APPENDIX

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APPENDIX A

FOR PUBLICATION

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

UNITED STATES OF AMERICA, *Plaintiff-Appellant*, v. CALIFORNIA STEM CELL TREATMENT CENTER, INC., a California corporation; CELL SURGICAL NETWORK CORPORATION, a California corporation; ELLIOTT B. LANDER, M.D., individual; MARK BERMAN, M.D., individual, *Defendants-Appellees*.	No.22-56014 D.C. No. 5:18-cv-01005-JGB-KK OPINION

Appeal from the United States District Court
for the Central District of California
Jesus G. Bernal, District Judge, Presiding

Argued and Submitted February 7, 2024
Pasadena, California

Filed September 27, 2024

Before: Kim McLane Wardlaw, Michelle T. Friedland, and Jennifer Sung, Circuit Judges.

Judge Friedland delivered the opinion of the Court as to Parts I, II, III.A, and III.B, in which Judge Wardlaw and Judge Sung joined. Judge Sung delivered the opinion of the Court as to Part III.C, in which Judge Wardlaw joined. Judge Friedland filed a concurring opinion in the result as to Part III.C.

SUMMARY[1]

Food, Drug, and Cosmetic Act

The panel reversed the district court's judgment following a bench trial in favor of Defendants, doctors who create and administer a stem cell mixture called stromal vascular fraction ("SVF"), in the Food and Drug Administration's action alleging that Defendants were violating the Food, Drug, and Cosmetic Act ("FDCA") by improperly manufacturing and labeling SVF.

Under the FDCA, 21 U.S.C. § 301 *et seq.*, the FDA is tasked with ensuring that "drugs" are safe and effective. Under the FDCA and the Public Health Service Act, 42 U.S.C. § 201 *et seq.*, the FDA also regulates human cells, tissues, and cellular and tissue-based products, abbreviated as "HCT/Ps."

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[1] This summary constitutes no part of the opinion of the court. It has been prepared by court staff for the convenience of the reader.

In Part III.B of the opinion, the panel held that Defendants' SVF constitutes a "drug" under the FDCA based on the plain text of the statute.

In Part III.C of the opinion, the panel rejected Defendants' argument that even if SVF is a "drug," their same-day SVF treatment for patients is completely exempt from FDA regulation under the "same surgical procedure" exception ("SSP exception"), which applies to "an establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure." 21 C.F.R. § 1271.15(b). Because the text of the HCT/P regulations does not provide a clear answer to the meaning of the SSP exception, the panel examined the SSP exception's context and structure and resolved the seeming textual ambiguity in the FDA's favor. The SSP exception applies to a procedure only if the removed HCT/P and the implanted HCT/P are the same. For Defendants' SVF procedure, the removed HCT/P is the fat tissue, not the cells targeted for implantation. Because the SVF procedure removes fat tissue but implants SVF, the procedure is not exempt from regulation under the SSP exception.

Concurring in the result of Part III.C, Judge Friedland agreed with the majority's conclusion that Defendants' same-day version of the SVF treatment did not fall under the SSP exception, but she would arrive at this conclusion for a different reason. After examining the HCT/P regulations' text, structure, purpose, and history, she would hold that the SSP exception is genuinely ambiguous, and that the court owes *Auer* deference to the FDA's reasonable interpretation of the SSP exception such that

Defendants' treatments do not fall under the SSP exception.

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OPINION

FRIEDLAND, Circuit Judge:

This case requires us to decide whether the Food and Drug Administration can regulate certain stem cell mixtures advertised as treatments for a host of medical conditions. Defendants are doctors who create such a mixture by removing fat tissue from a patient and breaking it down to concentrate the portion containing stem cells. The result is a mixture of stem cells, other types of cells, and cell debris called stromal vascular fraction ("SVF"), which they then administer to the patient. For example, Defendants inject SVF directly into a patient's knee to treat osteoarthritis. In recent years, clinics offering similar stem cell mixtures have proliferated despite concerns over whether such treatments are safe and effective.

After inspecting Defendants' two clinics, the FDA brought this lawsuit, claiming various violations of the Federal Food, Drug, and Cosmetic Act. Defendants argue that their SVF is not a "drug" within the meaning of the Act and that, even if it is, some of their uses of SVF fall under an exception from FDA regulation for certain surgical procedures. We reject

both arguments. Accordingly, we reverse the district court's entry of judgment in favor of Defendants.

I.

A.

Defendants are two California-licensed physicians and the entities they co-founded: the California Stem Cell Treatment Center and the Cell Surgical Network. The California Stem Cell Treatment Center operates two clinics in Beverly Hills and Rancho Mirage. At those clinics, as part of what they call "patient-funded investigational research," Defendants offer stem cell treatments to "[p]atients who are looking for non-surgical alternatives to their degenerative disorders." Defendants advertise that they have "technology to produce a solution rich with your own stem cells" that they say can alleviate dozens of medical conditions, including Alzheimer's, arthritis, asthma, cancer, macular degeneration, multiple sclerosis, heart problems, pulmonary problems, Crohn's, Parkinson's, and erectile dysfunction. The treatments are not covered by insurance, so patients pay out of pocket. A single treatment typically costs $8,900, and a twelve-treatment option costs $41,500. Defendants have treated thousands of patients.

Through the Cell Surgical Network, Defendants also operate a network for "physicians who want[] to bring regenerative medicine into their own practices." Affiliates agree to follow Defendants' treatment protocol and pricing guidelines; share "research data"; and purchase Defendants' equipment for isolating cells, called the "Time Machine," for about $30,000.

The substance that Defendants produce is called "stromal vascular fraction," or "SVF." SVF is "a liquified mixture of cells and cell debris" derived from fat tissue. Fat tissue, which looks a bit like honeycomb when magnified, is a connective tissue primarily made up of fat cells. Fat tissue also comprises many other types of cells, including mesenchymal stem cells. Most of the cells are embedded in an "extracellular matrix," a structure made partly of collagen fibers that holds the cells in place. Fat tissue also contains interspersed blood vessels.

Defendants derive SVF from fat tissue using a multi-step process. First, after administering local anesthesia to a patient, Defendants use liposuction to remove fat tissue. The retrieved tissue is then centrifuged (spun at high speed) to separate and remove blood and anesthesia. The next step is called "enzymatic digestion." An enzyme blend is added to the tissue, and during a thirty-minute incubation period, the enzymes break down the extracellular matrix (the tissue's structural components). During this period, cells detach from the matrix and become free-floating. Through another round of centrifugation, the fat cells, which made up the bulk of the tissue, are removed and discarded. What is left is repeatedly flushed with a solution to wash away as much of the enzyme blend as possible and centrifuged to concentrate the remaining cells. The resulting "slurry" is pushed through a filter to remove the broken-down structural components. The end result, SVF, is a concentrated mixture of many types of cells, including stem cells, and cell debris. Defendants administer it in a variety of ways, including by injection, intravenous drip, and inhalation.

That entire process is sometimes done on one day: The patient undergoes liposuction, waits for the tissue to be processed, and receives SVF all during one visit. But in the "expanded" version, the collected tissue is not processed onsite. Instead, the tissue is sent to a cell bank for processing and the cells are replicated ("expanded") for later use in the same patient.

B.

In 2017, the FDA inspected the California Stem Cell Treatment Center clinics. The inspectors concluded that the clinics were manufacturing and administering unapproved drug products. They found violations of the FDA's manufacturing requirements and a lack of proper documentation of adverse health events related to the clinics' SVF treatments.

In 2018, the FDA filed this lawsuit and sought injunctive relief, alleging that Defendants were violating the Food, Drug, and Cosmetic Act by improperly manufacturing and labeling SVF. After a seven-day bench trial, the district court entered judgment in favor of Defendants, holding that Defendants' treatments were not subject to FDA regulation. The district court held that Defendants' SVF is not a "drug" under federal law, reasoning that "Defendants are engaged in the practice of medicine, not the manufacture of pharmaceuticals." The court also alternatively held, as to the same-day procedure, that Defendants' use of SVF falls within an exception to regulation for certain surgical procedures. That holding was based on the court's factual finding that the cells in the same-day SVF "are not altered, chemically or biologically" and that the procedure "does not create any new material or introduce any

foreign article" into the body. The FDA timely appealed.

II.

We review a district court's conclusions of law de novo and its findings of fact for clear error. *Yu v. Idaho State Univ.*, 15 F.4th 1236, 1241-42 (9th Cir. 2021).

III.

A.

Under the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 301 *et seq.*, the FDA is tasked with ensuring that "drugs" are safe and effective, as part of its mission to protect public health. *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133-34 (2000) (citing 21 U.S.C. § 393(b)D(2)); *see also Wyeth v. Levine*, 555 U.S. 555, 574 (2009) ("Congress enacted the FDCA to bolster consumer protection against harmful products.").

The FDCA requires all new drugs to receive premarket approval from the FDA, which in turn requires drug manufacturers to demonstrate each drug's safety and efficacy through clinical trials. *See Wyeth*, 555 U.S. at 566; *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 196 (2005) (citing 21 U.S.C. § 355). The FDCA also prohibits any act while a drug is being "held for sale . . . after shipment in interstate commerce" that results in the drug being "adulterated or misbranded."[1] 21 U.S.C. § 331(k). As

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[1] The phrase "held for sale" applies to physicians "engaged in the business of providing medical services in exchange for payment." *United States v. Kaplan*, 836 F.3d 1199, 1210 (9th Cir. 2016). "[T]he 'shipment in interstate commerce' requirement is

relevant here, a drug is "adulterated" if it is manufactured or handled without contaminant controls or does not conform to standards of quality, strength, and purity. *Id.* § 351. And a drug is "misbranded" if it lacks adequate directions for use or bears false or misleading labeling. *Id.* § 352.

Under the FDCA and the Public Health Service Act ("PHSA"), 42 U.S.C. § 201 *et seq.*, the FDA also regulates "human cells, tissues, and cellular and tissue-based products," abbreviated as "HCT/Ps." 21 C.F.R. § 1271.1(a); *Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing*, 66 Fed. Reg. 5447, 5449 (Jan. 19, 2001). HCT/Ps are defined 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). FDA regulations give as examples bone, ligament, skin, cornea, stem cells derived from blood, and reproductive tissue. *Id.*

The FDA has a "tiered, risk-based approach" to regulating HCT/Ps. 66 Fed. Reg. at 5448. That approach employs a hierarchy of oversight—full, limited, or no oversight—based on the FDA's assessment of the types of health risks posed by different categories of HCT/Ps. HCT/Ps at the top of the hierarchy are fully regulated as "drugs" under the FDCA, and/or as "biological products" under the PHSA, and are thus subject to premarket approval. 21 C.F.R. § 1271.20. HCT/Ps that meet certain criteria,

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satisfied even when only an ingredient is transported interstate." *Baker v. United States*, 932 F.2d 813, 814 (9th Cir. 1991).

such as being only "minimally manipulated," fall in the middle of the hierarchy and need only comply with regulations aimed at preventing the spread of infectious disease promulgated under the PHSA. *See id.* § 1271.10; 66 Fed. Reg. at 5449. Finally, HCT/Ps at the bottom of the hierarchy are not subject to any FDA oversight, even if they would otherwise be regulated as drugs under the FDCA.[2] 21 C.F.R. § 1271.15. As relevant to this case, the bottom category includes HCT/Ps that are removed from and implanted into the same patient during the same surgical procedure. *Id.* § 1271.15(b).

B.

The parties first dispute whether Defendants' SVF constitutes a "drug" under the FDCA. Based on the plain text of the statute, we agree with the FDA that Defendants' SVF is a drug.

"[T]he word 'drug' is a term of art for the purposes of the [FDCA]." *United States v. Article of Drug, Bacto-Unidisk*, 394 U.S. 784, 793 (1969). "Drug[s]" are defined in the Act as "articles 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." *Id.* at 789 (quoting 21 U.S.C. § 321(g)(1)). An "article" is just a general term for "a particular thing." *Samsung Elecs. Co. v. Apple Inc.*, 580 U.S. 53, 59 (2016) (quoting J. Stormonth, A Dictionary of the English Language 53 (1885)).

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[2] The FDA treats HCT/Ps falling in the bottom category as excepted from *all* FDA regulation even though the text refers only to being excused from the requirements in "this part." *See* 21 C.F.R. § 1271.15(b).

Defendants administer a particular thing—a liquified concentrate of cells and cell debris. And they do so with the undisputed intent, as reflected in their marketing, to treat a long list of diseases and to affect structures of the body, such as to regenerate cartilage.

Considering a similar stem cell treatment in *United States v. Regenerative Sciences, LLC*, 741 F.3d 1314 (D.C. Cir. 2014), the D.C. Circuit likewise held that the "plain language" of the FDCA compelled the conclusion that the stem cell mixture in that case was a "drug" under the FDCA. *Id.* at 1319. There, doctors extracted bone marrow or fluid from joints, isolated and cultured stem cells, combined the cells with an antibiotic to prevent bacterial contamination, and reinjected the mixture to treat orthopedic conditions. *Id.* at 1318. Although Defendants' treatment here does not involve an antibiotic and does not always involve culturing, the D.C. Circuit's holding that the mixture in its case was a "drug" did not hinge on those aspects of the treatment. *See id.* at 1319. The court simply reasoned that the FDCA's "wide-ranging definition[] clearly appl[ied] to the Mixture, an article derived mainly from human tissue and intended to treat orthopedic diseases and to affect musculoskeletal function."[3] *Id.*

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[3] The D.C. Circuit in *Regenerative Sciences* also held that the stem cell mixture was a "biological product" under the PHSA. 741 F.3d at 1319 (citing 42 U.S.C. § 262(i)(1)). We are not presented in this appeal with the question whether Defendants' SVF falls under the PHSA, and the FDA has made no arguments based on the PHSA's definition of a biological product. But we note that a product can be both a drug under the FDCA and a biological

Defendants do not seem to dispute that the "admittedly capacious" language of the FDCA, read literally, encompasses their treatments. Instead, they assert that the definition should not be read literally because its breadth is intolerable. But the Supreme Court has instructed that it is error to "refuse[] to apply the [FDCA's] language as written," holding that "Congress fully intended that the Act's coverage be as broad as its literal language indicates—and equally clearly, broader than any strict medical definition might otherwise allow." *Bacto-Unidisk*, 394 U.S. at 798. The Court explained that "remedial legislation such as the [FDCA] is to be given a liberal construction consistent with the Act's overriding purpose to protect the public health." *Id*.

Defendants conjure purportedly "absurd" results of a broad interpretation of "drugs," painting a picture of doctors having to pause during a vein graft to measure the vein's active ingredients or adhere a drug label. But "[t]he scope of the offense which Congress defined [in the FDCA] is not to be judicially narrowed as applied to drugs by envisioning extreme possible applications." *United States v. Sullivan*, 332 U.S. 689, 694 (1948). And the FDA has flexibility to tailor its specific requirements upon approval of a new drug. [4]

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product under the PHSA. *See id.* at 1319 & n.1; *see also* 42 U.S.C. § 262(j); 21 U.S.C. § 353(g)(1)(A).

[4] Indeed, the FDA has used its flexibility with respect to other autologous (*i.e.*, same-patient) stem cell treatments that have gone through the FDA's approval process for biological products. *See, e.g.*, FDA, ZYNTEGLO, https://www.fda.gov/ vaccines-blood-biologics/zynteglo.

Id. at 695; *see also, e.g.*, 21 U.S.C. § 352(e)(1)(B), (f) (explaining that exemptions from labeling requirements may be established). Hypothesized extreme applications of specific requirements are not a reason to infer that Defendants' SVF is not a "drug" under the FDCA.

Defendants next argue that this interpretation of "drugs" would impermissibly intrude upon the practice of medicine, which is regulated by the states. But in *United States v. Kaplan*, 836 F.3d 1199 (9th Cir. 2016), we rejected essentially the same argument. There, we held that a doctor could be criminally prosecuted under the FDCA for reusing in biopsies a "needle guide" that was intended for single use only. *Id.* at 1208-11. We explained that "[t]hough the regulation of the practice of medicine is delegated to the states, when a physician misuses medical devices and threatens public health, the physician may run afoul of the [FDCA]." *Id.* at 1203; *see also United States v. 9/1 Kg. Containers, More or Less, of an Article of Drug for Veterinary Use*, 854 F.2d 173, 176 (7th Cir. 1988) ("To regulate drugs is to be 'involved' in the 'practice of the healing arts.'"); *United States v. Evers*, 643 F.2d 1043, 1048 (5th Cir. 1981) ("Of course, while 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.").

Kaplan also invoked the D.C. Circuit's decision in *Regenerative Sciences*, which rejected an argument that "the FDA was improperly attempting to regulate the practice of medicine by regulating the stem cell procedure." *Kaplan*, 836 F.3d at 1210 (describing *Regenerative Scis.*, 741 F.3d at 1319). The D.C. Circuit

reasoned that the FDA's focus was the stem cell *mixture*, not the doctor's performance of any procedure. *Regenerative Scis.*, 741 F.3d at 1319. The court noted that the FDCA's regulatory scheme clearly applies to doctors—evidenced by the fact that the Act has specific carve-outs for doctors that "would be unnecessary if the FDCA did not otherwise regulate the distribution of drugs by licensed physicians." *Id.* at 1319-20. And the court observed that narrowing the scope of the FDCA "by classifying the distribution of drugs by doctors as the practice of medicine" would "create an enormous gap in the FDCA's coverage." *Id.* at 1320. Adopting the reasoning of *Regenerative Sciences*, we explained in *Kaplan* that the defendant doctor's practice-of-medicine arguments were "wide of the mark." 836 F.3d at 1210 (quoting *Regenerative Scis.*, 741 F.3d at 1319). *Kaplan* forecloses Defendants' similar argument here.

As a final effort to resist the FDA's interpretation, Defendants invoke the major questions doctrine, which, when it applies, requires an agency to "point to 'clear congressional authorization' for the power [the agency] claims." *West Virginia v. EPA*, 597 U.S. 697, 723 (2022) (quoting *Util. Air Regul. Grp. v. EPA*, 573 U.S. 302, 324 (2014)). But this is far from the sort of "extraordinary case[]" that would give us "'reason to hesitate before concluding that Congress' meant to confer such authority." *Id.* at 721 (quoting *Brown & Williamson Tobacco Corp.*, 529 U.S. at 159). The FDA is not asserting authority over surgery as a general category. Rather, it is asserting authority over doctors' creation or use of products that fall within Congress's definition of "drugs." That is unlike the

situations in which the major questions doctrine has been applied.

First, this case does not present a matter of extreme "economic and political significance." *Id.* (quoting *Brown & Williamson Tobacco Corp.*, 529 U.S. at 160); *cf. id.* at 724-25 (reasoning that carbon emission standards were meant to "substantially restructure the American energy market"); *Biden v. Nebraska*, 143 S. Ct. 2355, 2373 (2023) (noting that the significance of the student loan forgiveness program was "staggering by any measure," with an economic impact amounting to "nearly one-third of the Government's $1.7 trillion in annual discretionary spending"); *Ala. Ass'n of Realtors v. Dep't of Health & Hum. Servs.*, 594 U.S. 758, 764 (2021) (per curiam) (describing the "sheer scope" of an eviction moratorium, which covered at least 80% of the country).

Second, the FDA's regulation of human cell and tissue products does not represent a sudden assertion or "transformative expansion" of authority. *West Virginia*, 597 U.S. at 724 (quoting *Util. Air.*, 573 U.S. at 324). The FDA's assertion of power rests on key provisions of the FDCA, not a rarely used "gap filler." *Id.* And the FDA's regulation of human cell and tissue products is longstanding. As early as 1993, the FDA was regulating "somatic cell therapy products," including "autologous" cell therapies (*i.e.*, therapies using a patient's own cells), as "drugs" under the FDCA. *Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products*, 58 Fed. Reg. 53248, 53249 (Oct. 14, 1993). In 1997, the FDA proposed its current "unified approach to the regulation of both traditional and new [human cellular and tissue-based] products." FDA,

Proposed Approach to Regulation of Cellular and Tissue-Based Products 6 (Feb. 28, 1997) ("*Proposed Approach*"); 66 Fed. Reg. at 5447-69 (finalizing the rule in 2001).

Third, unlike in the only Supreme Court case addressing the major questions doctrine in the context of the FDCA, there is no mismatch between Defendants' SVF and the statutory scheme. In *Brown & Williamson Tobacco Corp.*, the Court held that the FDA did not have authority over tobacco products. 529 U.S. at 161. The Court reasoned that faithful application of the FDCA—which requires that the FDA balance a product's therapeutic benefits against the risk of harm—would require an outright ban on tobacco products because they cannot safely be used for *any* therapeutic benefit. *Id.* at 141-43. But a ban would have contradicted Congress's clear intent in tobacco-specific legislation to permit the sale of tobacco products. *Id.* at 143. Thus, "there is no room for tobacco products within the FDCA's regulatory scheme." *Id.* Here, by contrast, SVF fits comfortably within the FDCA because it is sold and administered to patients for therapeutic purposes, and there is no reason to think that Congress intended it to be outside the FDCA's scope. In fact, recent legislation suggests that Congress presupposes that the FDA regulates stem cell therapies. *See* 21st Century Cures Act, Pub. L. No. 114-255, § 3033, 130 Stat. 1033, 1101-03 (2016) (codified as amended at 21 U.S.C. § 356) (amending a section of the FDCA to create an expedited review process for "regenerative advanced therapies," including "cell therapy" and "human cell and tissue products").

Consistent with the Supreme Court's instruction that the FDCA's definition of "drug" is "as broad as its literal language indicates," *Bacto-Unidisk*, 394 U.S. at 798, we hold that Defendants' SVF is a "drug."

* * *

Part III.C:

SUNG, Circuit Judge, with whom WARDLAW, Circuit Judge, joins:

C.

Defendants argue that even if their SVF is a "drug," their same-day SVF treatment is completely exempt from FDA regulation under what is called the "same surgical procedure" exception ("SSP exception").[5] The SSP exception applies to "an establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure." 21 C.F.R. § 1271.15(b). The FDA maintains that the SSP exception does not apply to Defendants' same-day SVF treatment. On appeal, the parties do not dispute the facts about the same-day SVF treatment. Rather, they offer competing interpretations of the SSP exception. For the reasons explained below, we conclude that the FDA's interpretation is correct, and we hold that Defendants' same-day version of the SVF treatment does not qualify for the SSP exception.

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[5] Defendants do not challenge the district court's conclusion that their use of SVF in the "expanded" version of the treatment, which involves shipping the tissue to a cell bank and culturing cells, does not fall under the SSP exception.

1.

"If [a] regulation is unambiguous and 'there is only one reasonable construction of [the] regulation,' then we" simply apply that meaning. *Mountain Cmtys. for Fire Safety v. Elliott*, 25 F.4th 667, 675 (9th Cir. 2022) (quoting *Kisor v. Wilkie*, 588 U.S. 558, 575 (2019)). If the text seems to have more than one plausible meaning, then we must try to resolve the ambiguity by "carefully consider[ing] the text, structure, history, and purpose of [the] regulation." *Kisor*, 588 U.S. at 575 (internal quotation marks and citation omitted). If, after "exhaust[ing] all the 'traditional tools' of construction," we determine that "the interpretive question still has no single right answer," then we consider whether the agency's interpretation is reasonable, and if so, whether it is entitled to deference under *Auer v. Robbins*, 519 U.S. 452 (1997). *Id.* at 575–76. But, in many cases, our tools of construction will resolve the seeming ambiguity "out of the box, without resort to *Auer* deference." *Id.* at 575.

2.

Again, the SSP exception applies to: "[A]n establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure." 21 C.F.R. § 1271.15(b). "HCT/Ps" are defined as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." *Id.* § 1271.3(d).

The FDA and Defendants agree on several important points. First, they agree that the SSP

exception applies to a procedure only if the removed HCT/P and the implanted HCT/P are "the same." Second, they agree that fat tissue is an HCT/P, and that the SVF procedure removes fat tissue, but implants SVF. Third, they agree that Defendants subject the removed fat tissue to significant processing to produce SVF. Fourth, they agree that fat tissue and SVF are not the same. In the FDA's view, all this adds up to an easy case: Because fat tissue and SVF are not the same, the SSP exception does not apply to the SVF procedure.

But, Defendants point out (and the FDA does not dispute) that the cells they extract from the fat tissue are also, by definition, HCT/Ps. Consequently, the SVF procedure can be characterized as removing two different kinds of HCT/Ps: the fat tissue and the cells within the fat tissue. When determining whether a procedure removes and implants the same HCT/Ps, Defendants argue that the SSP exception requires us to compare the implanted HCT/P with the HCT/P that was "the target of the removal, rather than the largest system removed." Under that interpretation of the SSP exception, the SVF procedure removes and implants the same HCT/Ps because it targets the cells within fat tissue for removal and implants those cells. And, under that interpretation, the SVF procedure removes and implants the same HCT/Ps even though Defendants subject the removed fat tissue to significant processing to extract and isolate the targeted cells. In Defendants' view, the SSP exception applies no matter how much processing the removed

tissue undergoes, so long as the extracted cells are implanted in the same surgical procedure.[6]

The FDA maintains that the SSP exception requires us to view the removed HCT/P as a whole, before it has undergone any significant processing. Under that interpretation, the HCT/P removed by the SVF procedure is the fat tissue, not the cells.

Thus, the parties' interpretive dispute boils down to the following question: When determining whether the removed and implanted HCT/Ps are the same, which removed HCT/P is the correct comparator? Do we consider the HCT/P that was removed as a whole, before any significant processing? Or only the portion of the removed HCT/P that will be implanted, even if extensive processing is needed to extract that portion from the whole?

Each party argues that its interpretation is compelled by the regulation's text. The FDA focuses on the word "such," which is used to refer back to something already mentioned—an antecedent. *Such*, Black's Law Dictionary (12th ed. 2024) (defining "such" as "[t]hat or those; having just been mentioned"). Therefore, the phrase "removes HCT/P's from an individual and implants such HCT/P's into the same individual" means that, to fall under the SSP exception, the HCT/P implanted must be the same HCT/P removed. But, as discussed above, Defendants concede that the removed and implanted HCT/P must

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[6] It is undisputed that Defendants' same-day treatment involves the same patient and the "same surgical procedure" as required for the SSP exception.

be the same, and instead argue that the implanted SVF should be compared to the cells within the removed tissue, not the tissue as a whole. The term "such" does not tell us which comparator to use.

For their part, Defendants focus on the regulatory definition of HCT/Ps. Recall that the FDA defines HCT/Ps as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." 21 C.F.R. § 1271.3(d).

Defendants first argue that the definition signals that the focus in the SSP exception should be on the article that the doctor "intend[s] for implantation"—here, the cells. But the HCT/P definition includes an article that "contain[s]" the cells that are intended for implantation. And here, the removed fat tissue contains the cells that are intended for implantation. Thus, even if the doctor's intent is relevant, the fat tissue could still be the correct comparator.

Defendants next argue that the FDA's focus on the largest system removed would render part of the HCT/P definition superfluous. The definition refers to "cells *or* tissues," and Defendants argue that cells can generally only be removed from the body within tissue or other larger systems. It is true that isolated cells would rarely fall under the SSP exception as interpreted by the FDA. But rarely does not mean never. As the FDA points out, at least one type of cell can be removed in isolation,[7] and the regulation

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[7] The FDA's expert testified that she was aware of one type of cell that can be removed in isolation: an ovocyte, or egg cell.

addresses an area of evolving science. Moreover, the HCT/P definition does not apply solely to the SSP exception—it applies across numerous provisions regulating cells or cell-based products. *Id.* § 1271.3 (establishing definitions that apply across 21 C.F.R. pt. 1271); *see also, e.g.*, *id.* § 1271.145 (providing that HCT/Ps must be stored "in a way that prevents the introduction, transmission, or spread of communicable diseases"). Thus, even if the inclusion of "cells" in the definition of "HCT/P" served no purpose in the context of the SSP exception, the word "cells" would not be superfluous in the context of those other provisions.

In sum, neither party's textual arguments fully resolve the interpretive dispute. Although the FDA's reading is more straightforward and consistent with the SSP exception's plain text, Defendants' reading is plausible. So, we consider the SSP exception's context and structure.

The SSP exception is part of a broader framework that regulates the "manufacture" of HCT/Ps. "Manufacture means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue . . . . "*Id.* § 1271.3(e). As noted above, this framework establishes three tiers of regulation for HCT/Ps: 1) full regulation; 2) limited exemption from regulation; and 3) complete exemption from regulation. HCT/Ps are subject to full regulation unless they qualify for an exception. *Id.* § 1271.20. To qualify for limited exemption from regulation, an HCT/P must meet the criteria set out in § 1271.10(a); in relevant part, the HCT/P cannot be more than

"minimally manipulated."[8] There are several ways to qualify for complete exemption, including by meeting the requirements for the SSP exception at issue here. *See id.* § 1271.15.[9]

The FDA points out that when an HCT/P is more than "minimally manipulated," it is subject to full regulation. Thus, the FDA argues, the SSP exception should not be interpreted as completely exempting procedures that involve substantial manipulation of HCT/Ps. Defendants, however, point out that the limited exemption expressly incorporates the minimal manipulation requirement, *see* 21 C.F.R. § 1271.10(a), but the SSP exception does not, *see id.* § 1271.15(b). That omission, Defendants argue, implies that a surgical procedure can qualify for the SSP exception *regardless of* how much an HCT/P is manipulated. That is, a surgical procedure could "alter the relevant biological characteristics"[10] of the cells or tissues that are implanted and still qualify for the SSP exception.[11]

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[8] HCT/Ps in this category must also be "intended for homologous use only," meaning the HCT/P must perform the "same basic function" when reimplanted; must "not involve the combination of the cells or tissues with another article;" and must "not have a systemic effect" (with some additional nuances to those requirements). 21 C.F.R. §§ 1271.10(a)(2)-(4), 1271.3(c).

[9] Defendants do not dispute that they manufacture HCT/Ps; they argue only that they qualify for the SSP exception.

[10] 21 C.F.R. § 1271.3(f) (defining minimal manipulation).

[11] Although Defendants maintain that the SVF procedure does *not* biologically alter the stromal vascular cells targeted for implantation, under their interpretation of the SSP exception, that fact is irrelevant.

In Defendants' view, "it is not strange at all that some procedures would be exempted under the SSP exception, even if they would not qualify for the [limited] minimal manipulation exemption" provided for under § 1271.10(a), because the limited exemption is "available to establishments that transfer HCT/Ps from one donor to a different recipient," while the SSP exemption is available only to establishments that remove HCT/Ps and implant them back into the same patient.

In our view, the FDA's understanding of the regulatory framework makes more sense: The tiered structure more strongly implies that a surgical procedure cannot qualify for the SSP exception if it involves more than minimal manipulation of HCT/Ps. But, even assuming the FDA is right about that point, the SVF procedure could still qualify for the SSP exception—if the correct comparator is the cells, not the fat tissue. That's because the regulations define "minimal manipulation" differently for structural tissue (which includes fat tissue), *see id.* § 1271.3(f)(1), and cells or nonstructural tissues, *see id.* § 1271.3(f)(2). For fat tissue, minimal manipulation means "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement." *Id.* § 1271.3(f)(1). But for cells, minimal manipulation means "processing that does not alter the relevant biological characteristics of cells." *Id.* § 1271.3(f)(2). It is undisputed that Defendants' SVF procedure significantly alters the removed fat tissue to produce the implanted SVF. But, the district court specifically found that the procedure does not biologically alter the cells that Defendants extract

from the fat tissue, and the FDA has not challenged that finding on appeal. Thus, if the targeted cells are the correct comparator, as Defendants argue, then the SVF procedure does not involve more than minimal manipulation.

All this means that we still need to figure out whether the correct comparator is the removed HCT/P as a whole or only the portion targeted for removal. Because neither the SSP exception nor the related regulations expressly answer that question, we turn to the regulations' purpose and history.

When the FDA first proposed the HCT/P regulatory framework, it explained that, "[i]n the past, most human tissue used in medicine was comprised of such body components as skin, bone, corneas, and heart valves that were transplanted for replacement purposes, and semen and ova implanted for reproductive purposes." *Proposed Approach* at 8. And, the "FDA's regulation of the conventional tissues used for replacement purposes ha[d] focused on preventing the transmission of communicable disease . . . . " *Id.* However, "[i]n recent years, scientists ha[d] developed innovative methods of manipulating and using human cells and tissues for therapeutic uses," and the FDA identified several public health and regulatory concerns associated with the use of such products. *Id.* at 9. Thus, the FDA proposed regulating cells and tissues "with a tiered approach based on risk and the necessity for FDA review." *Id.*

A chief purpose of the regulations would be "ensuring that clinical safety and effectiveness is demonstrated for tissues that are highly processed." *Id.* at 6. The FDA stated its intent to "require that

cells and tissues be handled according to procedures designed to prevent contamination and to preserve tissue function and integrity." *Id.* at 6-7. The FDA explained, "Improper handling can alter or destroy the integrity or function of cells or tissues. Improper handling also can allow cells or tissues to become contaminated (e.g., bacterial contamination during collection, processing, storage, or transplantation, or cross contamination from other contaminated tissues)." *Id.* at 15.

In this context, the FDA also stated that it "would not assert any regulatory control over cells or tissues that are removed from a patient and transplanted back into that patient during a single surgical procedure," because "[t]he communicable disease risks, as well as safety and effectiveness risks, would generally be no different from those typically associated with surgery." *Id.* at 12.[12] The FDA identified "skin or vein grafts" as examples of surgical

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[12] Defendants argue that their interpretation of the SSP exception is supported by the FDA's statement that "[a]utologous use of *cells* and tissues harvested and transplanted in a single surgical procedure would be subject to no FDA oversight." *Proposed Approach* at 15 (emphasis added). They assert that the FDA must have known that cells generally cannot be removed from the body in isolation, so the FDA must have intended for the SSP exception to cover procedures that process tissue to extract cells. Because that assertion is unfounded, Defendants' argument is unpersuasive. As noted above, egg cells can be removed in isolation, and the FDA was anticipating scientific advances when it proposed the HCT/P regulations. *See id.* at 8 (discussing implantation of ova for reproductive purposes); *id.* at 27 (discussing intent to balance protecting public health with encouraging research and innovation).

procedures that would qualify for complete exemption from regulation. *Id.* at 20.

Consistent with the FDA's proposal, the final rule established "a tiered, risk-based regulatory scheme that . . . tailor[s] the degree of scrutiny afforded to different HCT/P's to the risks associated with each of them." *See* 66 Fed. Reg. at 5464. The SSP exception is at the bottom tier: procedures covered by the SSP exception are completely exempt from regulation. This means that covered procedures should involve relatively low risk—risk no greater than that typically associated with conventional surgery. And, because processing HCT/Ps introduces risk, covered procedures should not involve significant processing.

Defendants' interpretation of the SSP exception conflicts with the HCT/P regulations' structure and purposes. Under their interpretation, the SSP exception would exempt surgical procedures that subject HCT/Ps to substantial processing, even if such processing introduces risk far greater than that associated with conventional surgery. HCT/Ps could be subjected to any number of processing steps to isolate, extract, or potentially even recombine its subcomponents (perhaps in ways currently unimaginable) with no FDA oversight, so long as those subcomponents came from the same person and were removed and implanted on the same day.[13]

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[13] In an exceedingly similar case regarding "body-fat derived stem cell therapy," the Eleventh Circuit agreed with the FDA that, to qualify for the SSP exception, "'such HCT/Ps' must be in their original form (rather than subjected to extensive processing)." *United States v. US Stem Cell Clinic, LLC*, 998 F.3d

The FDA's interpretation is more consistent with the SSP exception's plain meaning. And it is the only interpretation that makes sense in light of the HCT/P regulations' tiered, risk-based framework, and its purpose and history. The seeming textual ambiguity is resolved in the FDA's favor.[14] When determining whether a surgical procedure "removes HCT/P's and implants such HCT/P's," the removed HCT/P must be viewed as a whole, before any significant processing. For Defendants' SVF procedure, the removed HCT/P is the fat tissue, not the cells targeted for implantation. Because the SVF procedure removes fat tissue but implants SVF, the procedure is not exempt from regulation under the SSP exception.

* * *

We REVERSE and REMAND for further proceedings.[15]

FRIEDLAND, Circuit Judge, concurring in the result of part III.C:

I agree with the majority's conclusion that Defendants' same-day version of the SVF treatment does not fall under the SSP exception, but I would arrive at this conclusion for a different reason. I believe that the SSP exception provision is ambiguous,

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1302, 1305, 1310 (11th Cir. 2021) ("hold[ing] the same surgical procedure exception unambiguously does not apply"). We agree with the Eleventh Circuit's reasoning and conclusion.

[14] Because no genuine ambiguity remains, we do not need to decide whether the FDA's interpretation is entitled to *Auer* deference.

[15] Defendants shall bear all costs of appeal. *See* Fed. R. App. P. 39(a)(3).

and that we owe deference to the FDA's interpretation of it.

1.

When the meaning of a regulation is in doubt, "we must 'look to the administrative construction of the regulation.'" *Goffney v. Becerra*, 995 F.3d 737, 744 (9th Cir. 2021) (quoting *Bowles v. Seminole Rock & Sand Co.*, 325 U.S. 410, 413-14 (1945)). The practice of deferring to agency interpretations of ambiguous regulations is commonly known as *Auer* deference. *Id.* (citing *Auer v. Robbins*, 519 U.S. 452 (1997)).

An agency is entitled to *Auer* deference only when the regulation in question is "genuinely ambiguous," meaning that it is "susceptible to more than one reasonable reading." *Kisor v. Wilkie*, 588 U.S. 558, 566, 573 (2019). In cabining the scope of *Auer* deference, the Supreme Court has cautioned that we "cannot wave the ambiguity flag just because [we] found the regulation impenetrable on first read." *Id.* at 575. Instead, we must first "exhaust all the traditional tools of construction" by examining the "text, structure, history, and purpose of a regulation." *Id.* (quotation marks omitted). "[O]nly when that legal toolkit is empty and the interpretive question still has no single right answer" can we consider deferring to an agency's reasonable interpretation. *Id.* at 575-76. Before deferring, we must also confirm that "the interpretation is the agency's authoritative or official position, the interpretation in some way implicates the agency's substantive expertise, and the agency's reading of its rule reflects the agency's fair and considered judgment." *Nat'l Parks Conservation Ass'n*

v. FERC, 6 F.4th 1044, 1050-51 (9th Cir. 2021) (citing *Kisor*, 588 U.S. at 574-79).

2.

As to the text of the HCT/P regulations, I agree with the majority's thoughtful analysis, which concludes that the text does not provide a clear answer to the interpretive dispute. My analysis diverges from the majority's only when we turn to the purpose and history of the HCT/P regulations. Although the majority concludes that the regulations' purpose and history support the FDA's interpretation, I believe that evidence cuts both ways, leaving the SSP exception genuinely ambiguous.

The FDA's reading of the SSP exception, focusing on the tissue removed from the body rather than only the targeted cells within that tissue, appears to be consistent with the purpose of the HCT/P regulations. In its 1997 proposal for the current regulatory approach, the FDA stated it was concerned with the "clinical safety and effectiveness . . . [of] tissues that are highly processed" and the risk that processing and/or improper handling could result in contamination or damage to tissue or cell function and integrity. FDA, *Proposed Approach to Regulation of Cellular and Tissue-Based Products* 6, 7 (1997) ("*Proposed Approach*"); *see also id.* at 9 (listing overarching public health concerns). The FDA's concern with contamination and safety, particularly when an HCT/P is processed and manipulated, is consistent with requiring an HCT/P to be in its "original form" as it was in the body for it to be excepted from regulation. FDA, *Same Surgical Procedure Exception Under 21 CFR 1271.15(b):*

Questions and Answers Regarding the Scope of the Exception 5 (2017).

But other statements by the FDA in the leadup to the promulgation of the HCT/P regulations support Defendants' argument that the SSP exception was always meant to capture targeted cells. For example, the FDA stated that "[a]utologous use of *cells* and tissues harvested and transplanted in a single surgical procedure would be subject to no FDA oversight." *Proposed Approach* at 15 (emphasis added). Defendants point out that the FDA must have known that cells generally cannot be removed from the body in isolation, so some processing would be required.[1]

Additionally, the FDA's *Proposed Approach* indicated that certain amounts of cell and tissue processing could occur without there being a concerning amount of manipulation. Within the context of creating a regulatory framework to prevent "product contamination" and loss of "product integrity and function" in the processing of HCT/Ps, the FDA identified example procedures that it considered "minimal manipulation." *Id.* at tbl. 1; *id.* at 16. These included "extraction or separation of cells from structural tissue, in which the remaining structural tissue's characteristics relating to carrying out

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[1] Although the FDA was aware that one type of cell—egg cells, or oocytes—can be removed in isolation, it likely was not referring to egg cells in the context of the SSP exception. Egg cells generally would not be removed and then implanted in the same person during a single surgical procedure. In vitro fertilization, for example, cannot be accomplished within a single surgical procedure.

reconstruction and/or repair were unaltered," and "selection of stem cells from amongst lymphocytes and mature cells of other lineages." *Id.* at 16, 18. Compared to Defendants' same-day SVF procedure, these example procedures seem to present comparable levels of complexity and risk for contamination or damage to product function and integrity. In contrast, the FDA identified procedures such as cell "expansion, encapsulation, activation, or genetic modification," as involving concerning amounts of manipulation. *Id.* at 17-18; *Establishment Registration and Listing for Manufacturer of Human Cellular and Tissue-Based Products*, 63 Fed. Reg. 26744, 26748 (May 14, 1998) (same). Particularly given the district court's factual finding that the targeted cells are not altered by Defendants' same-day SVF procedure, the distinctions in levels of manipulation discussed in the *Proposed Approach* suggest that the procedure does not trigger the FDA's core regulatory concerns, supporting Defendants' interpretation of the SSP exception.

Because the HCT/P regulations' text, structure, purpose, and history do not determine whether we should view the relevant antecedent HCT/P as the targeted cells or the whole system removed from the body, I believe our "legal toolkit is empty and the interpretive question still has no single right answer." *Kisor*, 588 U.S. at 575. I view the SSP exception as genuinely ambiguous because both the FDA's and Defendants' interpretations are reasonable.[2]

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[2] I recognize that in a similar case, the Eleventh Circuit agreed with the FDA's interpretation of the SSP exception and concluded that the exception was unambiguous. *See United States v. US*

3.

Because I conclude that the SSP is ambiguous, I now discuss the remaining criteria for deferring to an agency's interpretation of a regulation and explain why they lead me to ultimately agree with the majority that the FDA's interpretation prevails.

First, there is no doubt that the FDA's interpretation is the agency's "'authoritative' or 'official position.'" *Id.* at 577 (quoting *United States v. Mead Corp.*, 533 U.S. 218, 257-59, 258 n.6 (2001) (Scalia, J., dissenting)). The Supreme Court in *Kisor* explained that an "authoritative" interpretation is one "actually made by the agency . . . rather than any more ad hoc statement not reflecting the agency's views." *Id.* The FDA's interpretation of the SSP exception comes from an official guidance document, drafted and finalized "consistent with FDA's good guidance practices regulation." *Same Surgical Procedure Exception: Questions and Answers Regarding the Scope of the Exception; Guidance for Industry; Availability*, 82 Fed. Reg. 54289, 54290 (Nov. 17, 2017) (citing 21 C.F.R. § 10.115(a)). That regulation states that such guidance documents "describe the agency's interpretation of or policy on a regulatory issue" and "represent the agency's current thinking." 21 C.F.R. § 10.115(b)(1), (d)(3). The FDA's interpretation of the SSP exception thus "emanate[s] from those actors,

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Stem Cell Clinic, LLC, 998 F.3d 1302, 1308-10 (11th Cir. 2021). Although I agree with parts of the Eleventh Circuit's analysis, for the reasons explained I do not agree that the tools of interpretation lock in the FDA's reading as the only reasonable one.

using those vehicles, understood to make authoritative policy in the relevant context."[3] *Kisor*, 588 U.S. at 577.

The FDA's interpretation also implicates its substantive expertise in protecting public health by assessing and addressing risks. *See, e.g.*, 21 U.S.C. § 393. The HCT/P framework is a "complex and highly technical regulatory program" that reflects such risk assessments. *Kisor*, 588 U.S. at 572 (quoting *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994)). Courts are not in a good position to assess which protocols, procedures, or uses of human cell and tissue products pose health risks warranting regulation. The interpretive issue in this case certainly does not "fall more naturally into a judge's bailiwick." *Id.* at 578.

Finally, the FDA's reading of the SSP exception reflects "fair and considered judgment" and does not present unfair surprise. *Id.* at 579 (quoting *Christopher v. SmithKline Beecham Corp.*, 567 U.S. 142, 155 (2012)). The FDA has taken the position that fat-derived SVF does not fall within the SSP exception since at least 2014, when it first issued draft guidance in response to "numerous inquiries regarding HCT/Ps manufactured from [fat] tissues." FDA, *Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) From Adipose Tissue: Regulatory Considerations* 2, 7-8 (2014); *Human Cells, Tissues, and Cellular and Tissue-Based Products From*

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[3] Contrary to Defendants' assertions, an agency interpretation need not establish legally enforceable responsibilities to be sufficiently authoritative for *Auer* deference purposes. *See, e.g.*, *Auer*, 519 U.S. at 462 (deferring to an amicus brief).

Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry; Availability, 79 Fed. Reg. 77414 (Dec. 24, 2014) (announcing draft availability). Indeed, Defendants admitted that they were aware that one of their affiliates received a warning letter from the FDA in 2015 stating that their use of fat-derived SVF violated the FDCA. Based on that history, the FDA's current interpretation is not merely a "convenient litigating position." *Kisor*, 588 U.S. at 579 (quoting *Christopher*, 567 U.S. at 155).

* * *

Because I conclude that the SSP exception is ambiguous, the FDA's interpretation is reasonable, and all the remaining criteria for *Auer* deference are satisfied, I would defer to the FDA's interpretation. Under that interpretation, the antecedent HCT/P here is the removed fat tissue, and the SVF implanted is not "such HCT/P." Thus, I agree with the majority that Defendants' treatments do not fall under the SSP exception.

APPENDIX B

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

UNITED STATES OF AMERICA, Plaintiff-Appellant, v. CALIFORNIA STEM CELL TREATMENT CENTER, INC., a California corporation; et al., Defendants-Appellees.	No. 22-56014 D.C. No. 5:18-cv-01005-JGB-KK Central District of California, Riverside ORDER

Before: WARDLAW, FRIEDLAND, and SUNG, Circuit Judges.

The panel has voted to deny Appellee's petition for rehearing en banc. The full court has been advised of the petition for rehearing en banc, and no judge has requested a vote on whether to rehear the matter en banc. Fed. R. App. P. 40.

The petition for rehearing en banc is DENIED.

APPENDIX C

UNITED STATES DISTRICT COURT
CENTRAL DISTRICT OF CALIFORNIA —
EASTERN DIVISION

UNITED STATES OF AMERICA, Plaintiff, v. CALIFORNIA STEM CELL TREATMENT CENTER, INC., et al. Defendants.	Case No. EDCV 18-1005 JGB (KKx) **FINDINGS OF FACT AND CONCLUSIONS OF LAW**

This is a statutory injunction proceeding in which the United States, on behalf of the U.S. Food and Drug Administration ("FDA"), seeks to permanently enjoin Defendants California Stem Cell Treatment Center, Inc., Cell Surgical Network Corporation, and Drs. Elliot B. Lander, M.D., and Mark Berman, M.D., from performing various stem cell treatments on patients. The United States alleges these treatments violate the Federal Food, Drug, and Cosmetic Act ("FDCA"). Specifically, the United States alleges that three of Defendants' stromal vascular stem cell treatments violate: 21 U.S.C. § 331(k) by causing the adulteration of drugs; 21 U.S.C. § 331(k) by causing the misbranding of drugs; and 21 U.S.C. § 331(c) by receiving drugs that are misbranded.

The case was tried to the Court on May 4, 5, 6, 7, 11, 12, and 13, 2021. Oral closing arguments occurred on August 20, 2021. Because of the ongoing Covid-19 pandemic, the United States appeared via videoconference. At the August 20, 2021 closing arguments, the Court ordered supplemental briefing, which was submitted by both sides on August 27, 2021, and September 1, 2021. ("Pl's Supp Br.," Dkt. No. 179; "Defs Supp Br.," Dkt. No. 178; "Pl's Supp Opp.," Dkt. No. 181; "Defs Supp Opp.," Dkt. No. 180.)

The Court, having considered all the evidence presented by the parties, the written submissions from both sides, and the argument of counsel, issues the following Findings of Fact and Conclusions of Law.

I. FINDINGS OF FACT

A. General Facts

1. Defendant California Stem Cell Treatment Center ("CSCTC") is a California professional corporation founded in 2010, with its principal place of business located at 72-780 Country Club Drive, Suite 301, Rancho Mirage, California 92270 ("CSCTC Rancho Mirage"). California Stem Cell Treatment Center has a second location at 120 South Spalding Drive, Suite 300, Beverly Hills, California 90212 ("CSCTC Beverly Hills."). ("Stip. Facts," Dkt. No. 113-1 ¶ 1.)

2. Defendant Elliot B. Lander, M.D., a surgeon and board-certified urologist, is the co-owner and Co-Medical Director of CSCTC. He is the most responsible individual at CSCTC Rancho Mirage and performs his duties there, within the jurisdiction of this Court. He manages all

firm employees at CSCTC Rancho Mirage. ("Pl. SOF," Dkt. No. 169-1 ¶ 3.)

3. Defendant Mark Berman, M.D., a board-certified cosmetic surgeon, is the co-owner and Co-Medical Director of CSCTC.[1] He performs his duties at the CSCTC Beverly Hills facility, within the jurisdiction of this Court. He is the most responsible individual at CSCTC Beverly Hills. (*Id.* ¶ 4.)

4. Defendant Cell Surgical Network Corporation ("CSN") is a California corporation founded and owned by Dr. Berman and Dr. Lander that is registered to do business at 72-780 Country Club Drive, Suite 301, Rancho Mirage, California 92270, the same address as CSCTC Rancho Mirage. (Stip. Facts ¶ 2.)

5. CSN operates a one-employee warehouse in Palm Desert, California, from which equipment and supplies are shipped to CSN affiliates. (*Id.* ¶ 3.)

6. Drs. Berman and Lander are the co-owners and Co-Medical Directors of CSN. They are also the co-owners of Cells On Ice, Inc., which has assisted in the recovery of adipose tissue sent outside of the State of California. (Pl. SOF ¶ 6.)

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[1] There have been news accounts of Mr. Berman's death in May 2022. The parties have not filed a judicially noticeable document verifying the accounts. The Court's Findings of Fact are written in light of the lack of verification.

B. The "SVF Surgical Procedure"

7. Defendants offer patients a treatment called the "SVF Surgical Procedure." In this procedure, a licensed physician targets stromal vascular fraction cells ("SVF Cells") for extraction and then implants those same cells that were removed back into the same patient during the same procedure. ("Defs. SOF," Dkt. No. 168-1 ¶ 1.)

8. SVF Cells are comprised of multiple cell types found within adipose tissue; these include mesenchymal stem cells ("MSC Cells"), hematopoietic cells, early (progenitors) and mature lineage stages of endothelia, pericyte progenitor cells (also called perivascular cells), red blood cells, white blood cells, lymphocytes, and fibroblasts among other cells. SVF Cells are the naturally occurring part of the adipose tissue that does not contain the adipocytes (fat cells). (*Id.* ¶ 2.)

9. Surgeons routinely work on both tissues and cells that make up tissues. Surgery universally involves dissection (cutting and separation) of tissues through mechanical or chemical means, and has evolved to where surgeons can isolate cells following removal from a patient's body. Dissected tissues and cells that have been isolated can be surgically relocated and re-purposed to other parts of a patient's body. (*Id.* ¶ 4.)

10. Surgery is intended for the treatment and prevention of disease in the human body. It can treat chronic and systemic conditions, and it is

intended to affect the structure or function of the human body. There are no FDA-approved or disapproved surgical procedures. (*Id.* ¶¶ 5-8.)

11. Accordingly, the surgical treatments at issue here have not been licensed or approved by the United States Food and Drug Administration. There are not now, nor have there ever been, any approved new drug applications for the surgical treatments ("NDAs") filed with FDA pursuant to 21 U.S.C. § 355(b) or (j). And there are not now, nor have there ever been any approved biologics license applications ("BLAs") filed with FDA pursuant to 42 U.S.C. § 262 for the treatments. (Stip. Facts ¶¶ 7-9.)

12. The SVF Surgical Procedure targets for removal mesenchymal stem cells and the hemopoietic or angiogenic stem cells located within the adipose tissue, not the adipose tissue itself. (Defs. SOF ¶ 10.)

13. The SVF Surgical Procedure involves collecting the patient's SVF Cells naturally contained in the patient's adipose tissue and relocating those SVF Cells back into the same patient. The SVF Cells are already in circulation within the body. The SVF Surgical Procedure increases the number of available SVF Cells in circulation or around an injured area. (*Id.* ¶ 11.)

14. The entire SVF Surgical Procedure, including the extraction, isolation, and reimplantation of SVF Cells occurs in California during a single, outpatient procedure at a surgical clinic. (*Id.* ¶ 12.)

15. During the SVF Surgical Procedure, a licensed physician collects the patient's SVF Cells using a technique called "mini-liposuction via subdermal local anesthesia," which permits the liposuction of the SVF Cells, along with the adipose and connective tissue that contains the SVF Cells, under local anesthesia. Many cells are mechanically separated ("mechanical cutting") from the adipose tissue during the liposuction procedure, as is common in all surgeries. Next, the removed adipose tissue is centrifuged to remove the anesthesia and to further mechanically dissociate the SVF Cells from the adipose tissue. The physician then uses surgical tools—namely, Liberase enzymes and a centrifuge device—to isolate the SVF Cells from adipocytes (fat cells). Finally, the SVF Cells are filtered through a hundred micron filter and viewed through a special micrograph to ensure that the SVF Cells are free-floating, round, and do not contain clumps of particles or debris. The SVF Cells are then suspended in a sterile saline solution, after which they are relocated back into the patient's body. Saline is a benign crystalloid, widely used in the practice of medicine. No new product is created by the use of saline as a delivery mechanism. (*Id.* ¶¶ 13-15, 21-22.)

16. All of the materials used to isolate SVF Cells during the SVF Surgical Procedure are FDA-approved drugs or FDA-cleared devices. (*Id.* ¶ 17.)

17. The SVF Cells are not altered, chemically or biologically, at any point during the SVF

Surgical Procedure. There are no genes added to or removed from the SVF Cells during the SVF Surgical Procedure. The SVF Surgical Procedure does not change the size or genetic makeup of the SVF Cells. The procedure does not alter the biological characteristics of the SVF cells, nor does it affect their ability to proliferate. (*Id.* ¶¶ 23-24.)

18. The SVF Surgical Procedure does not create any new material or introduce any foreign article into the body. Unlike manufactured drugs, the SVF Surgical Procedure does not create any cellular or tissue-based product that did not previously exist within the patient. (*Id.* ¶¶ 44.)

19. Drs. Berman and Lander are board certified surgeons. Drs. Berman and Lander and their practices are regulated by the State of California Medical Board. Dr. Berman's facility in Beverly Hills is accredited by the Accreditation Association for Ambulatory Health Care ("AAAHC") per California law. The operating rooms in which Drs. Berman and Lander perform the SVF Surgical Procedure comply with all health and safety standards established by the California State Medical Board for outpatient procedures. (*Id.* ¶¶ 51-52.)

C. The "Expanded MSC Surgical Procedure"

20. In addition to the SVF Surgical Procedure, Drs. Berman and Lander perform a procedure whereby a patient's adipose tissue is removed and sent to a GMP-compliant tissue bank to isolate MSC Cells. The MSC Cells are then

replicated and stored until the same patients request that they be returned for implantation into her body (the "Expanded MSC Surgical Procedure"). (*Id.* ¶ 61.)

21. During the Expanded MSC Surgical Procedure, a qualified candidate undergoes liposuction at either Dr. Berman or Dr. Lander's medical facilities. Drs. Berman and Lander do not perform the remainder of the SVF Surgical Procedure on the harvested adipose tissue but send the tissue to a GMP-compliant third party. (*Id.* ¶ 62.)

22. A patient is eligible for the Expanded MSC Surgical Procedure where the individual has a medical condition that will require multiple treatments, but the individual is unable or unwilling to undergo multiple liposuctions. (*Id.* ¶ 63.)

23. Drs. Berman and Lander do not adulterate, manufacture, process or store the patient's adipose tissue during the Expanded MSC Surgical Procedure. The third party isolates the MSC Cells from the adipose tissue using a technique that is similar to the SVF Surgical Procedure. The third party then places the MSC Cells in a culture, in which the MSC Cells naturally begin to replicate (i.e., expand in number), thereby creating a sufficient number of cells under GMP conditions for multiple treatments (the "Expanded MSC Cells"). Replication or propagation is a natural state for stem cells and the Expanded MSC Cells retain all of the biological characteristics of the MSC

Cells. The Expanded MSC Cells retain their cell markers, and do not differentiate while in the culture or during storage. The third-party tissue bank places the Expanded MSC Cells into a sterile vial labeled with the patient's name, date, and description pursuant to well-defined patient identifier protocols. The third-party tissue bank places the Expanded MSC Cells into a sterile vial labeled with the patient's name, date, and description pursuant to well-defined patient identifier protocols. (*Id.* ¶¶ 64-69.)

24. The Expanded MSC Cells are intended for autologous use, which refers to the "implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered." *See* 21 C.F.R. § 1271.3(a).

25. Defendants can (and do) administer the Expanded MSC Cells weeks, months, and even years after the patient's adipose tissue is removed. ("US SOF," Dkt. No. 169-1 ¶ 22.)

26. At the time of the inspection in 2017, Drs. Berman and Lander were sending the adipose tissue to American Cryostem ("ACS") for isolation of the MSC Cells and storage of the same. (Defs. SOF ¶ 71.)

27. Drs. Berman and Lander believed that ACS was a GMP facility based on ACS's representations. Drs. Berman and Lander ceased utilizing ACS in connection with the Expanded MSC Surgical Procedure following notice from the FDA that

ACS was not complying with GMP regulations. (*Id.* ¶ 72.)

28. The third party that Drs. Berman and Lander currently use is registered with the FDA and has been inspected by the FDA, with no resulting deficiency letters. (*Id.* ¶ 73.)

29. The Government did not present any evidence that Defendants are adulterating any material in connection with the Expanded MSC Surgical Procedure. (*Id.* ¶ 79.)

30. Only licensed practitioners can perform the Expanded MSC Surgical Procedure. (*Id.* ¶ 80.)

31. At all times, the vials containing the Expanded MSC Cells are labeled with the patient's name, date, and description pursuant to patient identifier protocols. (*Id.* ¶ 82.)

32. The Government did not present any evidence that Defendants label or mislabel any material regulated by the FDA in connection with the Expanded MSC Surgical Procedure. Nor did it present any evidence regarding the labeling Defendants receive from any GMP facility in connection with the Expanded MSC Surgical Procedure, or that any such labeling is deficient. (*Id.* ¶¶ 83-84.)

33. Drs. Berman and Lander do not charge for the Expanded MSC Cells; they only charge a surgical fee for the liposuction procedure. Patients paid a separate facility fee to the third party for the banking or storage of the Expanded MSC Cells. (*Id.* ¶¶ 85-86.)

D. The "SVF/ACAM2000 Treatment"

34. Drs. Berman and Lander partnered with StemImmune to study the safety of utilizing SVF Cells as a mechanism to deliver ACAM2000, an oncolytic virus, to cancer cells ("SVF/ACAM2000 Treatment"). (*Id.* ¶ 87.)

35. The SVF/ACAM2000 Treatment was a limited experimental treatment only available to individuals with terminal cancer for whom traditional treatment had failed. Drs. Berman and Lander would prepare the SVF Cells using their standard method, then add the ACAM2000 to the SVF Cells ACAM2000 ("SVF/ACAM2000 Cells"), before deploying into the same patient's body. (*Id.* ¶ 88.)

36. The combination of SVF and ACAM2000 Cells is a manufactured product. (Pls. SOF ¶ 160.)

37. ACAM2000 is an FDA-approved vaccine. (Defs. SOF ¶ 89.)

38. The federal government maintains exclusive control over ACAM2000 as part of the country's Strategic National Stockpile and it may only be distributed by specific government agencies. It is not publicly available, but researchers may request vials for studies. (*Id.* ¶ 91.)

39. Drs. Berman and Lander cannot perform the SVF/ACAM2000 Treatment without access to ACAM2000. (*Id.* ¶ 92.)

40. The FDA confiscated vials of ACAM2000 from StemImmune's laboratories at the University of California, San Diego in August 2017. Dr. Berman last performed the SVF/ACAM2000 Treatment before the FDA's 2017 confiscation. Dr. Lander last performed the SVF/ACAM2000

Treatment in June 2016. Drs. Berman and Lander have no desire or intention to perform the SVF/ACAM2000 Treatment outside of proper FDA regulatory approval or a determination that that SVF/ACAM2000 Cells are not a drug and do not fall under FDCA regulations. (*Id.* ¶ 94-97.) 41. The ACAM2000 that Defendants used for the SVF/ACAM2000 Surgical Procedure was shipped in interstate commerce from the Centers for Disease Control ("CDC") in Georgia. (Pls. SOF ¶ 173.)

42. The SVF/ACAM2000 Cells were not placed in any container for preservation, storage, or later use. (Defs. SOF ¶ 102.)

43. The SVF/ACAM2000 Treatment was performed at all times by Drs. Berman and Lander, who are licensed physicians. Drs. Berman and Lander performed the SVF/ACAM2000 Treatment pursuant to the IRB-approved study protocols, which included detailed step-by-step instructions on how to extract and isolate the SVF Cells, reconstitute the ACAM2000 vaccine, and implant the SVF/ACAM2000 Cells. (*Id.* ¶ 103.)

II. CONCLUSIONS OF LAW

A. General

1. The Federal Food, Drug, and Cosmetic Act ("FDCA") defines a drug as any "article," or component thereof, that is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or is "intended to affect the structure or any function of the body of man or other animals." *See* 21 U.S.C. § 321(g)(1)(B),

(C), and (D). However, surgical procedures—standard in the practice of medicine—are also intended for the diagnosis, cure, mitigation, treatment, or prevention of disease. When passing the FDCA, Congress explicitly rejected any attempt 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." 21 U.S.C. § 396. Indeed, Congress recognized the limitations of the FDA and rejected "any intent to directly regulate the practice of medicine." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 n.5 (2001).

2. The line between "drug" and "procedure" is especially muddy when licensed medical doctors enter a patient's body, extract that patient's cells, and reintroduce those cells to that patient after some amount of cellular processing. The United States argues that this scenario constitutes the production of FDCA drugs. Defendants argue that this is mere surgery, the exclusive province of the medical practitioners, and not something which the FDCA may regulate.

3. The Court concludes that neither Defendants' SVF Surgical Procedure nor its Expanded MSC Procedure are "drugs" within the meaning of the FDCA. In contrast, Defendants' SVF/ACAM2000 Treatment involves the creation of a drug under the FDCA.

4. Accordingly, the SVF Procedure and Expanded MSC Procedure are not subject to the FDCA's adulteration and misbranding provisions. *See* 21 U.S.C. §§ 351, 352; 21 C.F.R. § 1271.20; Final Rule Concerning Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5447, 5449 and 5456 (Jan. 19, 2001) (to be codified at 21 C.F.R. Part 1270).

5. Neither the SVF Procedure nor the Expanded MSC Procedure involves creating "prescription drugs" within the meaning of 21 U.S.C. § 353(b)(1)(A), nor does it involve creating "new drugs" within the meaning of 21 U.S.C. § 321(p).

6. Additionally, Defendants' SVF Procedure—but not the Expanded MSC Procedure—also qualifies for the Same Surgical Procedure Exception. The SSP Exception exempts from FDA oversight any "establishment that removes HCT/Ps from an individual and implants such HCT/Ps into the same individual during the same surgical procedure." 21 C.F.R. § 1271.15.

7. "HCT/Ps" is an acronym for "[h]uman cells, tissues, or cellular or tissue-based products," and HCT/Ps are defined in Section 1271.3(d) 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).

8. "Construction which gives effect to all of the words of a statute or regulation is preferred

over an interpretation which renders some of the statute or regulation ineffective." *First Charter Financial Corp. v. United States*, 669 F.2d 1342, 1350 (9th Cir. 1982) (internal citation omitted). The definition of HCT/Ps specifies that HCT/Ps are "articles containing ***or*** consisting of human cells or tissues," in the disjunctive, indicating that articles containing and articles consisting of human cells or tissues may be two different things. 21 C.F.R. § 1271.3(d) (emphasis added). The adipose tissue Defendants remove from patients clearly consists of human cells. And whatever is injected back into patients as part of Defendants' SVF Surgical Procedure and Expanded MSC Surgical Procedure certainly contains such cells.

9. Most critically, the definition of HCT/Ps states that HCT/Ps are "articles . . . ***intended for*** implantation, transplantation, infusion, or transfer into a human recipient." 21 C.F.R. § 1271.3(d) (emphasis added). The cellular products Defendants create in the course of all procedures at issue here are clearly intended for transfer back into human recipients.

10. Accordingly, SVF Cells removed from patients as part of Defendants' procedures are HCT/Ps. The adipose tissue Defendants remove from patients to produce their CSCTC products is an HCT/P. 21 C.F.R. § 1271.3(d).

11. Because the entire SVF Surgical Procedure, including the extraction, isolation, and reimplantation of SVF Cells occurs during a

single, outpatient procedure at a surgical clinic, Defendants' SVF Surgical Procedure involves introducing HCT/Ps back into patients during the "same surgical procedure," as they were extracted, triggering the SSP exception. 21 C.F.R. § 1271.15(b). The same is not true of the Expanded MSC Procedure. Though the cells extracted for both the SVF Surgical Procedure and the Expanded MSC Procedure are HCT/Ps, only the SVF Surgical Procedure qualifies for the SSP Exception.

B. The SVF Surgical Procedure

12. For Claim One, the Government must prove: (1) that the SVF Surgical Procedure involves a drug, (2) that the SVF Surgical Procedure involves a drug that is held for sale in interstate commerce; and (3) that the methods used in, or the facilities or controls used for, the manufacture of the drug are not in conformity with current Good Manufacturing Practices ("cGMP"). 21 U.S.C. §§ 331(k), 352(a)(2)(B).

13. For Claim Two, the Government must prove: (1) that the SVF Surgical Procedure involves a drug, (2) that the SVF Surgical Procedure involves a drug that is held for sale in interstate commerce; and (3) that it does not contain adequate directions for use or the symbol "Rx." 21 U.S.C. §§ 352(f), 352(b)(2).

14. The Same Surgical Procedure Exception ("SSP Exception") is a complete defense to Claims One and Two, and Defendants have established that the SSP Exception applies to the SVF Surgical Procedure.

15. Additionally and alternatively, the Government failed to carry its burden because the SVF Surgical Procedure is not a drug.

16. In evaluating whether the SVF Surgical Procedure satisfies the requirements of the SSP Exception, the appropriate focus is on the SVF Cells. The SSP Exception unambiguously states that the focus is on the target of the removal—either the cell or the tissue—rather than the largest system removed. This is the only permissible interpretation of the SSP Exception, which explicitly includes both "tissues" and/or "cells," through its use of the term "HCT/Ps." *See* 21 C.F.R. §§ 1271.3(d); 1271.15(b). Cells can only be removed from a patient along with larger systems, such as the tissues or organs that they comprise. Focusing on the "tissue" removed while ignoring the target "cells" would eliminate the word "cells" from HCT/Ps and violate the canons of statutory construction.

17. The SVF Surgical Procedure is autologous because it involves collecting a patient's cell population naturally occurring in the patient's adipose tissue and relocating that cell population back into the same patient.

18. The SSP Exception does not have any requirement that the HCT/Ps be unaltered before reinsertion into the patient . *See* 21 C.F.R. § 1271.15(b). Any reference to whether the HCT/Ps are manipulated and/or altered are located in a different, inapplicable, regulation

21 C.F.R. § 1271.10 (discussing "minimal manipulation").

19. Regardless, the SVF Surgical Procedure does not alter the biological characteristics of the SVF Cells and those cells remain "such HCT/P" that were removed from the patient. There is no evidence that the cells are anything other than autologous cells removed from, belonging to, and returned back to the patient.

20. The GMP-grade Liberase enzyme used by Defendants does not affect ability of the SVF Cells to differentiate. When Liberase is used on SVF Cells, their cell surface marker expression remains similar, and their viability does not significantly change.

21. The Court finds that Dr. Berman and Dr. Lander are well qualified to opine and testify on the practice of medicine, development of surgical procedures, the SVF Surgical Procedure, and the effect of Liberase on the SVF Cells. The Court finds Defendants' evidence and testimony more credible than Dr. Yong given her failure to analyze the appropriate enzyme. Further, Defendants have actually tested the product at issue (as published in a peer-reviewed journal), while the Government has never collected a sample or tested the SVF Cells or Liberase.

22. In conclusion, the SSP Exception applies to the SVF Surgical Procedure and is a complete defense to Claims One and Two. Because the SSP Exception applies to the SVF Surgical Procedure, Defendants do not fall under FDA

jurisdiction and are not governed by the FDCA or associated regulations; therefore, the Government is not entitled to injunctive relief against Defendants.

23. Further, the SSP Exception is unambiguous, thus there is no need for deference to the FDA's interpretation. *See Kisor v. Wilkie*, 139 S. Ct. 2400, 2414 (2019) ("[T]he possibility of deference can arise only if a regulation is genuinely ambiguous."); *Christensen v. Harris Cnty.*, 529 US 576, 588 (2000) ("The regulation in this case, however, is not ambiguous . . . . To defer to the agency's position would be to permit the agency, under the guise of interpreting a regulation, to create de facto a new regulation.").

24. The SSP Exception does not require that the surgeon implant everything that was removed—including the removed blood and excess artery—for it to apply. The SSP Exception Guidance expressly recognizes that processing steps such as "rinsing [and] cleansing" or "sizing and shaping," including "dilation," "cutting," "meshing," of HCT/Ps do not take a procedure out of the SSP Exception. *See* Food & Drug Admin., Regulatory Considerations.

25. Drs. Berman and Lander may lawfully use FDA-cleared medical devices and FDA-approved pharmaceuticals in any manner that they determine is best to care for and treat their patients. Each step of the SVF Surgical Procedure uses FDA-cleared and/or approved

medical devices and pharmaceuticals. *See* 21 U.S.C. § 396.

C. The Expanded MSC Surgical Procedure

26. For Claim Three, the Government must prove: (1) that the Expanded MSC Surgical Procedure involves a drug, (2) that the Expanded MSC Surgical Procedure involves a drug that is held for sale in interstate commerce; and (3) that the methods used in, or the facilities or controls used for, the manufacture of the drug are not in conformity with current Good Manufacturing Practices ("cGMP"). 21 U.S.C. §§ 331(k), 352(a)(2)(B).

27. For Claim Four, the Government must prove: (1) that the Expanded MSC Surgical Procedure involves a drug, (2) that the Expanded MSC Surgical Procedure involves a drug that is held for sale in interstate commerce; and (3) that it does not contain adequate directions for use of the symbol "Rx." 21 U.S.C. §§ 352(f), 352(b)(2).

28. For Claim Five, the Government must prove: (1) that the Expanded MSC Surgical Procedure involves a drug, (2) that the Expanded MSC Surgical Procedure involves a drug that is held for sale in interstate commerce; and (3) Defendants received a misbranded drug for pay or otherwise.

29. As a threshold matter, the cells involved in the Expanded MSC Surgical Procedure are not drugs. They are human cells removed from patients and then reintroduced into those same patients. They are not fungible goods that can

be sold, mass produced, or patented. *See Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 579 (2013) (holding that naturally-occurring human body parts that are a "product of nature and not patent eligible merely because it has been isolated.").

30. Defendants are engaged in the practice of medicine, not the manufacture of pharmaceuticals.

D. The SVF/ACAM2000 Treatment

31. For Claim Six, the Government must prove: that (1) the SVF/ACAM2000 Treatment involves a drug, (2) the SVF/ACAM2000 Treatment involves a drug that is held for sale in interstate commerce; and (3) the methods used in, or the facilities or controls used for, the manufacture of the drug are not in conformity with current Good Manufacturing Practices ("cGMP"). 21 U.S.C. §§ 331(k), 352(a)(2)(B).

32. For Claim Seven, the Government must prove: (1) that the SVF/ACAM2000 Treatment involves a drug, (2) that the SVF/ACAM2000 Surgical Procedure involves a drug that is held for sale in interstate commerce; and (3) that it does not contain adequate directions for use of the symbol "Rx." 21 U.S.C. §§ 352(f), 352(b)(2).

33. Unlike the SVF Surgical Procedure, the SVF/ACAM2000 Treatment constitutes the manufacture of a drug.

34. Because the ACAM2000 was shipped in interstate commerce from Georgia, the Court finds that the SVF/ACAM2000 Treatment

satisfies section 331(k)'s "after shipment in interstate commerce" requirement.

35. However, the Government has not met its burden of establishing standing to pursue injunctive relief regarding the SVF/ACAM2000 Treatment because Drs. Berman and Lander stopped performing the treatment by June 2017, before the initiation of this lawsuit and before the seizure of the ACAM2000. Defendants cannot perform the SVF/ACAM2000 Treatment without the ACAM2000, which is in the exclusive control of the Government and otherwise inaccessible to Defendants. Drs. Berman and Lander have no desire to or intention of performing the SVF/ACAM2000 Treatment absent formal regulatory approval.

E. Attorneys' Fees

36. The Court declines to award attorneys' fees to Defendants.

37. Congress enacted the Equal Access to Justice Act under 28 U.S.C. § 2412 ("Section 2412") to limit the United States government's immunity to an award for costs and fees. Section 2412 was designed as a gap-filler and applies in the absence of another statute that addresses the issue of attorneys' fees in the case at issue. 28 U.S.C. § 2412(b), (d) ("except as otherwise specifically provided by statute . . ."). Section 2412 is generally applicable whenever the federal government is a party in a civil action. 28 U.S.C. § 2412(d). Given the Government's vast resources and power, Congress determined

that parties should be entitled to attorneys' fees where the Government lacks substantial justification for bringing a civil action. Accordingly, Section 2412(d) permits a court to award attorneys' fees and other expenses to a prevailing party unless the Court finds that the Government was "substantially justified." The Supreme Court has concluded that the standard for substantial justification is no different than a "reasonable basis" test. *Pierce v. Underwood*, 487 U.S. 552, 565 (1988). The Court makes one determination regarding the action as a whole, not to each cause of action. *See Ibrahim v. U.S. Dept. of Homeland Sec.*, 835 F.3d 1048, 1054–57 (2016) (holding that court's decision regarding substantial justification requires a "single inquiry focused on the government's conduct in the case as a whole").

38. Though the Court finds that the SVF Surgical Procedure and Expanded MSC Procedure to not be drugs, and that the SSP Exception unambiguously applies to the SVF Surgical Procedure, other courts have concluded otherwise. *See United States v. U.S. Stem Cell Clinic, LLC*, 403 F. Supp. 3d 1279 (S.D. Fla. 2019). The Government had a reasonable basis to commence this suit, and accordingly, an award of attorneys' fees is not warranted.

Dated: August 30, 2022

THE HONORABLE JESUS G. BERNAL
United States District Judge

APPENDIX D

§ 321. DEFINITIONS; GENERALLY

For the purposes of this chapter—

(a)(1) The term "State", except as used in the last sentence of section 372(a) of this title, means any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico.

(2) The term "Territory" means any Territory or possession of the United States, including the District of Columbia, and excluding the Commonwealth of Puerto Rico and the Canal Zone.

(b) The term "interstate commerce" means (1) commerce between any State or Territory and any place outside thereof, and (2) commerce within the District of Columbia or within any other Territory not organized with a legislative body.

(c) The term "Department" means Department of Health and Human Services.

(d) The term "Secretary" means the Secretary of Health and Human Services.

(e) The term "person" includes individual, partnership, corporation, and association.

(f) The term "food" means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article.

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

(2) The term "counterfeit drug" means a drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely

purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor.

(h)(1) The term "device" (except when used in paragraph (n) of this section and in sections 331(i), 343(f), 352(c), and 362(c) of this title) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

(A) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(B) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(C) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 360j(o) of this title.

(2) The term "counterfeit device" means a device which, or the container, packaging, or labeling of which, without authorization, bears a trademark, trade name, or other identifying

mark or imprint, or any likeness thereof, or is manufactured using a design, of a device manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such device and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other device manufacturer, processor, packer, or distributor.

(i) The term "cosmetic" means (1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap.

(j) The term "official compendium" means the official United States Pharmacopœia, official Homœopathic Pharmacopœia of the United States, official National Formulary, or any supplement to any of them.

(k) The term "label" means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this chapter that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the

retail package of such article, or is easily legible through the outside container or wrapper.

(l) The term "immediate container" does not include package liners.

(m) The term "labeling" means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.

(n) If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

(o) The representation of a drug, in its labeling, as an antiseptic shall be considered to be a representation that it is a germicide, except in the case of a drug purporting to be, or represented as, an antiseptic for inhibitory use as a wet dressing, ointment, dusting powder, or such other use as involves prolonged contact with the body.

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

(q)(1)(A) Except as provided in clause (B), the term "pesticide chemical" means any substance that is a pesticide within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act, including all active and inert ingredients of such pesticide. Notwithstanding any other provision of law, the term "pesticide" within

such meaning includes ethylene oxide and propylene oxide when such substances are applied on food.

(B) In the case of the use, with respect to food, of a substance described in clause (A) to prevent, destroy, repel, or mitigate microorganisms (including bacteria, viruses, fungi, protozoa, algae, and slime), the following applies for purposes of clause (A):

(i) The definition in such clause for the term "pesticide chemical" does not include the substance if the substance is applied for such use on food, or the substance is included for such use in water that comes into contact with the food, in the preparing, packing, or holding of the food for commercial purposes. The substance is not excluded under this subclause from such definition if the substance is ethylene oxide or propylene oxide, and is applied for such use on food. The substance is not so excluded if the substance is applied for such use on a raw agricultural commodity, or the substance is included for such use in water that comes into contact with the commodity, as follows:

(I) The substance is applied in the field.

(II) The substance is applied at a treatment facility where raw agricultural commodities are the only food treated, and the treatment is in a

manner that does not change the status of the food as a raw agricultural commodity (including treatment through washing, waxing, fumigating, and packing such commodities in such manner).

(III) The substance is applied during the transportation of such commodity between the field and such a treatment facility.

(ii) The definition in such clause for the term "pesticide chemical" does not include the substance if the substance is a food contact substance as defined in section 348(h)(6) of this title, and any of the following circumstances exist: The substance is included for such use in an object that has a food contact surface but is not intended to have an ongoing effect on any portion of the object; the substance is included for such use in an object that has a food contact surface and is intended to have an ongoing effect on a portion of the object but not on the food contact surface; or the substance is included for such use in or is applied for such use on food packaging (without regard to whether the substance is intended to have an ongoing effect on any portion of the packaging). The food contact substance is not excluded under this subclause from such definition if any of the following circumstances exist: The substance is applied for such use on a

semipermanent or permanent food contact surface (other than being applied on food packaging); or the substance is included for such use in an object that has a semipermanent or permanent food contact surface (other than being included in food packaging) and the substance is intended to have an ongoing effect on the food contact surface. With respect to the definition of the term "pesticide" that is applicable to the Federal Insecticide, Fungicide, and Rodenticide Act, this clause does not exclude any substance from such definition.

(2) The term "pesticide chemical residue" means a residue in or on raw agricultural commodity or processed food of—

(A) a pesticide chemical; or

(B) any other added substance that is present on or in the commodity or food primarily as a result of the metabolism or other degradation of a pesticide chemical.

(3) Notwithstanding subparagraphs (1) and (2), the Administrator may by regulation except a substance from the definition of "pesticide chemical" or "pesticide chemical residue" if—

(A) its occurrence as a residue on or in a raw agricultural commodity or processed food is attributable primarily to natural causes or to human activities not involving the use of any substances for a pesticidal purpose in the production, storage, processing, or

transportation of any raw agricultural commodity or processed food; and

(B) the Administrator, after consultation with the Secretary, determines that the substance more appropriately should be regulated under one or more provisions of this chapter other than sections 342(a)(2)(B) and 346a of this title.

(r) The term "raw agricultural commodity" means any food in its raw or natural state, including all fruits that are washed, colored, or otherwise treated in their unpeeled natural form prior to marketing.

(s) The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include—

(1) a pesticide chemical residue in or on a raw agricultural commodity or processed food; or

(2) a pesticide chemical; or

(3) a color additive; or

(4) any substance used in accordance with a sanction or approval granted prior to September 6, 1958, pursuant to this chapter, the Poultry Products Inspection Act or the Meat Inspection Act of March 4, 1907, as amended and extended;

(5) a new animal drug; or

(6) an ingredient described in paragraph (ff) in, or intended for use in, a dietary supplement.

(t)(1) The term "color additive" means a material which—

(A) is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source, and

(B) when added or applied to a food, drug, or cosmetic, or to the human body or any part thereof, is capable (alone or through reaction with other substance) of imparting color thereto;

except that such term does not include any material which the Secretary, by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring.

(2) The term "color" includes black, white, and intermediate grays.

(3) Nothing in subparagraph (1) of this paragraph shall be construed to apply to any pesticide chemical, soil or plant nutrient, or other agricultural chemical solely because of its effect in aiding, retarding, or otherwise affecting, directly or indirectly, the growth or other natural physiological processes of produce of the soil and thereby affecting its color, whether before or after harvest.

(u) The term "safe" as used in paragraph (s) of this section and in sections 348, 360b, 360ccc, and 379e of this title, has reference to the health of man or animal.

(v) The term "new animal drug" means any drug intended for use for animals other than man, including any drug intended for use in animal feed but not including such animal feed,—

(1) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof; except that such a drug not so recognized shall not be deemed to be a "new animal drug" if at any time prior to June 25, 1938, it was subject to the Food and Drug Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) the composition of which is such that such drug, as a result of investigations to determine

its safety and effectiveness for use under such conditions, has become so recognized but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions. Provided that any drug intended for minor use or use in a minor species that is not the subject of a final regulation published by the Secretary through notice and comment rulemaking finding that the criteria of paragraphs (1) and (2) have not been met (or that the exception to the criterion in paragraph (1) has been met) is a new animal drug.

(w) The term "animal feed", as used in paragraph (w) of this section, in section 360b of this title, and in provisions of this chapter referring to such paragraph or section, means an article which is intended for use for food for animals other than man and which is intended for use as a substantial source of nutrients in the diet of the animal, and is not limited to a mixture intended to be the sole ration of the animal.

(x) The term "informal hearing" means a hearing which is not subject to section 554, 556, or 557 of Title 5 and which provides for the following:

(1) The presiding officer in the hearing shall be designated by the Secretary from officers and employees of the Department who have not participated in any action of the Secretary which is the subject of the hearing and who are not directly responsible to an officer or employee of the Department who has participated in any such action.

(2) Each party to the hearing shall have the right at all times to be advised and accompanied by an attorney.

(3) Before the hearing, each party to the hearing shall be given reasonable notice of the matters to be considered at the hearing, including a comprehensive statement of the basis for the action taken or proposed by the Secretary which is the subject of the hearing and a general summary of the information which will be presented by the Secretary at the hearing in support of such action.

(4) At the hearing the parties to the hearing shall have the right to hear a full and complete statement of the action of the Secretary which is the subject of the hearing together with the information and reasons supporting such action, to conduct reasonable questioning, and to present any oral or written information relevant to such action.

(5) The presiding officer in such hearing shall prepare a written report of the hearing to which shall be attached all written material presented at the hearing. The participants in the hearing shall be given the opportunity to review and correct or supplement the presiding officer's report of the hearing.

(6) The Secretary may require the hearing to be transcribed. A party to the hearing shall have the right to have the hearing transcribed at his expense. Any transcription of a hearing shall be included in the presiding officer's report of the hearing.

(y) The term "saccharin" includes calcium saccharin, sodium saccharin, and ammonium saccharin.

(z) The term "infant formula" means a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk.

(aa) The term "abbreviated drug application" means an application submitted under section 355(j) of this title for the approval of a drug that relies on the approved application of another drug with the same active ingredient to establish safety and efficacy, and—

(1) in the case of section 335a of this title, includes a supplement to such an application for a different or additional use of the drug but does not include a supplement to such an application for other than a different or additional use of the drug, and

(2) in the case of sections 335b and 335c of this title, includes any supplement to such an application.

(bb) The term "knowingly" or "knew" means that a person, with respect to information—

(1) has actual knowledge of the information, or

(2) acts in deliberate ignorance or reckless disregard of the truth or falsity of the information.

(cc) For purposes of section 335a of this title, the term "high managerial agent"—

(1) means—

(A) an officer or director of a corporation or an association,

(B) a partner of a partnership, or

(C) any employee or other agent of a corporation, association, or partnership,

having duties such that the conduct of such officer, director, partner, employee, or agent may fairly be assumed to represent the policy of the corporation, association, or partnership, and

(2) includes persons having management responsibility for—

(A) submissions to the Food and Drug Administration regarding the development or approval of any drug product,

(B) production, quality assurance, or quality control of any drug product, or

(C) research and development of any drug product.

(dd) For purposes of sections 335a and 335b of this title, the term "drug product" means a drug subject to regulation under section 355, 360b, or 382 of this title or under section 262 of Title 42.

(ee) The term "Commissioner" means the Commissioner of Food and Drugs.

(ff) The term "dietary supplement"—

(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

(A) a vitamin;

(B) a mineral;

(C) an herb or other botanical;

(D) an amino acid;

(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or

(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);

(2) means a product that—

(A)(i) is intended for ingestion in a form described in section 350(c)(1)(B)(i) of this title; or

(ii) complies with section 350(c)(1)(B)(ii) of this title;

(B) is not represented for use as a conventional food or as a sole item of a meal or the diet; and

(C) is labeled as a dietary supplement; and

(3) does—

(A) include an article that is approved as a new drug under section 355 of this title or licensed as a biologic under section 262 of Title 42 and was, prior to such approval, certification, or license, marketed as a dietary supplement or as a food unless the Secretary has issued a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful under section 342(f) of this title; and

(B) not include—

(i) an article that is approved as a new drug under section 355 of this title, certified as an antibiotic under section 357 of this title, or licensed as a biologic under section 262 of Title 42, or

(ii) an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter.

Except for purposes of paragraph (g) and section 350f of this title, a dietary supplement shall be deemed to be a food within the meaning of this chapter.

(gg) The term "processed food" means any food other than a raw agricultural commodity and includes any raw agricultural commodity that has been subject to processing, such as canning, cooking, freezing, dehydration, or milling.

(hh) The term "Administrator" means the Administrator of the United States Environmental Protection Agency.

(ii) The term "compounded positron emission tomography drug" —

(1) means a drug that—

(A) exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for the purpose of providing dual photon positron emission tomographic diagnostic images; and

(B) has been compounded by or on the order of a practitioner who is licensed by a State to compound or order compounding for a drug described in subparagraph (A), and is compounded in accordance with that State's law, for a patient or for research, teaching, or quality control; and

(2) includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of such a drug.

(jj) The term "antibiotic drug" means any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof.

(kk) Priority supplement

The term "priority supplement" means a drug application referred to in section 101(4) of the Food and Drug Administration Modernization Act of 1997 (111 Stat. 2298).

***(ll)*(1)** The term "single-use device" means a device that is intended for one use, or on a single patient during a single procedure.

(2)(A) The term "reprocessed", with respect to a single-use device, means an original device that has previously been used on a patient and has been subjected to additional processing and manufacturing for the purpose of an additional single use on a patient. The subsequent processing and manufacture of a reprocessed single-use device shall result in a device that is reprocessed within the meaning of this definition.

(B) A single-use device that meets the definition under clause (A) shall be considered a reprocessed device without regard to any description of the device used by the manufacturer of the device or other persons, including a description that uses the term "recycled" rather than the term "reprocessed".

(3) The term "original device" means a new, unused single-use device.

(mm)(1) The term "critical reprocessed single-use device" means a reprocessed single-use device that is intended to contact normally sterile tissue or body spaces during use.

(2) The term "semi-critical reprocessed single-use device" means a reprocessed single-use device that is intended to contact intact mucous membranes and not penetrate normally sterile areas of the body.

(nn) The term "major species" means cattle, horses, swine, chickens, turkeys, dogs, and cats, except that the Secretary may add species to this definition by regulation.

(oo) The term "minor species" means animals other than humans that are not major species.

(pp) The term "minor use" means the intended use of a drug in a major species for an indication that occurs infrequently and in only a small number of animals or in limited geographical areas and in only a small number of animals annually.

(qq) The term "major food allergen" means any of the following:

(1) Milk, egg, fish (e.g., bass, flounder, or cod), Crustacean shellfish (e.g., crab, lobster, or shrimp), tree nuts (e.g., almonds, pecans, or walnuts), wheat, peanuts, soybeans, and sesame.

(2) A food ingredient that contains protein derived from a food specified in paragraph (1), except the following:

(A) Any highly refined oil derived from a food specified in paragraph (1) and any ingredient derived from such highly refined oil.

(B) A food ingredient that is exempt under paragraph (6) or (7) of section 343(w) of this title.

(rr)(1) The term "tobacco product" means any product made or derived from tobacco, or containing nicotine from any source, that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product).

(2) The term "tobacco product" does not mean an article that is a drug under subsection (g)(1), a device under subsection (h), or a combination product described in section 353(g) of this title.

(3) The products described in paragraph (2) shall be subject to subchapter V of this chapter.

(4) A tobacco product shall not be marketed in combination with any other article or product regulated under this chapter (including a drug, biologic, food, cosmetic, medical device, or a dietary supplement).

(5) The term "tobacco product" does not mean an article that is a food under paragraph (f), if such article contains no nicotine, or no more than trace amounts of naturally occurring nicotine.

(ss) The term "critical food" means a food that is—

(1) an infant formula; or

(2) a medical food, as defined in section 360ee(b)(3) of this title.

APPENDIX E

42 U.S.C.A. § 262

§ 262. REGULATION OF BIOLOGICAL PRODUCTS

(a) Biologics license

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

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

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

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

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

(iii) the expiration date of the biological product.

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

(B) Pediatric studies

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

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

(i) on the basis of a demonstration that—

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

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

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

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

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

(E)(i) The Secretary may rely upon qualified data summaries to support the approval of a supplemental application, with respect to a qualified indication for a drug, submitted under this subsection, if such supplemental application complies with the requirements of subparagraph (B) of section 505(c)(5) of the Federal Food, Drug, and Cosmetic Act.

(ii) In this subparagraph, the terms "qualified indication" and "qualified data summary" have the meanings given such terms in section 505(c)(5) of the Federal Food, Drug, and Cosmetic Act.

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

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

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

(c) Inspection of establishment for propagation and preparation

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

(d) Recall of product presenting imminent hazard; violations

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

be issued in accordance with section 554 of Title 5.

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

(e) Interference with officers

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

(f) Penalties for offenses

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

(g) Construction with other laws

Nothing contained in this chapter shall be construed as in any way affecting, modifying, repealing, or superseding the provisions of the Federal Food, Drug, and Cosmetic Act.

(h) Exportation of partially processed biological products

A partially processed biological product which—

(1) is not in a form applicable to the prevention, treatment, or cure of diseases or injuries of man;

(2) is not intended for sale in the United States; and

(3) is intended for further manufacture into final dosage form outside the United States, shall be subject to no restriction on the export of the product under this chapter or the Federal Food, Drug, and Cosmetic Act if the product is manufactured, processed, packaged, and held in conformity with current good manufacturing practice requirements or meets international manufacturing standards as certified by an international standards organization recognized by the Secretary and meets the requirements of section 801(e)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 381(e)).

(i) "Biological product" defined

In this section:

(1) The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine

(or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

(2) The term "biosimilar" or "biosimilarity", in reference to a biological product that is the subject of an application under subsection (k), means—

(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and

(B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

(3) The term "interchangeable" or "interchangeability", in reference to a biological product that is shown to meet the standards described in subsection (k)(4), means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

(4) The term "reference product" means the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k).

(j) Application of Federal Food, Drug, and Cosmetic Act

The Federal Food, Drug, and Cosmetic Act, including the requirements under sections 505(o), 505(p), and 505-1 of such Act, applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505 of such Act.

(k) Licensure of biological products as biosimilar or interchangeable

(1) In general

Any person may submit an application for licensure of a biological product under this subsection.

(2) Content

(A) In general

(i) Required information

An application submitted under this subsection shall include information demonstrating that—

(I) the biological product is biosimilar to a reference product based upon data derived from—

(aa) analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;

(bb) an assessment of toxicity (which may rely on, or consist of, a

study or studies described in item (aa) or (cc)); and

(cc) a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product;

(II) the biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product;

(III) the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product;

(IV) the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product; and

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

(ii) Determination by Secretary

The Secretary may determine, in the Secretary's discretion, that an element described in clause (i)(I) is unnecessary in an application submitted under this subsection.

(iii) Additional information

An application submitted under this subsection—

(I) shall include publicly-available information regarding the Secretary's previous determination that the reference product is safe, pure, and potent;

(II) may include any additional information in support of the application, including publicly-available information with respect to the reference product or another biological product; and

(III) may include information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product.

(B) Interchangeability

An application (or a supplement to an application) submitted under this subsection may include information demonstrating that the biological product meets the standards described in paragraph (4).

(3) Evaluation by Secretary

Upon review of an application (or a supplement to an application) submitted under this subsection, the Secretary shall license the biological product under this subsection if—

(A) the Secretary determines that the information submitted in the application (or the supplement) is sufficient to show that the biological product—

(i) is biosimilar to the reference product; or

(ii) meets the standards described in paragraph (4), and therefore is interchangeable with the reference product; and

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

(4) Safety standards for determining interchangeability

Upon review of an application submitted under this subsection or any supplement to such application, the Secretary shall determine the biological product to be interchangeable with the reference product if the Secretary

determines that the information submitted in the application (or a supplement to such application) is sufficient to show that—

(A) the biological product—

(i) is biosimilar to the reference product; and

(ii) can be expected to produce the same clinical result as the reference product in any given patient; and

(B) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

(5) General rules

(A) One reference product per application

A biological product, in an application submitted under this subsection, may not be evaluated against more than 1 reference product.

(B) Review

An application submitted under this subsection shall be reviewed by the division within the Food and Drug Administration that is responsible for the review and approval of the application under which the reference product is licensed.

(C) Risk evaluation and mitigation strategies

The authority of the Secretary with respect to risk evaluation and mitigation strategies under the Federal Food, Drug, and Cosmetic Act shall apply to biological products licensed under this subsection in the same manner as such authority applies to biological products licensed under subsection (a).

(6) Exclusivity for first interchangeable biological product

The Secretary shall not make approval as an interchangeable biological product effective with respect to an application submitted under this subsection that relies on the same reference product for which a prior biological product has received a determination of interchangeability for any condition of use, until the earlier of—

(A) 1 year after the first commercial marketing of the first interchangeable biosimilar biological product to be approved as interchangeable for that reference product;

(B) 18 months after—

(i) a final court decision on all patents in suit in an action instituted under subsection (l)(6) against the applicant that submitted the application for the first approved interchangeable biosimilar biological product; or

(ii) the dismissal with or without prejudice of an action instituted under subsection (l)(6) against the applicant that submitted the application for the first approved interchangeable biosimilar biological product; or

(C)(i) 42 months after approval of the first interchangeable biosimilar biological product if the applicant that submitted such application has been sued under subsection (l)(6) and such litigation is still ongoing within such 42-month period; or

(ii) 18 months after approval of the first interchangeable biosimilar biological product if the applicant that submitted such application has not been sued under subsection (l)(6).

For purposes of this paragraph, the term "final court decision" means a final decision of a court from which no appeal (other than a petition to the United States Supreme Court for a writ of certiorari) has been or can be taken, and the term "first interchangeable biosimilar biological product" means any interchangeable biosimilar biological product that is approved on the first day on which such a product is approved as interchangeable with the reference product.

(7) Exclusivity for reference product

(A) Effective date of biosimilar application approval

Approval of an application under this subsection may not be made effective by the Secretary until the date that is 12 years

after the date on which the reference product was first licensed under subsection (a).

(B) Filing period

An application under this subsection may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed under subsection (a).

(C) First licensure

Subparagraphs (A) and (B) shall not apply to a license for or approval of—

(i) a supplement for the biological product that is the reference product; or

(ii) a subsequent application filed by the same sponsor or manufacturer of the biological product that is the reference product (or a licensor, predecessor in interest, or other related entity) for—

(I) a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or

(II) a modification to the structure of the biological product that does not result in a change in safety, purity, or potency.

(D) Deemed licenses

(i) No additional exclusivity through deeming

An approved application that is deemed to be a license for a biological product under this section pursuant to section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009 shall not be treated as having been first licensed under subsection (a) for purposes of subparagraphs (A) and (B).

(ii) Application of limitations on exclusivity

Subparagraph (C) shall apply with respect to a reference product referred to in such subparagraph that was the subject of an approved application that was deemed to be a license pursuant to section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009.

(iii) Applicability

The exclusivity periods described in section 527, section 505A(b)(1)(A)(ii), and section 505A(c)(1)(A)(ii) of the Federal Food, Drug, and Cosmetic Act shall continue to apply to a biological product after an approved application for the biological product is deemed to be a license for the biological product under subsection (a) pursuant to section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009.

(8) Guidance documents

(A) In general

The Secretary may, after opportunity for public comment, issue guidance in accordance, except as provided in subparagraph (B)(i), with section 701(h) of the Federal Food, Drug, and Cosmetic Act with respect to the licensure of a biological product under this subsection. Any such guidance may be general or specific.

(B) Public comment

(i) In general

The Secretary shall provide the public an opportunity to comment on any proposed guidance issued under subparagraph (A) before issuing final guidance.

(ii) Input regarding most valuable guidance

The Secretary shall establish a process through which the public may provide the Secretary with input regarding priorities for issuing guidance.

(C) No requirement for application consideration

The issuance (or non-issuance) of guidance under subparagraph (A) shall not preclude the review of, or action on, an application submitted under this subsection.

(D) Requirement for product class-specific guidance

If the Secretary issues product class-specific guidance under subparagraph (A), such guidance shall include a description of—

(i) the criteria that the Secretary will use to determine whether a biological product is highly

similar to a reference product in such product class; and

(ii) the criteria, if available, that the Secretary will use to determine whether a biological product meets the standards described in paragraph (4).

(E) Certain product classes

(i) Guidance

The Secretary may indicate in a guidance document that the science and experience, as of the date of such guidance, with respect to a product or product class (not including any recombinant protein) does not allow approval of an application for a license as provided under this subsection for such product or product class.

(ii) Modification or reversal

The Secretary may issue a subsequent guidance document under subparagraph (A) to modify or reverse a guidance document under clause (i).

(iii) No effect on ability to deny license

Clause (i) shall not be construed to require the Secretary to approve a product with respect to which the Secretary has not indicated in a guidance document that the science and experience, as described in clause (i), does not allow approval of such an application.

(9) Public listing

(A) In general

(i) Initial publication

Not later than 180 days after December 27, 2020, the Secretary shall publish and make

available to the public in a searchable, electronic format—

(I) a list of each biological product, by nonproprietary name (proper name), for which, as of December 27, 2020, a biologics license under subsection (a) or this subsection is in effect, or that, as of such date of enactment, is deemed to be licensed under this section pursuant to section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009;

(II) the date of licensure of the marketing application and the application number; and

(III) with respect to each biological product described in subclause (I), the licensure status, and, as available, the marketing status.

(ii) Revisions

Every 30 days after the publication of the first list under clause (i), the Secretary shall revise the list to include each biological product which has been licensed under subsection (a) or this subsection during the 30-day period or deemed licensed under this section pursuant to section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009.

(iii) Patent information

Not later than 30 days after a list of patents under subsection (l)(3)(A), or a supplement to such list under subsection (l)(7), has been provided by the reference product sponsor to the subsection (k) applicant respecting a biological product included on the list published under this subparagraph, the reference product sponsor shall provide such

list of patents (or supplement thereto) and their corresponding expiry dates to the Secretary, and the Secretary shall, in revisions made under clause (ii), include such information for such biological product. Within 30 days of providing any subsequent or supplemental list of patents to any subsequent subsection (k) applicant under subsection (l)(3)(A) or (l)(7), the reference product sponsor shall update the information provided to the Secretary under this clause with any additional patents from such subsequent or supplemental list and their corresponding expiry dates.

(iv) Listing of exclusivities

For each biological product included on the list published under this subparagraph, the Secretary shall specify each exclusivity period under paragraph (6) or paragraph (7) for which the Secretary has determined such biological product to be eligible and that has not concluded.

(B) Revocation or suspension of license

If the license of a biological product is determined by the Secretary to have been revoked or suspended for safety, purity, or potency reasons, it may not be published in the list under subparagraph (A). If such revocation or suspension occurred after inclusion of such biological product in the list published under subparagraph (A), the reference product sponsor shall notify the Secretary that—

(i) the biological product shall be immediately removed from such list for the same period as the revocation or suspension; and

(ii) a notice of the removal shall be published in the Federal Register.

(l) Patents

(1) Confidential access to subsection (k) application

(A) Application of paragraph

Unless otherwise agreed to by a person that submits an application under subsection (k) (referred to in this subsection as the "subsection (k) applicant") and the sponsor of the application for the reference product (referred to in this subsection as the "reference product sponsor"), the provisions of this paragraph shall apply to the exchange of information described in this subsection.

(B) In general

(i) Provision of confidential information

When a subsection (k) applicant submits an application under subsection (k), such applicant shall provide to the persons described in clause (ii), subject to the terms of this paragraph, confidential access to the information required to be produced pursuant to paragraph (2) and any other information that the subsection (k) applicant determines, in its sole discretion, to be appropriate (referred to in this subsection as the "confidential information").

(ii) Recipients of information

The persons described in this clause are the following:

(I) Outside counsel

One or more attorneys designated by the reference product sponsor who are employees of an entity other than the reference product sponsor (referred to in this paragraph as the "outside counsel"), provided that such attorneys do not engage, formally or informally, in patent prosecution relevant or related to the reference product.

(II) In-house counsel

One attorney that represents the reference product sponsor who is an employee of the reference product sponsor, provided that such attorney does not engage, formally or informally, in patent prosecution relevant or related to the reference product.

(iii) Patent owner access

A representative of the owner of a patent exclusively licensed to a reference product sponsor with respect to the reference product and who has retained a right to assert the patent or participate in litigation concerning the patent may be provided the confidential information, provided that the representative informs the reference product sponsor and the subsection (k) applicant of his or her agreement to be subject to the confidentiality provisions set forth in this paragraph, including those under clause (ii).

(C) Limitation on disclosure

No person that receives confidential information pursuant to subparagraph (B) shall disclose any confidential information to any other person or entity, including the reference product sponsor employees, outside scientific consultants, or other

outside counsel retained by the reference product sponsor, without the prior written consent of the subsection (k) applicant, which shall not be unreasonably withheld.

(D) Use of confidential information

Confidential information shall be used for the sole and exclusive purpose of determining, with respect to each patent assigned to or exclusively licensed by the reference product sponsor, whether a claim of patent infringement could reasonably be asserted if the subsection (k) applicant engaged in the manufacture, use, offering for sale, sale, or importation into the United States of the biological product that is the subject of the application under subsection (k).

(E) Ownership of confidential information

The confidential information disclosed under this paragraph is, and shall remain, the property of the subsection (k) applicant. By providing the confidential information pursuant to this paragraph, the subsection (k) applicant does not provide the reference product sponsor or the outside counsel any interest in or license to use the confidential information, for purposes other than those specified in subparagraph (D).

(F) Effect of infringement action

In the event that the reference product sponsor files a patent infringement suit, the use of confidential information shall continue to be governed by the terms of this paragraph until such time as a court enters a protective order regarding the information. Upon entry of such order, the subsection (k) applicant may redesignate confidential information

in accordance with the terms of that order. No confidential information shall be included in any publicly-available complaint or other pleading. In the event that the reference product sponsor does not file an infringement action by the date specified in paragraph (6), the reference product sponsor shall return or destroy all confidential information received under this paragraph, provided that if the reference product sponsor opts to destroy such information, it will confirm destruction in writing to the subsection (k) applicant.

(G) Rule of construction

Nothing in this paragraph shall be construed—

(i) as an admission by the subsection (k) applicant regarding the validity, enforceability, or infringement of any patent; or

(ii) as an agreement or admission by the subsection (k) applicant with respect to the competency, relevance, or materiality of any confidential information.

(H) Effect of violation

The disclosure of any confidential information in violation of this paragraph shall be deemed to cause the subsection (k) applicant to suffer irreparable harm for which there is no adequate legal remedy and the court shall consider immediate injunctive relief to be an appropriate and necessary remedy for any violation or threatened violation of this paragraph.

(2) Subsection (k) application information

Not later than 20 days after the Secretary notifies the subsection (k) applicant that the application has

been accepted for review, the subsection (k) applicant—

(A) shall provide to the reference product sponsor a copy of the application submitted to the Secretary under subsection (k), and such other information that describes the process or processes used to manufacture the biological product that is the subject of such application; and

(B) may provide to the reference product sponsor additional information requested by or on behalf of the reference product sponsor.

(3) List and description of patents

(A) List by reference product sponsor

Not later than 60 days after the receipt of the application and information under paragraph (2), the reference product sponsor shall provide to the subsection (k) applicant—

(i) a list of patents for which the reference product sponsor believes a claim of patent infringement could reasonably be asserted by the reference product sponsor, or by a patent owner that has granted an exclusive license to the reference product sponsor with respect to the reference product, if a person not licensed by the reference product sponsor engaged in the making, using, offering to sell, selling, or importing into the United States of the biological product that is the subject of the subsection (k) application; and

(ii) an identification of the patents on such list that the reference product sponsor would be prepared to license to the subsection (k) applicant.

(B) List and description by subsection (k) applicant

Not later than 60 days after receipt of the list under subparagraph (A), the subsection (k) applicant—

(i) may provide to the reference product sponsor a list of patents to which the subsection (k) applicant believes a claim of patent infringement could reasonably be asserted by the reference product sponsor if a person not licensed by the reference product sponsor engaged in the making, using, offering to sell, selling, or importing into the United States of the biological product that is the subject of the subsection (k) application;

(ii) shall provide to the reference product sponsor, with respect to each patent listed by the reference product sponsor under subparagraph (A) or listed by the subsection (k) applicant under clause (i) —

(I) a detailed statement that describes, on a claim by claim basis, the factual and legal basis of the opinion of the subsection (k) applicant that such patent is invalid, unenforceable, or will not be infringed by the commercial marketing of the biological product that is the subject of the subsection (k) application; or

(II) a statement that the subsection (k) applicant does not intend to begin commercial marketing of the biological product before the date that such patent expires; and

(iii) shall provide to the reference product sponsor a response regarding each patent identified by the reference product sponsor under subparagraph (A)(ii).

(C) Description by reference product sponsor

Not later than 60 days after receipt of the list and statement under subparagraph (B), the reference product sponsor shall provide to the subsection (k) applicant a detailed statement that describes, with respect to each patent described in subparagraph (B)(ii)(I), on a claim by claim basis, the factual and legal basis of the opinion of the reference product sponsor that such patent will be infringed by the commercial marketing of the biological product that is the subject of the subsection (k) application and a response to the statement concerning validity and enforceability provided under subparagraph (B)(ii)(I).

(4) Patent resolution negotiations

(A) In general

After receipt by the subsection (k) applicant of the statement under paragraph (3)(C), the reference product sponsor and the subsection (k) applicant shall engage in good faith negotiations to agree on which, if any, patents listed under paragraph (3) by the subsection (k) applicant or the reference product sponsor shall be the subject of an action for patent infringement under paragraph (6).

(B) Failure to reach agreement

If, within 15 days of beginning negotiations under subparagraph (A), the subsection (k) applicant and the reference product sponsor fail to agree on a final and complete list of which, if any, patents listed under paragraph (3) by the subsection (k) applicant or the reference product sponsor shall be the subject of an action for patent infringement under

paragraph (6), the provisions of paragraph (5) shall apply to the parties.

(5) Patent resolution if no agreement

(A) Number of patents

The subsection (k) applicant shall notify the reference product sponsor of the number of patents that such applicant will provide to the reference product sponsor under subparagraph (B)(i)(I).

(B) Exchange of patent lists

(i) In general

On a date agreed to by the subsection (k) applicant and the reference product sponsor, but in no case later than 5 days after the subsection (k) applicant notifies the reference product sponsor under subparagraph (A), the subsection (k) applicant and the reference product sponsor shall simultaneously exchange—

(I) the list of patents that the subsection (k) applicant believes should be the subject of an action for patent infringement under paragraph (6); and

(II) the list of patents, in accordance with clause (ii), that the reference product sponsor believes should be the subject of an action for patent infringement under paragraph (6).

(ii) Number of patents listed by reference product sponsor

(I) In general

Subject to subclause (II), the number of patents listed by the reference product sponsor under clause (i)(II) may not exceed the number of

patents listed by the subsection (k) applicant under clause (i)(I).

(II) Exception

If a subsection (k) applicant does not list any patent under clause (i)(I), the reference product sponsor may list 1 patent under clause (i)(II).

(6) Immediate patent infringement action

(A) Action if agreement on patent list

If the subsection (k) applicant and the reference product sponsor agree on patents as described in paragraph (4), not later than 30 days after such agreement, the reference product sponsor shall bring an action for patent infringement with respect to each such patent.

(B) Action if no agreement on patent list

If the provisions of paragraph (5) apply to the parties as described in paragraph (4)(B), not later than 30 days after the exchange of lists under paragraph (5)(B), the reference product sponsor shall bring an action for patent infringement with respect to each patent that is included on such lists.

(C) Notification and publication of complaint

(i) Notification to Secretary

Not later than 30 days after a complaint is served to a subsection (k) applicant in an action for patent infringement described under this paragraph, the subsection (k) applicant shall provide the Secretary with notice and a copy of such complaint.

(ii) Publication by Secretary

The Secretary shall publish in the Federal Register notice of a complaint received under clause (i).

(7) Newly issued or licensed patents

In the case of a patent that—

(A) is issued to, or exclusively licensed by, the reference product sponsor after the date that the reference product sponsor provided the list to the subsection (k) applicant under paragraph (3)(A); and

(B) the reference product sponsor reasonably believes that, due to the issuance of such patent, a claim of patent infringement could reasonably be asserted by the reference product sponsor if a person not licensed by the reference product sponsor engaged in the making, using, offering to sell, selling, or importing into the United States of the biological product that is the subject of the subsection (k) application, not later than 30 days after such issuance or licensing, the reference product sponsor shall provide to the subsection (k) applicant a supplement to the list provided by the reference product sponsor under paragraph (3)(A) that includes such patent, not later than 30 days after such supplement is provided, the subsection (k) applicant shall provide a statement to the reference product sponsor in accordance with paragraph (3)(B), and such patent shall be subject to paragraph (8).

(8) Notice of commercial marketing and preliminary injunction

(A) Notice of commercial marketing

The subsection (k) applicant shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k).

(B) Preliminary injunction

After receiving the notice under subparagraph (A) and before such date of the first commercial marketing of such biological product, the reference product sponsor may seek a preliminary injunction prohibiting the subsection (k) applicant from engaging in the commercial manufacture or sale of such biological product until the court decides the issue of patent validity, enforcement, and infringement with respect to any patent that is—

(i) included in the list provided by the reference product sponsor under paragraph (3)(A) or in the list provided by the subsection (k) applicant under paragraph (3)(B); and

(ii) not included, as applicable, on—

(I) the list of patents described in paragraph (4); or

(II) the lists of patents described in paragraph (5)(B).

(C) Reasonable cooperation

If the reference product sponsor has sought a preliminary injunction under subparagraph (B), the reference product sponsor and the subsection (k) applicant shall reasonably cooperate to expedite such further discovery as is needed in connection with the preliminary injunction motion.

(9) Limitation on declaratory judgment action

(A) Subsection (k) application provided

If a subsection (k) applicant provides the application and information required under paragraph (2)(A), neither the reference product sponsor nor the subsection (k) applicant may, prior to the date notice is received under paragraph (8)(A), bring any action under section 2201 of Title 28 for a declaration of infringement, validity, or enforceability of any patent that is described in clauses (i) and (ii) of paragraph (8)(B).

(B) Subsequent failure to act by subsection (k) applicant

If a subsection (k) applicant fails to complete an action required of the subsection (k) applicant under paragraph (3)(B)(ii), paragraph (5), paragraph (6)(C)(i), paragraph (7), or paragraph (8)(A), the reference product sponsor, but not the subsection (k) applicant, may bring an action under section 2201 of Title 28 for a declaration of infringement, validity, or enforceability of any patent included in the list described in paragraph (3)(A), including as provided under paragraph (7).

(C) Subsection (k) application not provided

If a subsection (k) applicant fails to provide the application and information required under paragraph (2)(A), the reference product sponsor, but not the subsection (k) applicant, may bring an action under section 2201 of Title 28 for a declaration of infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product.

(m) Pediatric studies

(1) Application of certain provisions

The provisions of subsections (a), (d), (e), (f), (h), (i), (j), (k), (l), (n), and (p) of section 505A of the Federal Food, Drug, and Cosmetic Act shall apply with respect to the extension of a period under paragraphs (2) and (3) to the same extent and in the same manner as such provisions apply with respect to the extension of a period under subsection (b) or (c) of section 505A of the Federal Food, Drug, and Cosmetic Act.

(2) Market exclusivity for new biological products

If, prior to approval of an application that is submitted under subsection (a), the Secretary determines that information relating to the use of a new biological product in the pediatric population may produce health benefits in that population, the Secretary makes a written request for pediatric studies (which shall include a timeframe for completing such studies), the applicant agrees to the request, such studies are completed using appropriate formulations for each age group for which the study is requested within any such timeframe, and the reports thereof are submitted and accepted in accordance with section 505A(d)(4) of the Federal Food, Drug, and Cosmetic Act—

(A) the periods for such biological product referred to in subsection (k)(7) are deemed to be 4 years and 6 months rather than 4 years and 12 years and 6 months rather than 12 years; and

(B) if the biological product is designated under section 526 for a rare disease or condition, the period for such biological product referred to in section 527(a) is deemed to be 7 years and 6 months rather than 7 years.

(3) Market exclusivity for already-marketed biological products

If the Secretary determines that information relating to the use of a licensed biological product in the pediatric population may produce health benefits in that population and makes a written request to the holder of an approved application under subsection (a) for pediatric studies (which shall include a timeframe for completing such studies), the holder agrees to the request, such studies are completed using appropriate formulations for each age group for which the study is requested within any such timeframe, and the reports thereof are submitted and accepted in accordance with section 505A(d)(4) of the Federal Food, Drug, and Cosmetic Act—

(A) the periods for such biological product referred to in subsection (k)(7) are deemed to be 4 years and 6 months rather than 4 years and 12 years and 6 months rather than 12 years; and

(B) if the biological product is designated under section 526 for a rare disease or condition, the period for such biological product referred to in section 527(a) is deemed to be 7 years and 6 months rather than 7 years.

(4) Exception

The Secretary shall not extend a period referred to in paragraph (2)(A), (2)(B), (3)(A), or (3)(B) if the determination under section 505A(d)(4) is made later than 9 months prior to the expiration of such period.

(n) Date of approval in the case of recommended controls under the CSA

(1) In general

In the case of an application under subsection (a) with respect to a biological product for which the Secretary provides notice to the sponsor that the Secretary intends to issue a scientific and medical evaluation and recommend controls under the Controlled Substances Act, approval of such application shall not take effect until the interim final rule controlling the biological product is issued in accordance with section 201(j) of the Controlled Substances Act.

(2) Date of approval

For purposes of this section, with respect to an application described in paragraph (1), references to the date of approval of such application, or licensure of the product subject to such application, shall mean the later of—

(A) the date an application is approved under subsection (a); or

(B) the date of issuance of the interim final rule controlling the biological product.

APPENDIX F

21 C.F.R. § 1271.15

§ 1271.15 Are there any exceptions from the requirements of this part?

(a) You are not required to comply with the requirements of this part if you are an establishment that uses HCT/P's solely for nonclinical scientific or educational purposes.

(b) You are not required to comply with the requirements of this part if you are an establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure.

(c) You are not required to comply with the requirements of this part if you are a carrier who accepts, receives, carries, or delivers HCT/P's in the usual course of business as a carrier.

(d) You are not required to comply with the requirements of this part if you are an establishment that does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/P's solely for implantation, transplantation, infusion, or transfer within your facility.

(e) You are not required to comply with the requirements of this part if you are an establishment that only recovers reproductive cells or tissue and immediately transfers them into a sexually intimate partner of the cell or tissue donor.

(f) You are not required to register or list your HCT/P's independently, but you must comply with all other applicable requirements in this part, if you are an individual under contract, agreement, or other arrangement with a registered establishment and engaged solely in recovering cells or tissues and sending the recovered cells or tissues to the registered establishment.