FDCA's broad authority over drugs made by physicians in only two very narrow respects. Congress did not exclude physicians from the definition of "person" and did not exclude articles manufactured by physicians from the definition of "drug," the FDCA's adulteration and misbranding provisions, the premarket approval requirement for "new drugs," the statute's "prohibited acts," or its enforcement tools. *See* 21 U.S.C. §§ 321(e), (g) & (p), 331, 332, 333, 334, 351, 352 & *passim*. *See United States v. Algon Chem., Inc*., 879 F.2d 1154, 1163 (3d Cir. 1989) (exemptions in sections 360(g)(2) and 374(a)(2)(B) "indicate that when Congress intended to exempt medical practitioners it knew how to do so.").

> Finally, in 1997, Congress added 21 U.S.C. § 396, titled "Practice of Medicine":
>
> Nothing 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. . . .

This amendment – the FDCA's only reference to the term "practice of medicine" – clearly endorses FDA's longstanding position on the FDCA's application to the practice of medicine (*i.e.*, that the agency generally will not interfere with a physician prescribing *lawfully marketed products* for uses other than those for which they are approved, licensed, or cleared by FDA). *See* Pl.'s MTD at 19 n.12 (quoting notices published by FDA in the Federal Register); *United States v. 9/1 Kg. Containers*, 854 F.2d 173, 176 (7th Cir. 1988) ("Congress gave the FDA comprehensive powers to license the manufacture of drugs and limit their sales. To regulate drugs is to be 'involved' in the 'practice of the healing arts.'").

In short, the plain and unambiguous language of the FDCA demonstrates that the broad authority Congress granted to FDA to regulate the conditions under which drugs are made and how those drugs are labeled covers all products that fall within the statutory definition, even if they are made by or for licensed physicians, or, as here, a limited liability corporation with non-physician shareholders. *See* Pl.'s Ex. G at Art. I. Even assuming *arguendo* that the statutory language were ambiguous on this issue, FDA's interpretation adheres to the most natural reading of the statutory language and is consistent with the broad remedial purposes of the statute. Thus, it is plainly permissible and must be upheld under step two of *Chevron, U.S.A., Inc. v. NRDC*, 467 U.S. 837, 843-44 (1984). *See Barnhart v. Walton*, 535 U.S. 212, 218 (2002).[3]

2. In the absence of any textual basis for the broad "practice of medicine" exemption they ask this Court to read into the FDCA, Defendants and the *amici* take the novel (and impermissible) approach to statutory construction of ignoring the statutory language altogether. Eschewing the text, Defendants argue that the "practice of medicine" should be defined by: Colorado law;[4] its "ordinary meaning"; the definition the government gave to a different phrase in

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[3]Relying on *Gonzales v. Oregon*, 546 U.S. 243 (2006), Defendants argue that FDA's interpretation of the FDCA in relation to the "practice of medicine" should not be afforded deference. Defs.' MSJ Opp. at 40. Congress has delegated broad rulemaking authority to FDA. *See* 21 U.S.C. § 371; *NVE Inc. v. HHS*, 436 F.3d 182, 186 (3d Cir. 2006) ("The FDCA also grants to the Secretary of Health and Human Services broad power 'to promulgate regulations for the efficient enforcement of the Act.' 21 U.S.C. § 371(a)."). This is in sharp contrast to *Gonzales,* where the Court refused to defer to the Attorney General's interpretation of the phrase "legitimate medical practice" because Congress had delegated authority on issues of medical policy under the CSA to the Department of Health and Human Services, not the Attorney General. *Gonzales*, 546 U.S. at 274.

[4]Defendants claim that the "Colorado Medical Board" disagrees with FDA's assertion that the "Regenexx procedure constitutes the manufacturing of a federally regulated drug." Defs.' Ex. 5 (Centeno Aff.) ¶ 6. The Colorado Medical Board reviewed a complaint about the Centeno-Schultz Clinic's "procedures regarding stem cells" and determined that no action was

Gonzales v. Oregon, 546 U.S. 243 (2006), a case construing the Controlled Substances Act, not the FDCA; and its use in the "Belmont Report"[5] (Defs.' Ex. 4). Defs.' MSJ Opp. at 13, 39-40. These arguments hinge on the incorrect premise that the FDCA contains an explicit exemption for the "practice of medicine," and that the struggle here is how to define the phrase. The FDCA contains no such exemption. As noted above, the FDCA uses the phrase "practice of medicine" only once, and there in accordance with FDA's view. *See* 21 U.S.C. § 396. Defendants' exotic method of construing the FDCA is more one of invention than legal interpretation and should be rejected. *See Barnhart v. Sigmon Coal Co.*, 534 U.S. 438, 461-62 (2002) ("courts must presume that a legislature says in a statute what it means and means in a statute what it says there. When the words of a statute are unambiguous, then, the first canon is also the last: 'judicial inquiry is complete.'") (quoting *Conn. Nat'l Bank v. Germain*, 503 U.S. 249, 253-54 (1992)).

The *amici*'s efforts to read an exemption into the FDCA that would excuse Defendants' conduct are equally unpersuasive. To support the assertion that Congress did not intend the FDCA to interfere with the practice of medicine, the *amici* cite statements by a Senator in the Congressional Record that the "bill 'makes certain that the medical practitioner shall not be interfered with in his practice,'" AAOM Brf. at 9 (citing 78 Cong. Rec. 2728 (1934)), and in a Senate Report that the bill was "'not intended as a medical practices act and [would] not interfere with the practice of the healing art[s],'" AAPS Brf. at 9 (quoting S. Rep. No. 74-361, 74th Cong.

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warranted based on the complaint. *See* Defs.' Ex. 9. The Colorado Medical Board did not opine on the issue of whether RS LLC's cultured cell product is a drug under the FDCA. *See id.*

[5]The Belmont Report was prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavior Research in 1978, and Defendants offer no explanation of how it is relevant to construing the *intent of Congress* when it adopted the definition of drug in 1938.

1st Sess. at 3 (1935)). The Senate Report's statement concerned a phrase that was not included in the final legislation passed in 1938, and, critically, AAPS' selective quotation omits the italicized language:

> The expression 'and not to regulate the legalized practice of the healing art' was inserted in the definition [of drug] to make it clear that the bill is not intended as a medical practices act and will not interfere with the practice of the healing art by chiropractors and others in the States where they are licensed by law to engage in such practice. *It is not intended to permit the sale in interstate commerce or otherwise in Federal jurisdiction of adulterated or misbranded drugs or devices under the guise of the practice of a healing art. It is likewise not intended to permit the false advertising of drugs and devices under such guise*.

S. Rep. No. 74-361 at 3 (emphasis added). Courts have consistently rejected reliance upon this legislative history to create the very loophole in the FDCA that Defendants seek here. *See* Pl.'s MSJ at 35-36 (citing cases); *cf. Gonzales v. Raich*, 545 U.S. 1, 28 (2005) ("the dispensing of new drugs, even when doctors approve their use, must await federal approval.") (citing *United States v. Rutherford*, 442 U.S. 544 (1979)).

AAOM also cites a statement purportedly from "S. Rep. No. 87-1552 at 1998 (1962)" as evidence that Congress reiterated its intent that FDA not interfere with the practice of medicine when enacting the Drug Amendments of 1962. *See* AAOM Brf. at 9. There is, however, no such report, and the quoted statement that AAOM portrays as evidence of *Congressional intent* was in fact made by a representative of the Pharmaceutical Manufacturers Association ("PMA") in a Senate hearing. *See* Drug Industry Antitrust Act, Hearings Before the Subcomm. on Antitrust and Monopoly of the Comm. of the Judiciary, 87th Cong., 1st Sess. at 1998 (Dec. 7, 1961). Even so, the statement does not aid AAOM's position. PMA testified that before introducing a drug every manufacturer should be required to submit to FDA "substantial evidence not only that the drug is

safe but also that it produces the results claimed." *Id.* at 1996. The statement AAOM quotes supports the view that FDA serves as the gatekeeper for determining whether a drug should be approved, and after it receives approval, a physician may use the drug off-label as he or she deems appropriate for patients: "FDA clearance would assure physicians that a drug effectively produces certain physiological actions, but the physician . . . would determine whether these specific physiological effects would be useful . . . to particular patients." *Id.* at 1998.[6]

AAOM also cites two cases to support its assertion that courts agree that "FDA lacks statutory power to regulate physicians treating their patients," AAOM Brf. at 10, but fails to reveal that the statements it quotes addressed off-label use – that is, a physician's decision to use an *FDA-approved* drug for an indication not included on its label – which is not at issue here. *See United States v. Evers*, 453 F. Supp. 1141, 1150 (D. Ala. 1978) ("When physicians go beyond the directions given in the package insert it does not mean they are acting illegally or unethically"); *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001) ("'off-label' usage of medical devices (use of a device for some other purpose than that for which it has been approved by the FDA) is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine.").

3. Finally, Defendants and *amicus* AAPS argue that this enforcement action preempts Colorado law, and therefore the statutory construction issue here must be considered in

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[6]Even if any of the cited statements from the legislative history supported the *amici*'s position, which they do not, they cannot overcome the statutory language. *Performance Coal Co. v. Fed. Mine Safety and Health Review Comm'n*, 642 F.3d 234, 238 (D.C. Cir. 2011) ("Because congressional intent is best divined from the statutory language itself, resort to legislative history is inappropriate when the statute is unambiguous."); *see Sigmon Coal*, 534 U.S. at 457 ("Floor statements from two Senators cannot amend the clear and unambiguous language of a statute.").

light of the "presumption against preemption." Defendants apparently believe a finding that Defendants' cultured cell product is adulterated and misbranded under the FDCA would have a preemptive effect because their conduct is permitted by C.R.S. § 12-36-106. Defendants' premise that the Colorado statute permits Defendants' conduct is both incorrect and ultimately irrelevant.

The Colorado statute defines the "practice of medicine" broadly in order to delineate what conduct triggers the requirement to hold a medical license, C.R.S. § 12-36-106; nonetheless, the statute's definition does not address a corporation or a physician *making* a drug. *See id.* § 12-36-106(2). Thus, the notion that § 12-36-106 expressly authorizes conduct forbidden under the FDCA is not correct. Moreover, Colorado law does not permit a limited liability corporation like RS LLC to "practice medicine" or the individual defendants to practice medicine through it.[7]

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[7]Under Colorado law, in order for a physician to practice medicine through a corporation, the corporate name must contain the words "professional corporation" or "professional company"; the corporation must be "organized solely for the purpose of permitting individuals to conduct the practice of medicine through a corporate entity, so long as all the individuals are actively licensed physicians or physician assistants in the state of Colorado"; and "all shareholders of the corporation" must be "persons licensed by the board to practice medicine in the state of Colorado who at all times own their shares in their own right." *See* C.R.S. § 12-36-134; *see also* Defs.' Ex. 6 (Michaels Aff.) ¶ 4.

RS LLC does not meet any of these requirements. Although originally formed as "Regenerative Sciences, PLLC" in 2005, Pl.'s Ex. H, the company changed its name and structure in 2006. Defs.' Ex. 6 ¶ 5; Pl.'s Ex. G. At that time, the corporation became "Regenerative Sciences, LLC," a Colorado Limited Liability Company. Its owners are no longer solely licensed physicians. *See id.* at Art. I ("The choice of entity . . . has now been changed from a professional limited liability company . . . to a limited liability company (LLC) ***to reflect the addition of non-professional members***.") (emphasis added); *see also* Pl.'s SMF ¶ 6; Defs.' Resp. to Pl.'s SMF ¶ 6. In addition, the Articles of Incorporation state that RS LLC is no longer organized to practice medicine: "The purposes for which this limited liability company is formed are developing regenerative sciences and to engage in any other lawful business." Pl.'s Ex. G Art. VII; *see also* Defs.' Ex. 6 (Michaels Aff.) ¶ 7 (Defendants' attorney claims that RS LLC was formed for the "purpose of providing capital for the research and development of the Regenexx procedure, and to hold the assets pertaining to the Regenexx procedure, including but not limited to intellectual property, foreign licensing agreements, and medical equipment."). Plainly, RS LLC does not meet the requirements of C.R.S. § 12-36-134. It is, moreover, deemed

Most importantly, Defendants' argument is also irrelevant to resolution of the instant motion. Defendants' preemption argument is aimed at showing that the government cannot establish jurisdiction over their conduct unless it makes a "clear" and "manifest" showing regarding Congressional intent. *See* Defs.' MSJ Opp. at 2-3; AAPS Brf. at 9. Defendants conclude that such clear Congressional intent to regulate the practice of medicine is absent here. This argument misstates the relevant question. This enforcement action does not represent an effort by FDA to license physicians or preempt Colorado's criteria for doing so. Instead, this suit reflects FDA's effort to control the conditions under which a drug is made and how it is labeled. Defendants cite no authority suggesting that regulation of drug manufacturing and labeling falls within traditional State police powers. Thus, their contention that some kind of heightened burden applies to the statutory construction issue here is incorrect. In any event, as AAPS acknowledges, federal law trumps state law when the two conflict. *Id.* Thus, even assuming *arguendo* that Congress were required to convey to FDA the authority to regulate Defendants' cultured cell product "in the clearest possible way," it has done so, as set forth above.

In summary, to prevail on this issue, Defendants must establish either that the FDCA unambiguously forecloses FDA jurisdiction over their cultured cell product or that FDA's interpretation is not a permissible construction of ambiguous statutory language. *See Univ. of Tex. M.D. Anderson Cancer Ctr. v. Sebelius*, __ F.3d__ , No. 10-5201, 2011 U.S. App. Lexis 12394 *4 (D.C. Cir. June 17, 2011). Defendants have shown neither, and their attempt to create a loophole

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"unprofessional conduct" for a physician to practice medicine "as an employee of or in joint venture with any corporation other than a professional service corporation for the practice of medicine as described in section 12-36-134." C.R.S. § 12-36-117(1)(m). Because RS LLC cannot "practice medicine" nor serve as a vehicle through which Defendants "practice medicine," Defendants preemption arguments are unavailing.

in the FDCA to allow Defendants' conduct under the guise of the "practice of medicine" must be rejected.[8]

II. FDA JURISDICTION OVER DEFENDANTS' CONDUCT DOES NOT VIOLATE THE COMMERCE CLAUSE

As detailed in our opening brief, where, as here, one or more of a drug's components has been shipped in interstate commerce, manufacturing an article of drug from that component in a manner that renders the drug adulterated or misbranded violates 21 U.S.C. § 331(k). Defendants' cultured cell product is adulterated and misbranded for the reasons discussed in our opening brief, and, because Defendants manufacture it using components that have been shipped in interstate

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[8]Defendants' witness, Dr. Freeman, argues that RS LLC's cultured cell product cannot be a "drug" because there is no "similar example in the history of medicine where a bodily tissue or cell was taken from a patient, manipulated in some fashion, and therapeutically applied *only to that same patient*, in which the process was considered the manufacture of a drug." Defs.' Ex. 2 (Freeman Dec.) ¶ 2.a. However, FDA has licensed three autologous cellular products which fit that very description. *See* Pl.'s Ex. I (Supp. Bauer Dec.) ¶ 23.

Dr. Freeman also misses the mark when he suggests FDA's approach to RS LLC's cultured cell product is inconsistent with several other products. First, he claims that "*in vitro* fertilization (IVF) enjoys a specific exclusion from the BLA definition and falls outside the FDA regulatory framework" even though, according to him, IVF fits the criteria for more than minimal manipulation." Defs.' Ex. 2 (Freeman Dec.) ¶ 8.g. Reproductive tissue and semen are specifically listed as examples of HCT/Ps under 21 C.F.R. § 1271.3(d). As a result, like other HCT/Ps, 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. 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); *see also* Pl.'s Ex. I (Supp. Bauer Dec.) ¶¶ 17-18. Second, Dr. Freeman claims that skin grafts for burn victims fall within the practice of medicine. Defs.' Ex. 2 (Freeman Dec.) ¶ 8.a. FDA regulates skin grafts under the HCT/P regulations or under its authority over medical devices, depending on whether the skin graft meets the criteria in 21 C.F.R. § 1271.10. Finally, Dr. Freeman asserts that platelet rich plasma (PRP) is "excluded from the BLA requirement" even when it is activated with drugs to alter the biological characteristics of the platelets. Defs.' Ex. 2 (Freeman Dec.) ¶ 8.h. PRP (like other blood products) is excluded from the definition of an HCT/P, see 21 C.F.R. § 1271.3, and thus FDA does not apply the criteria in 21 C.F.R. § 1271.10 to its preparation.

commerce, Defendants violate section 331(k). In opposition, Defendants do not dispute that they use components that have been shipped in interstate commerce in making the cultured cell product. Instead, they and *amicus* AAOM argue that the interstate components used to make the cultured cell product are not sufficiently important to its manufacture to trigger jurisdiction under section 331(k) and that FDA's exercise of jurisdiction over Defendants' conduct is not permissible under the Commerce Clause because Defendants do not substantially affect interstate commerce. AAOM Brf. at 15-19; Defs.' MSJ Opp. at 32. Defendants and AAOM infuse their discussion of interstate commerce with their misreading of the scope of FDA's jurisdiction vis-á-vis the "practice of medicine." That issue is addressed above at 2-12. We address their arguments specific to interstate commerce below.

1. Defendants' arguments for reading section 331(k) narrowly are not supported by the statute, the case law, or the principles of statutory construction. The FDCA defines "drug" to include components of a drug, 21 U.S.C. § 321(g)(1)(D), and courts have consistently interpreted section 331(k) and section 321(g)(1)(D) to mean that the final drug product need not have been shipped in interstate commerce in completed form to establish a predicate for a 21 U.S.C. § 331(k) violation. Significantly, section 321(g)(1)(D)'s reference to "component" is not in any way restricted – it includes all components, not just the drug's active ingredient or ingredients that are "essential" to making the drug. Moreover, FDA has given "component" a broad meaning in its regulations. *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."). The narrow reading Defendants give to the statute is, therefore, not based on its text, and it is inconsistent with the admonition that the statute must be given liberal construction consistent with

its remedial purposes. *United States v. Sene X Eleemosynary Corp*., 479 F. Supp. 970, 981 (S.D. Fla. 1971) ("[t]he 'held for sale' standard of section 301 [21 U.S.C. § 331] has long been afforded a liberal reading . . . ."); *see also* H.R. Rep. No. 2139, 75th Cong., 3d Sess. at 3 (1938) (Congress enacted section 331(k) with the intent to "extend the protection of consumers contemplated by the law to the full extent constitutionally possible . . . .").

Defendants and AAOM's attempt to limit the *Baker* and *Dianovin* decisions is unpersuasive. In *Baker v. United States*, 932 F.2d 813, 814-15 (9th Cir. 1991), the court held that section 331(k) was violated when the defendant misbranded synthetic heroin that was made from components that had been shipped in interstate commerce. AAOM claims that *Baker* is inapplicable here because the "integral components of the heroin" had traveled in interstate commerce. AAOM Brf. at 17. The Ninth Circuit drew no such distinction. Citing *United States v. Generix Drug Corp.*, 460 U.S. 453, 457-61 (1983), the court noted that, as used in the FDCA, "drug" includes both active and inactive ingredients and "thus, 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 816. The court concluded, "We hold that wholly intrastate manufactures and sales of drugs are covered by 21 U.S.C. § 331(k) as long as an ingredient used in the final product travelled in interstate commerce." *Id.* at 816.

Defendants and AAOM also place great weight on the fact that the "vitamin K for injection" product in *United States v. Dianovin Pharms., Inc.*, 475 F.2d 100, 103 (1st Cir. 1973), was made in part from vitamin K that had been shipped in interstate commerce. But, as in *Baker*, the *Dianovin* court did not limit its reasoning based on the role of the interstate ingredient, explaining that the products "component raw materials were . . . drugs, being 'articles intended for

use as a component' of such drug. 21 U.S.C. § 321(g)(1)(D). . . . [Dianovin's] use of components shipped in interstate commerce to make vitamin K for injection brought [the defendants'] activities within § 331(k), and conferred jurisdiction . . . ." *Id.* at 103.

Indeed, Congress intended that, in actions to enforce the FDCA, "the connection with interstate commerce required for jurisdiction . . . shall be presumed to exist," 21 U.S.C. § 379a, and we are aware of no decision holding that FDA's jurisdiction under the "held for sale after shipment in interstate commerce" language in section 331(k) (or when used in the seizure provision in 21 U.S.C. § 334(a)) turns on *which* component moved in interstate commerce.[9]

Even assuming *arguendo* that AAOM were correct that jurisdiction under section 331(k) hinges on the role the components play in the manufacturing process – a position at odds with FDA's regulations and case law – jurisdiction would be present here. AAOM's arguments focus solely on the doxycycline Defendants use in making the cultured cell product [redacted], and it claims the components that have been shipped in interstate commerce "are not essential to the procedure" and "do not add to or change the nature of the cells used." AAOM

[9] *See, e.g., United States v. Detroit Vital Foods Inc.*, 330 F.2d 78, 81-82 (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 and later combined to make misbranded drug); *see also United States v. An Article of Food*, 752 F.2d 11, 14 (1st Cir. 1985) (the "'shipment in interstate commerce' requirement is satisfied when adulterated articles held for in-state sale contain ingredients shipped in interstate commerce"); *United States v. Undetermined Quantities of Clear Plastic Bags . . . WRM-Rid Dog Wormer*, 963 F. Supp. 641, 645 (S.D. Ohio 1997) (the held for sale after shipment in interstate commerce requirement in 21 U.S.C. § 334(a) is "satisfied if any component of the animal drug has been shipped in interstate commerce."). *See also United States v. Miami Serpentarium Labs., Inc.*, 1981-82 FDC L. Rptr. Dev. Trans. Binder ¶ 38,164 at 38,931 (S.D. Fla. Mar. 30, 1982) (Pl.'s Ex. F) ("an article of drug is deemed to have been shipped in interstate commerce upon a showing that any component has traveled in interstate commerce . . . . [I]t is immaterial whether the ingredient is characterized as 'active' or 'inactive.'").

Brf. at 15. This is not correct. First, the culture media Dulbecco's Modified Eagle's Medium (DMEM) and Minimum Essential Media, Alpha (AMEM) and the enzyme trypsin Defendants used are absolutely essential to the manufacturing process; they supply the nutrients that enable the cells to survive and grow outside the body and the enzyme needed to detach the cells from the plastic flasks in which they grow at the end of each cell passage. *See* Pl.'s Ex. B (Bauer Dec.) ¶ 32.b & c; *see also* Defs.' Ex. 5 (Centeno Aff.) ¶ 16, 20-21; Pl.'s SMF ¶ 9. Defendants also use heparin to prevent clotting of the patient's tissue while in culture, Defs.' Ex. 5 (Centeno Aff.) ¶ 114.b.; Pl.'s SMF ¶ 9; Defs.' Resp. to Pl.'s SMF ¶ 9, and in some cases they use [redacted], Pl.'s Ex. B (Bauer Dec.) ¶ 41.c.; Pl's Ex. A (Kreuzer Dec.) ¶ 17 & Ex. 52 at 2. All of these critical ingredients are shipped to Defendants in interstate commerce. *See* Pl.'s Ex. A (Kreuzer Dec.) ¶ 17; Pl.'s Ex. J (Teitell Dec.) ¶ 6; Pl.'s Exs. K&L.[10] Thus, even applying Defendants' and AAOM's cramped reading of FDA's authority, the government has clearly established the interstate commerce predicate for a violation of section 331(k).

2. Even though Defendants' business is commercial in nature, they receive numerous components in interstate commerce, and patients travel from outside Colorado to receive their drug, Defendants argue that their conduct "has no impact on interstate commerce" and therefore is beyond the reach of Congress' authority under the Commerce Clause. Defendants are wrong.

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[10]In addition, the doxycycline that Defendants add to the cell mixture at various stages of the manufacturing process, Pl's. SMF ¶¶ 22-23; Defs.' Resp. to Pl.'s SMF ¶¶ 22-23, and [redacted], also plays an integral role in one of the Defendants' CGMP violations. *See* Pl.'s Ex. D (Guilfoyle Dec.) ¶ 48 (discussing how the failure to perform suitability testing given the presence of doxycycline in the samples submitted for periodic sterility testing renders the results of those tests meaningless and unreliable); Pl.'s Ex. B (Bauer Dec.) ¶¶ 49, 52.

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). In considering Commerce Clause challenges, *Raich* 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. It was sufficient 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), where the Court upheld Congress's power to regulate home-grown wheat intended solely for home consumption, *Raich* reiterated that Congress can reach purely local activity that is not commercial, so 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. More recently, *Raich* has been applied to uphold statutes criminalizing the intrastate production and possession of child pornography based on the fact that equipment used to produce the banned images had traveled in interstate commerce. *See United States v. Paige*, 604 F.3d 1268, 1274 (11th Cir. 2010); *United*

States v. Bowers, 594 F.3d 522, 528 (6th Cir. 2010); *United States v. Gallenardo*, 579 F.3d 1076, 1081 (9th Cir. 2009); *United States v. Malloy*, 568 F.3d 166, 179-180 (4th Cir. 2009); *United States v. Fadl*, 498 F.3d 862, 865-866 (8th Cir. 2007); *United States v. Jeronimo-Bautista*, 425 F.3d 1266, 1272-73 (10th Cir. 2005).

Against this backdrop, the government's application of section 331(k) to Defendants' conduct is clearly permissible, as the facts here support a greater nexus with interstate commerce than the facts in *Wickard*, *Raich,* and their progeny. In this case, FDA seeks to regulate conduct that is commercial in nature.[11] Moreover, Defendants not only receive many of their ingredients from out-of-state locations, *see supra* at 16, they also affect interstate commerce by attracting patients from outside the State of Colorado to receive their cultured cell product. *See* Pl.'s Ex. J ¶ 7.[12] *See, e.g.*, *United States v. Wilson*, 73 F.3d 675 (7th Cir. 1995) (statute prohibiting blockades

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[11] *See Regenerative Sciences v. FDA*, Civ. No. 1:10-cv-01055-RMC (D.D.C.) (Dkt. No. 1) ¶ 35a & b (noting that 43 patients whose reinjections were then scheduled had paid RS LLC $236,500 for their procedures, and that 242 patients' cells were then in cryostorage for which the patients had "paid [RS LLC] $5-8000 each for stem cell treatments").

Defendants' argument relies upon cases where, unlike here, the conduct was not commercial in nature. *See, e.g.*, *Jones v. United States*, 529 U.S. 848 (2000) (statute criminalizing the use of fire or an explosive to damage or destroy "any . . . property used in interstate or foreign commerce or in any activity affecting interstate or foreign commerce" did not apply to a private residence that had no commercial use). Defendants also rely on *A.L.A. Schechter Poultry Corp. v. United States*, 295 U.S. 495, 550 (1935), an outdated decision that does not reflect current jurisprudence. *See Mead v. Holder*, 766 F. Supp. 2d 16, 35 (D.D.C. 2011) (describing *A.L.A. Schechter* as "quite narrow" and having been decided when "the focus of Commerce Clause jurisprudence was only beginning to shift toward Congress's power to regulate").

[12] Indeed, the State of New York has required RS LLC to obtain a New York provisional tissue bank license because it believes Defendants solicit patients from that state. *See* www.regenexx.com/common-questions/ at 11 (accessed July 28, 2011) (Pl.'s Ex. O Attch. 1) ("New York state asserted that we needed a New York tissue banking license to treat NY patients. While we disagreed . . ., we did apply for . . . a provision license"); Pl.'s Ex. M Attch. 2 at 5 (showing patients who traveled from New York to RS LLC in 2009). As stated above,

of reproductive health clinics was valid exercise of Commerce Clause authority [*Lopez* category three] because the clinics purchase, use, and distribute goods from other States and because there is a substantial interstate market in which women seek health services and providers of such services travel interstate).

Defendants and AAOM impermissibly focus on whether Defendants' cultured cell product, by itself, substantially affects interstate commerce, *see, e.g.,* AAOM Brf. at 18, but, as just noted, the issue must be considered in the aggregate. Section 331(k) is part of a larger regulatory program that seeks to "extend [FDCA's] coverage to every article that had gone through interstate commerce until it finally reached the ultimate consumer." *See United States v. Sullivan*, 332 U.S. 689, 697 (1948); *United States v. Evers*, 643 F.2d 1043, 1050 (5th Cir. 1981) ("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."). Moreover, legislative history makes clear that, in extending the scope of section 331(k) to its current form, Congress considered the negative impact adulterated and misbranded drugs could have on the economic value of out-of-state drugs.[13] Defendants' adulteration and misbranding of their cultured cell product could

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Congress may also "regulate and protect . . . persons or things in interstate commerce, even though the threat may come only from intrastate activities." *United States v. Lopez*, 514 U.S. 549, 558 (1995); *see Rancho Viejo, LLC v. Norton*, 323 F.3d 1062, 1066 (D.C. Cir. 2003) (citing *Lopez*).

[13]S. Rep. No. 80-1221 at 3-4 (1948) ("The defilement of products or deterioration in quality or misrepresentation through relabeling or other abusive acts which occur at any time before articles have been sold to consumers leads to dissatisfaction and lack of confidence which depresses the interstate demand for goods of the same type that are neither adulterated nor misbranded.").

depress the market for out-of-state drugs that are approved by FDA. Given these circumstances, there can be no serious question that Defendants' activities fall within the reach of federal power.

III. DEFENDANTS' PROCEDURAL CHALLENGES DO NOT PRECLUDE SUMMARY JUDGMENT

Defendants argue that the Court should not grant summary judgment because they have not yet taken discovery and because the government did not address all of their affirmative defenses in its opening brief. These arguments are without merit.

1. Defendants argue that summary judgment before discovery is disfavored and that the government's motion should be denied on that basis, Defs.' MSJ Opp. at 21, but they stipulated that the government could file a motion for summary judgment at any time after August 28, 2010. *See* Stipulated Order (Dkt. 10) ¶ 12. Moreover, Defendants' contention that motions for summary judgment are disfavored if filed before discovery is incorrect. The Federal Rules of Civil Procedure were recently amended to eliminate the waiting period for seeking summary judgment and to permit either party to move for summary judgment "at any time" after a case is filed up to thirty days after the close of all discovery. Fed. R. Civ. P. 56(b); *see also* Adv. Comm. Notes, 2009 Amendments (The previous rule's timing provisions requiring a party to wait 20 days to file for summary judgment, "are outmoded" and the "new rule allows a party to move for summary judgment at any time, even as early as the commencement of the action.").

Defendants' argument that this Court should deny the government's motion until they take discovery also should be rejected because Defendants have failed to follow Rule 56(d), which sets forth the procedure that must be followed if a nonmovant seeks to avoid summary judgment on the grounds that it needs to take discovery. Under Rule 56(d) (formerly numbered Rule 56(f)), a

court may, *inter alia*, defer ruling on summary judgment or allow time to take discovery, if "a nonmovant shows by affidavit or declaration, that, for specified reasons, it cannot present facts essential to justify its opposition . . . ." Fed. R. Civ. P. 56(d). The rule requires the nonmovant to "state concretely why additional discovery is needed to oppose a motion for summary judgment," *Messina v. Krakower*, 439 F.3d 755, 762 (D.C. Cir. 2006) (internal quotations and citations omitted). "[C]onclusory assertion[s] without any supporting facts to justify the proposition that the discovery sought will produce the evidence required" are insufficient. *Id.* Instead, the nonmovant must submit a declaration articulating "what facts [the nonmovant] intend[s] to discover that would create a triable issue and why [it] could not produce them in opposition to the motion." *Byrd v. EPA*, 174 F.3d 239, 248 n.8 (D.C. Cir. 1999) (conclusory assertions about the potential value of discovery are insufficient unless supported by specific discoverable facts).

Defendants have not filed a motion under Rule 56(d) or an affidavit of any kind, let alone one that states concretely what facts are needed, why they have been unable to produce them in response to a motion that was filed on January 7, 2011, and how those (unidentified) facts, if obtained, would defeat the government's motion. Defendants' failure to follow Rule 56(d) is fatal to their argument that this Court should deny the government's motion until they take discovery. *See Campfield v. State Farm Mut. Auto. Ins. Co.*, 532 F.3d 1111, 1124-25 (10th Cir. 2008) ("Because [plaintiff] failed to file an affidavit under Fed. R. Civ. P. 56(f) explaining 'why facts precluding summary judgment cannot be presented,' . . . he has waived the argument that the grant of summary judgment should be set aside for lack of sufficient discovery."); *see also Laughlin v. Metro. Wash. Airports Auth.*, 149 F.3d 253, 261 (4th Cir. 1998) (nonmoving's

"attorney had the responsibility, if he thought further discovery was necessary to adequately oppose summary judgment, to make a motion under Rule 56(f)").

2. Defendants' argument that summary judgment should be denied because the government did not anticipate and address their affirmative defenses in the government's opening brief is also wrong. It is a long established rule that a party raising an affirmative defense bears the burden of proving it. *Colbert v. Potter*, 471 F.3d 158, 165 (D.C. Cir. 2006); *Barth v. Gelb*, 2 F.3d 1180, 1187 (D.C. Cir. 1993); *Tendler v. Jaffe*, 203 F.2d 14, 17-18 (D.C. Cir. 1953). Even at the summary judgment stage, once a movant has satisfied its burden of establishing that there exists "no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law," *see* Fed. R. Civ. P. 56(c), a nonmovant may not defeat a summary judgment motion by resting on mere allegations or pleadings. *See Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986); *Celotex Corp. v. Catrett*, 477 U.S. 317, 324 (1986); *see also Harper v. Del. Valley Broad., Inc.*, 743 F. Supp. 1076, 1090-91 (D. Del. 1990) (stating that "[a] party resisting summary judgment cannot expect to rely on the bare assertions or mere cataloguing of affirmative defenses"; granting summary judgment against defendants who asserted affirmative defenses but failed to meet their burden of "com[ing] forward with evidence to support their affirmative defenses") (citing *Celotex*, 477 U.S. at 323-24), *aff'd,* 932 F.2d 959 (3d Cir.1991); *Pantry, Inc. v. Stop-N-Go Foods, Inc.*, 796 F. Supp. 1164, 1167 (S.D. Ind. 1992) (in the summary judgment context, "[j]ust as a plaintiff need not disprove an affirmative defense in the plaintiff's initial portion of presenting evidence at trial, a plaintiff/movant need not anticipate and raise the non-movant's affirmative defenses.") (citing *Harper*, 743 F. Supp. at 1090).

As a factual matter, the government's motion to dismiss Defendants' counterclaims and its motion for summary judgment clearly refute the arguments embodied in affirmative defenses I-X, as they are duplicative of Defendants' counterclaims, and, as explained in the government's opening briefs, legally invalid as a matter of law. Defendants have failed to explain why their defenses are not legally inadequate in the face of the government's opening briefs.

Defendants also charge the government with "sandbagging" because the government did not address affirmative defenses XI and XII in its opening briefs. *See* Defs.' MSJ Opp. at 22-23. As stated above, however, the party moving for summary judgment does not have the burden of disproving a nonmovant's affirmative defenses. *See, e.g.*, *Pantry*, 796 F. Supp. at 1167; *Harper*, 743 F. Supp. at 1090-91. Moreover, these affirmative defenses generally refer to FDA having "previously approved or licensed the manufacturing of autologous, culture expanded HCT/Ps by a drug manufacturing company in treating musculoskeletal injuries," but Defendants failed to identify which product purportedly supports these affirmative defenses until their opposition brief. *Compare* Defs.' Am. Answer (Dkt. 15) at 9-10 ("Answer") *with* Defs.' MSJ Opp. at 24 (identifying Carticel). In addition, in their opposition brief, Defendants rely on 21 U.S.C. § 353a as the basis for affirmative defenses XI and XII, but their Answer did not cite that section of the statute, or any other, as the basis for those defenses. *Compare* Answer at 9-10 *with* Defs.' MSJ Opp. at 23-24, 35-37. Defendants' argument that the government should have anticipated the facts Defendants now contend support their affirmative defenses and responded to their unspecified legal basis is without merit and would inappropriately shift Defendants' burden to Plaintiff.

For all of these reasons, Defendants' argument should be rejected.

IV. DEFENDANTS' CULTURED CELL PRODUCT IS MORE THAN MINIMALLY MANIPULATED

As detailed in the government's opening brief, because Defendants' cultured cell product is a drug within the meaning of 21 U.S.C. § 321(g)(1)(B) and (C), it must comply with all of the requirements of the FDCA, unless Defendants can show that it meets all of the criteria to be regulated solely under 21 C.F.R. Part 1271. Pl.'s MSJ at 20. To qualify for Part 1271's regulatory scheme, among other things, an HCT/P can be only "minimally manipulated" – i.e., the cells cannot be processed in a way that "alter[s] the relevant biological characteristics of cells . . . ." 21 C.F.R. §§ 1271.3(f)(2), 1271.10(a). Moreover, if information does not exist to show that the process meets the definition of minimal manipulation, the FDA considers the processing of cells to be "more than minimal manipulation" that cannot qualify for regulation solely under Part 1271. Proposed Registration Rule, 63 Fed. Reg. 26748 (May 14, 1998). FDA is entitled to substantial deference both with respect to its interpretation of its own regulations, *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994), and its evaluation of scientific information within the agency's area of scientific or technical expertise, *Am. Wildlands v. Kempthorne*, 530 F.3d 991, 1000 (D.C. Cir. 2008); Pl.'s MSJ at 22 n.20.

Contrary to Defendants' assertion, the facts material to determining that the cells in the cultured cell product are more than minimally manipulated are beyond dispute. *First*, Defendants' brief and supporting declarations overlook their admission that their "processing of the cultured cell product involves many steps, including selective culture and expansion of a multitude of different types of blood-forming and rare bone marrow stromal cells using plastic flasks, additives and nutrients, and environmental conditions such as temperature and humidity, ***to determine the***

growth and ***biological characteristics of the resulting cell population***." Pl.'s SMF ¶ 10 (emphasis added); Defs.' Resp. to Pl.'s SMF ¶ 10. Indeed, Defendants' website recognizes the critical role that chemical environment plays in determining the type of cell that will be formed. *See* www.regenexx.com/common-questions/index.html at 9 (accessed July 28, 2011) (Pl.'s Ex. O Attch. 1) ("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.").

Second, Defendants try to create a dispute about material *facts* by raising *legal* challenges to FDA's regulations (*e.g.*, alleged defects in the administrative record for Part 1271, and claims that the regulation is arbitrary and capricious). *See* Defs.' MSJ Opp. at 28-29. But all of Defendants' procedural challenges to FDA's definition of minimal manipulation, including the contention that it is arbitrary and capricious, are time-barred and unavailing for the reasons set forth in our motion to dismiss at 24-30. Defendants also take the nonsensical position that FDA expert Steven Bauer, Ph.D.'s declaration is a "post hac [sic] rationalization of the definition of 'minimal manipulation' not included in the administrative record" and that the Court's review must be confined to the administrative record. Defs.' MSJ Opp. at 31. FDA defined minimal manipulation, through notice and comment rulemaking, *see* Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5447 (Jan. 19, 2001), and is now applying that definition to a specific product in this enforcement proceeding. The fact that the agency did not attempt to anticipate and include in the administrative record its views on every conceivable type of manufacturing process for different HCT/Ps is not a defect in Dr. Bauer's declaration (or the administrative record).

Third, Defendants object that Dr. Bauer "never once examined . . . the cells" in Defendants' product in concluding that they are more than minimally manipulated. Defs.' MSJ Opp. at 28-29. This argument is unavailing. Dr. Bauer relied on a detailed review of Defendants' manufacturing SOPs and laboratory notebooks, which describe precisely how RS LLC processes the cells, and on published scientific literature examining how cells change (*e.g.*, the proteins and genes they express, the shapes of the cells, etc.) when they are cultured. *See, e.g.,* Pl.'s Ex. B (Bauer Dec.) ¶¶ 32, 37-41; Pl.'s Ex. I (Supp. Bauer Dec.) ¶ 9. All of Dr. Bauer's conclusions are concrete and well-supported.[14]

Fourth, Defendants try to find a disputed material fact by claiming that Dr. Bauer "relies entirely upon studies 'focused on MSCs grown with protocols designed to create tumors, MSCs grown for ridiculous periods of time,' and other irrelevant references." Defs.' MSJ Opp. at 31. This is not accurate.[15] For example, Dr. Bauer stated that Schallmoser *et al*.:

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[14]Defendants do not question Dr. Bauer's credentials or expertise, nor could they. *See* Ex. B. (Bauer Dec.) ¶¶ 4-11. Instead, Defendants criticize Dr. Bauer's declaration as discussed above, and as being "hypothetical" because, when explaining how the culturing results in the selection and alteration of the original bone marrow or synovial cells, because cells grow and respond to the tissue culture flasks and the composition of the culture media in which they are maintained, Dr. Bauer used the word "would" in the following sentence: "During this time, most of the cells from the original bone marrow aspirate would likely die and the remaining cells would change so they are different from the original cells in the bone marrow." *See id.* ¶ 37. Defendants ignore, however, that Dr. Bauer then illustrated the point he was making by referencing the wide spread cell death that *actually* did occur during manufacture of Defendants' cultured cell product, as evidenced by their own laboratory notebooks. *See id.* ¶¶ 39-40. Thus, Defendants' criticism of Dr. Bauer's declaration is unfounded.

[15]Dr. Bauer cited literature where the cells were cultured for longer periods than RS LLC's product to illustrate that the risk of tumor formation is not theoretical, not to show that the product is more than minimally manipulated. *See* Pl.'s Ex. B (Bauer Dec.) ¶ 17; *compare* Defs.' Ex. 5 (Centeno Aff.) ¶¶ 104-108.

> showed that bone marrow MSCs revealed significant gene expression changes upon long-term culture. Genes involved in cell differentiation, and cell death were up-regulated, whereas genes involved in proliferation were down-regulated. Changes in these genes could be detected as early as 18-22 days in culture and the differences were greater with each passage.

See Pl.'s Ex. B (Bauer Decl.) ¶ 37. Dr. Centeno attempts to distinguish this paper's findings because the authors cultured MSCs for longer periods of time that are "not at all comparable to the Regenexx procedure." Defs.' Ex. 5 (Centeno Aff.) ¶ 55.b.i. In particular, whereas Schallmoser detected changes as early as 18-22 days in culture, Dr. Centeno claims RS LLC's procedure "*usually* only cultures cells for between 11-17 days . . . ." *Id.* (emphasis added). But that claim is not consistent with the records collected by FDA investigators during the 2010 inspection. Defendants' SOPs permit cells to be cultured for [redacted], Pl.'s Ex. A (Kreuzer Dec.) Ex. 45 at 1 & Ex. 52 at 3, and, even though FDA collected only a limited number of processing records during the 2010 inspection, there are nevertheless many examples of patients' cells being processed in culture for at least [redacted], *see* Pl.'s Ex. J (Teitell Dec.) ¶ 5, the same time in which Schmallmoser reported gene changes. Thus, Dr. Centeno's basis for rejecting Dr. Bauer's conclusions is factually erroneous and certainly not a material issue that warrants a trial. Dr. Bauer addresses these and other points in a supplemental declaration filed herewith as Exhibit I.

Finally, Defendants did not attempt to address all of the points Dr. Bauer made in his declaration. For example, Dr. Bauer explained that Defendants sometimes add [redacted] is more than minimal manipulation. *See* Pl.'s MSJ at 22 n.21; Ex. B (Bauer Dec.) ¶ 41.c.; *see also id.* ¶ 41.a.&b.

In conclusion, Defendants' cultured cell product cannot meet the "minimal manipulation" criterion for regulation solely under Part 1271 either if their processing alters the relevant

biological characteristics of the cells or if information does not exist to show that its processing qualifies as minimal manipulation. 63 Fed. Reg. 26748. Dr. Bauer's declaration and Defendants' own statements and admissions establish that Defendants more than minimally manipulate the cells in the cultured cell product. Defendants bear the burden of proof on this point, *see* Pl.'s MSJ at 20-21, and they cannot establish the existence of disputed material facts. Therefore, the government is entitled to summary judgment on this issue.

V. THE ADULTERATION AND MISBRANDING CHARGES ARE BEYOND DISPUTE

In its motion for summary judgment, the government showed that there are no disputed issues of material fact related to Defendants' failure to comply with the adulteration and misbranding provisions in 21 U.S.C. §§ 351(a)(2)(B), 352(f)(1) and 353(b)(4). In opposition, Defendants claim that they are not required to comply with any of those provisions. In addition to their failed practice of medicine defense, discussed above, Defendants rely upon two legal arguments and two affirmative defenses, none of which involve disputed material facts.

1. Defendants attempt to counter the government's charge that the cultured cell product is not made in accordance with CGMP – a charge based on FDA's inspection findings, which Defendants admitted in their Answer, *see* Answer ¶¶ 31-32; Pl's Ex. A (Kreuzer Dec.) ¶¶ 12, 14 – by asserting that the CGMP regulations are inapplicable to their "medical practice." Defs.' MSJ Opp. at 36. Defendants claim this raises a disputed issue of material fact, but for the reasons discussed above and in our opening brief, FDA's jurisdiction over Defendants' cultured cell product is based on undisputed facts and the scope of FDA's jurisdiction, a question of law.[16]

[16]In his declaration, Dr. Centeno claims that the cultured cell product has not been shown to be unsafe. CGMP is prophylactic. It refers to processes and procedures related to the

Given Defendants' admissions, if the Court agrees that the cultured cell product is a drug under the FDCA, then it is deemed to be adulterated as a matter of law. 21 U.S.C. § 351(a)(2)(B).[17]

2. Our opening brief explained that Defendants' cultured cell product is misbranded under 21 U.S.C. § 352(f)(1) because its labeling fails to bear adequate directions for use, and it does not qualify for any regulatory exemption to that statutory requirement. Pl.'s MSJ at 30-33;

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manufacture, packaging, labeling, and holding of a product that are designed to build quality into the product. Failure to comply with CGMP is considered a violation, independent of whether the product is actually harmful or deficient in any way. *See, e.g.*, 21 C.F.R. § 210.1(b); *John D. Copanos & Sons, Inc. v. FDA*, 854 F.2d 510, 514 (D.C. Cir. 1988) ("Drugs produced in violation of these CGMP regulations are deemed to be adulterated without the agency having to show that they are actually contaminated."); *United States v. 789 Cases, More or Less, of Latex Surgeons' Gloves*, 799 F. Supp. 1275, 1287 (D.P.R. 1992). Here, Defendants have admitted the following serious violations, among others: failure to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that in-process materials and drug products conform to appropriate standards of identity, strength, quality, and purity, as required by 21 C.F.R. § 211.160(b); failure to ensure, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, prior to release, as required by 21 C.F.R. § 211.165(a); failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, as required by 21 C.F.R. § 211.113(b); *see also* 21 C.F.R. § 610.12; and failure to perform appropriate laboratory testing of each batch of drug product required to be free of objectionable microorganisms, as required by 21 C.F.R. § 211.165(b). Answer ¶ 32.

[17]Even though Defendants admitted the CGMP violations found during FDA's 2009 and 2010 inspections in their Answer, Answer ¶¶ 31-32, they now try to avoid some of those admissions in their response to the Statement of Material Facts. *See* Defs.' Resp. to Pl.'s SMF ¶¶ 14-15. When Defendants amended their Answer to add affirmative defenses, they did not change these admissions. *Compare* Answer (Dkt. 11) *with* Am. Answer (Dkt. 15). Defendants' admissions are binding. *Gibbs v. Cigna Corp.*, 440 F.3d 571, 578 (2d Cir. 2006) ("Facts admitted in an answer, as in any pleading, are judicial admissions that bind the defendant throughout [the] litigation."); *Nat'l Ass'n of Life Underwriters, Inc. v. Comm'r of Internal Revenue*, 30 F.3d 1526, 1530 (D.C. Cir. 1994) (admission in answer is binding). Moreover, Dr. Centeno acknowledges that RS LLC's processing does not meet CGMP standards. Defs.' Ex. 5 (Centeno Aff.) ¶ 96 ("FDA has held a . . . medical cell culture process to drug mass manufacturing guidelines and like any medical procedure . . ., the medical process did not meet these guidelines."); *id.* ¶¶ 84-85.

see also supra n.1. We also explained that even if Defendants tried to devise adequate directions for use, they would not be able to do so because no well-controlled studies have been conducted using their cultured cell product on which to base such directions. *Id.* at 33-34.[18] In opposition, Defendants do not dispute the content of the cultured cell product's labeling, *see* Defs.' Resp. to

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[18]Overlooking their own bias, Defendants' affiants Dr. Centeno and Dr. Freeman claim that government witnesses Shannon and Muschler are biased and applied too rigorous a standard when they evaluated RS LLC's studies using its cultured cell product. *See* Defs.' Ex. 2 (Freeman Dec.) ¶ 8.o. ("no study is perfect" and the government's experts are making "trivial complaints about the research methodology."); *see also id.* ¶ 8.s. But FDA's regulation describing the attributes of a well-controlled clinical trial (21 C.F.R. § 314.126), which Drs. Shannon and Muschler discussed in their reviews, embodies indisputably valid scientific principles. *See Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 619 (1973) (the regulations "express well-established principles of scientific investigation," and "their strict and demanding standards, barring anecdotal evidence indicating that doctors 'believe' in the efficacy of a drug, are amply justified by the legislative history. The hearings underlying the 1962 [Drug Amendments] show a marked concern that impressions or beliefs of physicians, no matter how fervently held, are treacherous."); *see also Warner-Lambert Co. v. Heckler*, 787 F.2d 147, 155 (3d Cir. 1986). Adequate directions for use cannot be prepared without valid scientific data, *Miami Serpentarium*, 1981-82 FDC L. Rptr. Dev. Trans. Binder ¶ 38,164 at 38,931 (Pl.'s Ex. F), and the defects in Defendants' "studies" are not "trivial." *Inter alia*, not one of Defendants' studies uses a control group, "blinding," or any other method to address possible placebo effect or investigator bias, even though the studies' authors have a direct financial interest in the outcome. *See* Ex. E (Muschler Dec.) ¶¶ 26, 28-36; Pl.'s Ex. C (Shannon Dec.) ¶¶ 16-26, 29-32; *Warner-Lambert*, 787 F.2d at 159 (upholding agency decision that study was not well controlled without adequate steps minimize bias). In fact, Defendants' own case reports acknowledge the importance of conducting controlled trials. *See, e.g.*, Pl.'s Ex. A (Kreuzer Dec.) Ex. 17 at 26 [redacted]) (emphasis added); *id.* Ex. 21 at 351 ("no conclusion can be made from one case report"; "if similar findings are published from pilot studies and then *larger well-designed trials*, the results may have implications for interventional pain management.") (emphasis added).

In any event, any claimed dispute regarding the adequacy of RS LLC's studies does not present a genuine issue of material fact that would preclude entry of summary judgment. Defendants' objections to the government's criticisms of their studies are only relevant to the issue of whether Defendants *could* craft adequate directions for use for their cultured cell product if, in the future, they tried to do so. That issue need not be resolved in order to grant the government's motion for summary judgment, where the content of the Defendants' product labeling is undisputed and Defendants do not contend that they provide adequate directions for use or qualify for any exemption from that requirement.

Pl.'s SMF at 16, 18. Nor do they argue that the product's labeling bears adequate directions for use or that the product qualifies for any regulatory exemption to that statutory requirement. Thus, there is no factual dispute that Defendants do not comply with 21 U.S.C. § 352(f)(1). Defendants instead argue that they are not legally required to label their product in a manner that complies with 21 U.S.C. § 352(f)(1) based on the Fifth Circuit's decision in *Evers*, 643 F.2d 1043. Defs.' MSJ Opp. at 37.

Evers does not excuse Defendants' failure to comply with 21 U.S.C. § 352(f)(1). In *Evers*, unlike the case at bar, the doctor received an FDA-approved drug in interstate commerce and administered it to his own patients. The government alleged that Dr. Evers caused the drug to be misbranded under section 352(f)(1) while holding it for sale because he promoted it for an unapproved use. The Fifth Circuit disagreed, holding that because Dr. Evers administered the drug to his patients and did not distribute it to other physicians, he was not required to provide adequate directions for use by other physicians. 643 F.2d at 1052-53.

The Fifth Circuit found that "the FDCA [is] obviously intended to control the availability of drugs for prescribing by physicians" and considered the issue presented in *Evers* to be a "narrow" one. *Id*. at 1048, 1053. Essential to the court's decision was the fact that Dr. Evers was using *an FDA-approved* drug. As a result, Dr. Evers' promotion of "*a lawful prescription drug* for a use not approved by the FDA" did not cause the drug to be misbranded under the particular circumstances of the case. *Id.* at 1053 n.16 (emphasis added); *see also id.* at 1046-48.[19]

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[19]Interpreting *Evers*, the D.C. Circuit has explained the importance of the physician's use of an approved drug off-label to the outcome of that case:

> In Evers the court held that a physician did not violate the FDCA when he held certain ***approved drugs*** for treatment of his patients and simultaneously advertised

In sharp contrast, RS LLC's cultured cell product has not been approved by FDA for any purpose. Defs.' Resp. to SMF ¶¶ 19-20.[20] Thus, whereas Dr. Evers received a drug that (1) had been reviewed and approved by FDA for at least one indication, (2) was accompanied by an FDA-approved package insert that set forth the directions for use and other information the agency believed necessary, *see* 21 C.F.R. § 201.100, (3) was manufactured by a company registered with FDA, 21 U.S.C. § 360, and (4) was subject to periodic inspections for CGMP compliance, RS LLC's cultured product is none of those things. When the cultured cell product is manufactured and released by RS LLC and received by the Centeno-Schultz Clinic (for injection by one of its three physicians), it has not been approved by FDA for any use, let alone the myriad indications

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> and advocated a treatment program that involved an ***unapproved use*** of those drugs. . . . The ***practice-of-medicine exception exempted the physician from the duty not to advocate an unapproved use to his patients***. The duty ran to other physicians who might hear his advertisement of the unapproved treatment process and might therefore use the drugs without adequate instructions. Thus the physician neither 'held for sale' to the doctors to whom he owed a statutory duty not to misbrand, nor owed a duty to the patients to whom he 'held for sale.' Under these unique facts, no violation was made out.

Chaney v. Heckler, 718 F.2d 1174, 1182 n.20 (D.C. Cir. 1983) (emphasis added), *overruled on other grounds*, *Heckler v. Chaney*, 470 U.S. 821 (1985); *see also United States v. Algon Chem., Inc.*, 879 F.2d 1154, 1162 (3d Cir. 1989) (*Evers* presented "the issue of whether a doctor who prescribed an approved drug for an unorthodox use violated the misbranding provisions . . . .").

[20]The Fifth Circuit agreed that the FDCA requires a distributor to label a drug in a manner that complies with section 352(f)(1) or one of the regulatory exemptions to that requirement. *Evers*, 643 F.2d at 1052. Although Defendants quibble that RS LLC does not "distribute" the cultured cell product, there is no dispute that at the end of the manufacturing process, RS LLC sends the syringe containing the cultured cell product to the Centeno-Schultz Clinic (a separate corporation owned by Centeno-Schultz P.C. at a separate location in Broomfield, Colorado). *See* Pl.'s Ex. A (Kreuzer Dec.) ¶ 8 & Ex. 45 at 3 (explaining that the syringe is placed in a sterile bag and "Transfer[ed] to ordering physician."); Pl.'s Ex. J (Teitell Dec.) Ex. 17; Answer ¶ 8; Pl.'s Ex. M Attch. 1 at 4. Thus, for this reason also, the *Evers* decision does not excuse RS LLC's noncompliance with the FDCA.

for which Defendants promote it; it bears nothing resembling adequate directions for any use; and it is not made in compliance with CGMP. Thus, *Evers* provides no safe harbor that allows Defendants to circumvent 21 U.S.C. § 352(f)(1). *See 9/1 Kg. Containers*, 854 F.2d at 178 (veterinarians may not obtain and compound drugs from drugs that are not lawful, including those misbranded under section 352(f)(1)).

3. There is also no dispute that Defendants' product fails to bear the symbol "Rx only" in violation of 21 U.S.C. § 353(b)(4). Defendants admit that the cultured cell product "is administered by injection into, for example, the patient's joint or intervertebral disc using a type of x-ray device." Defs.' Resp. to Pl.'s SMF ¶ 13 (although denying that the "cultured cell product" exists). Given this admission, there can be no dispute that the method of using the cultured cell product and the collateral measures necessary for its use make it a prescription drug within the meaning of 21 U.S.C. § 353(b)(1)(A). *See* Pl.'s MSJ at 28-29.

Defendants likewise concede the absence of the "Rx only" symbol on their product label, Defs.' Resp. to Pl.'s SMF ¶ 17, but, again relying on the *Evers* decision, claim that compliance with 21 U.S.C. § 353(b)(4) is unnecessary. The *Evers* decision did not address section 353(b)(4), and is not applicable here for the reasons discussed above. Moreover, Congress' command here is unequivocal – a prescription drug "shall be deemed to be 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). Defendants cannot ignore this requirement simply because they disagree with the statute.

4. In affirmative defenses XI and XII, Defendants contend that they are exempt from the adulteration and misbranding provisions in 21 U.S.C. §§ 351(a)(2)(B) and 352(f)(1) because

they are "entitled to compound Genezyme's Carticel pursuant to 21 U.S.C. § 353a." Defs.' MSJ Opp. at 24. As demonstrated below, this argument is flawed on several grounds, the most obvious of which is that Defendants do not actually compound their cultured cell product using Carticel.

Carticel (autologous cultured chondrocytes) is an autologous biological drug product that is the subject of an FDA-approved Biologics License Application. To make the product, chondrocytes are harvested by taking a biopsy from the patient's normal, femoral articular cartilage, and the chondrocytes are then isolated and expanded through cell culture by Carticel's manufacturer, Genzyme. The finished product is shipped back to the patient's physician, who implants the autologous cultured chondrocytes into articular cartilage defects beneath a periosteal flap. *See* Pl.'s Ex. N § 11 (Carticel labeling).

The term "compounding" is not defined in the FDCA. The Supreme Court has defined compounding as "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 (2002); *see Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 387 (5th Cir. 2008). Under a provision added to the FDCA as part of the FDA Modernization Act of 1997, 21 U.S.C. § 353a, compounded drugs are exempt from three specified provisions of the FDCA – including the CGMP and labeling requirements in 21 U.S.C. §§ 351(a)(2)(B) and 352(f)(1) but not including the misbranding charge in 21 U.S.C. § 353(b)(4) – if and only if they comply with the criteria set forth in 21 U.S.C. § 353a(a)-(f). *Med. Ctr. Pharmacy*, 536 F.3d at 405. Because the exemption in section 353a is part of a comprehensive regulatory statute concerned with public

health and safety, it must be strictly construed against the person claiming its protection. *See United States v. Articles of Drug*, 745 F.2d 105, 113 (1st Cir. 1984); *United States v. Kanasco, Ltd.*, 123 F.3d 209, 212 (4th Cir. 1997). Moreover, Defendants bear the burden of showing that they meet every criterion in the section 353a exemption. *See Kanasco*, 123 F.3d at 211; *Articles of Drug*, 745 F.2d at 113; *United States v. An Article of Device*, 731 F.2d 1253, 1260-61 & n.3 (7th Cir. 1984).

Assuming *arguendo* that it is even possible to compound this particular biological drug product, Defendants do not comply with at least three of the statutory criteria in section 353a. *First*, section 353a requires that the drug be compounded "*using*" a bulk drug substance, as defined in 21 C.F.R. § 207.3(a)(4), that is the subject of a monograph in the United States Pharmacopoeia (USP) or National Formulary (NF), or, if such a monograph does not exist, is a drug substance that is a component of a drug approved by the Secretary. 21 U.S.C. § 353a(b)(1) (emphasis added).[21] Neither the USP nor the NF includes a monograph for Carticel, chondrocytes, cartilage, or any kind of stem cell. *See* USP 34-NF 29 1st Supp. (2011). Defendants contend that their cultured cell product falls within section 353a's safe harbor because they are "entitled to compound" Carticel. *See* Defs.' MSJ Opp. at 24. This argument fails because *Defendants do not actually compound their cultured cell product using Carticel* nor do they compound it using chondrocytes.[22]

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[21]Section 353a(b)(1)(A)(i)(III) also permits compounding from bulk drug substances that appear on a list developed by FDA through regulations issued under section 353a(d). This provision is not at issue here because no such list has been issued by the agency.

[22]Defendants do not even start their manufacturing process from the same source material as Carticel (i.e., femoral articular cartilage). Indeed, neither their manufacturing SOPs nor Dr. Centeno's affidavit mention using Carticel, chondrocytes, or cartilage in manufacturing the

Second, even assuming *arguendo* that Carticel contained a bulk drug substance within the meaning of 21 C.F.R. § 207.3(a)(4) and that Defendants used that bulk drug substance to make their cultured cell product,[23] to qualify for the section 353a safe harbor, Defendants also must show that the bulk drug substance they use is "manufactured by an establishment that is registered under section 510 [21 U.S.C. § 360]," and is accompanied by a valid certificate of analysis. 21 U.S.C. § 353a(b)(1)(A)(ii)&(iii). Defendants' product does not meet either of those criteria.

In sum, failure to satisfy any one of the criteria in section 353a is fatal to Defendants' argument, and they fail to meet three of them.[24] Defendants' manufacturing process is not in

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cultured cell product. Rather, their SOPs and Dr. Centeno's affidavit specify the source of the MSC's in the cultured cell product as the patient's *bone marrow or synovial fluid*. Defs.' Resp. to SMF ¶ 9 (admitting that "RS LLC then isolates what it describes as mesenchymal stem cells (MSCs) from the bone marrow or synovial fluid . . . ."); Pl.'s Ex. A (Kreuzer) Exs. 31 & 42; Defs.' Ex. 5 (Centeno Aff.) ¶¶ 13-14 ("marrow aspirate").

[23]Chondrocytes are not the same type of cells as MSCs. *See* Ex. E(Muschler Dec.) ¶ 44. Defendants try to avoid this defect in their argument by claiming that there is data showing that "15-17% of normal or arthritic cartilage contains cells which carry the same markers as MSCs." Defs.' Ex. 5 (Centeno Aff.) ¶ 145. This theoretical possibility does not change the fact that Defendants' manufacturing process does not use Carticel or the same bulk drug substance as Carticel. *See* Pl.'s Ex. I (Supp. Bauer Dec.) ¶ 22.

[24]There is a split in the Circuits as to whether section 353a's exemptions from, *inter alia*, 21 U.S.C. § 351(a)(2)(B) and 352(f)(1), remain good law in light of *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002), holding Section 353a's restrictions on the promotion of compounded products to be unconstitutional restrictions on commercial speech. *Compare W. States Med. Ctr. v. Shalala*, 238 F.3d 1090 (9th Cir. 2001) (not severable) *with Med. Ctr. Pharmacy*, 536 F.3d at 405 (severable). The D.C. Circuit has not yet addressed the severability issue, but there is no reason to reach it here because, under either scenario, Defendants' cultured cell product is adulterated and misbranded. Specifically, if section 353a were considered valid in this jurisdiction, Defendants cannot qualify for its safe harbor for the reasons discussed above. Alternatively, if section 353a were considered invalid in this jurisdiction, then its safe harbor would not be available to Defendants' cultured cell product, which would remain subject to all of the FDCA's requirements, and, as a result, adulterated and misbranded. Put another way, for the same reason it cannot qualify for section 353a's safe harbor – "compounding" using an ingredient that is not a component of a drug approved by FDA – it cannot meet the criteria for

dispute, and it does not involve use of Carticel[25] or any bulk drug substance permissible under section 353a to make the cultured cell product. The compounding safe harbor in section 353a thus does not excuse Defendants' violations of 21 U.S.C. § 351(a)(2)(B) and § 352(f)(1).

VI. DEFENDANTS' VIOLATIVE CONDUCT SHOULD BE ENJOINED

The government established in its opening brief that an injunction is necessary to stop Defendants' violative conduct and to prevent future violations. Pl.'s MSJ at 36-39. Defendants argue that this Court should not issue an injunction against them because the government "lacks the jurisdiction to regulate or define the practice of medicine," Defs.' MSJ Opp. at 44. That argument is incorrect for the reasons discussed above.

Defendants also dispute the necessity of injunctive relief because when faced with the threat of a motion for preliminary injunction in this case, they stipulated not to manufacture or distribute any cultured cell product during the pendency of this litigation. *See* Stipulated Order ¶ 7. The fact that Defendants have temporarily ceased their unlawful conduct under threat of litigation is no basis for denying injunctive relief here. "[C]laims that the illegal activities have been discontinued do not, standing alone, provide a defense to a statutory injunction. This is particularly true where, as in this case, the cessation of the unlawful acts appears to be a result of

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FDA enforcement discretion in FDA's compounding compliance policy guide. *See* Compliance Policy Guide on Pharmacy Compounding (available at http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ ucm074398.htm) (drugs cannot be compounded using ingredients that are not components of FDA approved drugs). Thus, Defendants' cultured cell product violates the FDCA irrespective of whether section 353a is considered good law.

[25]Defendants' affiant Dr. Freeman objects that FDA approved Carticel under the agency's accelerated approval regulations based on clinical evidence he finds lacking. Defs.' Ex. 2 (Freeman Aff.) ¶ 8.u. As a condition of approval, FDA required Carticel's manufacturer to submit additional information post-approval.

FDA pressure or threatened litigation." *United States v. 22 Rectangular or Cylindrical Finished Devices*, 714 F. Supp. 1159, 1167 (D. Utah 1989) (internal citations omitted); *United States v. Odessa Union Warehouse Co-op*, 833 F.2d 172, 176 (9th Cir. 1987) ("an inference arises from . . . past violations that future violations are likely to occur . . . . Courts must beware of attempts to forestall injunctions through remedial efforts and promises of reform that seem timed to anticipate legal action . . . ."); *Sene X*, 479 F. Supp. at 981.

Defendants also claim that injunctive relief is not necessary because if the Court publishes its findings, the decision would "reach the Colorado Board of Medicine" which would have "jurisdiction over the Defendants regardless of the outcome of this case." Defs.' MSJ Opp. at 45. The injunction the government seeks, *inter alia*, would require Defendants to cease manufacturing and distributing the cultured cell product unless and until it is manufactured in compliance with CGMP and labeled in accordance with the FDCA and FDA regulations. The Colorado Board of Medicine has neither the authority nor the expertise to oversee Defendants' compliance (or non-compliance) with these requirements. Defendants have failed to correct significant CGMP violations observed at RS LLC during two FDA inspections. Injunctive relief is essential to ensure that Defendants' operations comply with the law.

CONCLUSION

For the reasons set forth above and in our opening brief, Plaintiff respectfully requests that this Court grant Plaintiff's motion for summary judgment and enter the proposed order of permanent injunction.

DATED this 29th day of July, 2011.

Of Counsel:

WILLIAM B. SCHULTZ
Acting General Counsel

RALPH S. TYLER
Associate General Counsel
Food and Drug Division

ERIC M. BLUMBERG
Deputy Chief Counsel, Litigation

PAIGE H. TAYLOR
Senior Counsel
Food and Drug Administration
Office of the General Counsel
10903 New Hampshire Ave.
White Oak 31, Room 4380
Silver Spring, MD 20993-0002
(301)796-8720

Respectfully submitted,

TONY WEST
Assistant Attorney General

MAAME EWUSI-MENSAH FRIMPONG
Acting Deputy Assistant Attorney General

KENNETH L. JOST
Acting Director

/s/
PERHAM GORJI
Trial Attorney
Office of Consumer Protection Litigation
U.S. Department of Justice
P.O. Box 386
Washington, D.C. 20044
Tel: (202) 353-3881
Fax: (202) 514-8742
perham.gorji@usdoj.gov

CERTIFICATE OF SERVICE

I certify that on the 29th day of July, 2011, the undersigned caused a true and correct copy of the above-entitled to be served via the District Court's Electronic Filing System upon counsel of record for the defendant as follows:

William F. Coffield, Esq.
Coffield Law Group, LLP
1330 Connecticut Avenue, NW
Suite 220
Washington, DC 20036
(202) 429-4799 (o)
(202) 429-3902 (f)
wcoffield@coffieldlawgroup.com

s/ Perham Gorji
Perham Gorji