Public Copy -- Sealed Material Deleted

[ORAL ARGUMENT SCHEDULED SEPTEMBER 21, 2012]

Nos. 11-1268, -1279

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

CYTORI THERAPEUTICS INC, PETITIONER

v.

FOOD AND DRUG ADMINISTRATION, RESPONDENT

ON PETITIONS FOR REVIEW FROM THE FOOD AND DRUG ADMINISTRATION

BRIEF FOR RESPONDENT

STUART F. DELERY
Acting Assistant Attorney General

SCOTT R. MCINTOSH
(202) 514-4052
ADAM C. JED
(202) 514-8280
Attorneys, Appellate Staff
Civil Division, Room 7240
U.S. Department of Justice
950 Pennsylvania Avenue, N.W.
Washington, D.C. 20530

CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES

A. Parties and Amici.

The petitioner is Cytori Therapeutics, Inc. The respondent is the Food and Drug Administration.

B. Rulings Under Review.

These consolidated petitions seek review of two FDA decisions, one issued on June 27, 2011, and the other issued on July 29, 2011. The decisions are reproduced in the Joint Appendix at JA 200 and JA 384.

C. Related Cases.

We are aware of no related cases.

/s/ Adam C. Jed

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Cases: **Page**

---

* Authorities chiefly relied upon are marked with asterisks.

Statutes:

Regulations:

Legislative Materials:

Other Authorities:

GLOSSARY

Br.	Brief of Petitioner
CBER	Center for Biologics Evaluation and Research
CDRH	Center for Devices and Radiological Health
FDA	Food and Drug Administration
JA	Joint Appendix
PMA	Premarket Approval

Nos. 11-1268, -1279

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

CYTORI THERAPEUTICS INC, PETITIONER

v.

FOOD AND DRUG ADMINISTRATION, RESPONDENT

ON PETITIONS FOR REVIEW FROM THE FOOD AND DRUG ADMINISTRATION

BRIEF FOR RESPONDENT

STATEMENT OF JURISDICTION

On June 27, 2011, and July 29, 2011, the Food and Drug Administration (FDA) determined that two medical devices made by Cytori Therapeutics, Inc. are not substantially equivalent to valid predicate devices already on the market. JA 200-201, 384-385. These petitions, seeking review of those FDA decisions, were filed on July 27, 2011, and August 10, 2011. The jurisdiction of this Court is invoked under 21 U.S.C. § 360g(a)(8). As explained in Part I, this Court lacks jurisdiction and should dismiss the petitions.

STATEMENT OF ISSUES

Petitioner, Cytori Therapeutics, Inc., ("Cytori") developed a new system that is

designed to separate stromal vascular fraction, or adipose derived cells, from adipose tissue in a closed and sterile environment. The system is composed of a large physical apparatus and a new, [redacted] Cytori wants the system to be cleared by FDA for marketing as a medical device. Rather than going though the regular premarket approval process, however, Cytori submitted two notifications to FDA that it intends to market this system, under two different names, for two related uses, and does not need premarket approval because the devices are substantially equivalent to predicate devices already on the market. After exchanges with Cytori and internal scientific recommendations, FDA sent letters notifying Cytori that its devices are not substantially equivalent. These consolidated petitions for review present the following questions:

1. Whether this Court has jurisdiction over petitions for direct review of FDA decisions that new medical devices are not substantially equivalent to medical devices already on the market.

2. Whether FDA's decisions concerning these two medical devices were arbitrary and capricious.

STATUTES AND REGULATIONS

All applicable statutes and regulations are contained either in the petitioner's addendum or in the addendum at the end of this brief.

STATEMENT OF FACTS

I. Statutory and Regulatory Background

1. In 1976, in response to the pervasive problem of "dangerous health care products," such as "faulty pacemakers and the Dalkon Shield," Congress enacted the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, Pub. L. No. 94-295, 90 Stat. 539 (codified at 21 U.S.C. §§ 360c-360k). *Contact Lens Manf. Ass'n.* v. *FDA*, 766 F.2d 592, 593 (D.C. Cir. 1985); see also *Medtronic* v. *Lohr*, 518 U.S. 470, 476-77 (1996). The 1976 amendments established a system for classification and premarket clearance of medical devices. *Contact Lens Manf. Ass'n.*, 766 F.2d at 594.

The 1976 amendments established three device classes: Class I, Class II, and Class III. Class III devices are the most strictly regulated, see 21 U.S.C. § 360c(a)(1), and generally must receive premarket approval before release for commercial distribution. 21 U.S.C. § 360e(a); *Contact Lens Mfrs. Ass'n*, 766 F.2d at 594. Before a new Class III device may be introduced into the market, the manufacturer must provide FDA with "reasonable assurance" that the device is both safe and effective. See 21 U.S.C. § 360e(d)(2); *Medtronic*, 518 U.S. at 477. In contrast, Class II devices are subject to intermediate regulatory requirements, and Class I devices are subjected to minimal regulation. *Ibid.*; see 21 U.S.C. § 360c(a)(1).

Congress created different schemes for classification of devices that were already in use before the 1976 amendments ("pre-1976 devices"), and new medical

devices. FDA was required to classify pre-1976 devices into one of the three classes through notice and comment rulemaking, with input from expert advisory panels. See 21 U.S.C. § 360c(b)-(d). Congress classified all "new" devices as a matter of law into Class III. 21 U.S.C. § 360c(f)(1); *Contact Lens Mfrs. Ass'n*, 766 F.2d at 594.

Ordinarily, any Class III device, which includes any new medical device, see 21 U.S.C. § 360c(f)(1), must be reviewed by FDA for its safety and effectiveness and approved before it can be sold. However, as relevant here, Congress created a narrow means of bypassing the regular premarket approval process: If FDA issues an order that a device is "substantially equivalent" to a legally marketed pre-1976 device or other device that is classified as Class I or Class II (a "predicate device"), then premarket approval is not necessary. 21 U.S.C. § 360c(f)(1) & (i).

2. Before marketing a device, a manufacturer must submit a "premarket notification" pursuant to 21 U.S.C. § 360(k), describing the device and stating the class in which the device is classified.[1] See also 21 C.F.R. § 807.87. This is also commonly called a "510(k)" notification, after the statute's parallel cite in the Act. If a manufacturer seeks to avoid the premarket approval process, it may submit a "premarket notification" stating that its device is "substantially equivalent" to a

[1] In addition, certain devices are exempt from premarket review, see 21 U.S.C. § 360(*l*) & (m), as long as they do not exceed certain limitations.

predicate device.[2]

If FDA agrees that a device is substantially equivalent to a legally marketed predicate device, then premarket approval is not necessary. 21 U.S.C. § 360c(f)(1). If FDA disagrees, the manufacturer may within 30 days request a review of the otherwise-automatic Class III classification of the device. 21 U.S.C. § 360c(f)(2). This process is intended to allow for "de novo" classification of low-risk devices that were determined not to be substantially equivalent because there is no predicate device. If a request for "de novo" review is submitted, FDA must classify the device within sixty days. *Ibid.*

3. To be "substantially equivalent" to a predicate device, a new device must meet two requirements. First, it must have "the same intended use as the predicate device." 21 U.S.C. § 360c(i). Second, it must either (i) "ha[ve] the same technological characteristics as the predicate device"; *or* (ii) if it has different technological characteristics there must be "information submitted that the device is substantially equivalent to the predicate device * * * including appropriate clinical or scientific data" demonstrating "that the device is as safe and effective" *and* the device must "not raise different questions of safety and effectiveness than the predicate device."

---

[2] Alternatively, a sponsor can seek an order from FDA reclassifying the device into Class I or II, see 21 U.S.C. § 360(f)(3); see also *United States* v. *Universal Mgmt. Servs., Inc.*, 191 F.3d 750, 754 (6th Cir. 1999).

21 U.S.C. § 360c(i)(1)(A); see also 21 C.F.R. § 807.100(b)(2).

II. The FDA Determinations

These consolidated petitions for review concern two premarket notifications submitted by petitioner, Cytori Therapeutics, Inc., for two new medical devices, the "Celution 700/LAB" and the "StemSource 900/MB." These are the same physical device but have two different intended uses, and were accordingly submitted to two different FDA centers that regulate devices with different uses, the Center for Devices and Radiological Health ("CDRH"), and the Center for Biologics Evaluation and Research ("CBER"). A device producing a therapeutic biologic product must be reviewed by CBER.[3] A device "not assigned categorically or specifically to CBER" is reviewed by CDRH.[4] CDRH and CBER each determined that the device before it is not substantially equivalent to a predicate device.

A. Background

1. Cytori's new devices are comprised of a system designed for removing and isolating [redacted], or adipose-derived cells, from adipose tissue, also

[3] See Guidance for Industry and FDA Staff: Devices Used to Process Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), Jurisdictional Update (July 2007), *available at*, http://www.fda.gov/RegulatoryInformation/Guidances/ucm126052.htm.

[4] Intercenter Agreement Between the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health (Oct. 31, 1991), *available at*, http://www.fda.gov/combinationproducts/jurisdictional information/ucm121175.htm.

known as fat tissue, in a closed and sterile environment. The system is composed of a centrifuge, sample processing containers, tubing, and Celase, [redacted]. JA 19, 294-295.

Cytori has submitted numerous regulatory filings for similar devices that share the same technology platform. See JA 378 (chart summarizing submissions). Various FDA offices have informed Cytori that theses devices require premarket approval, and FDA has rejected a previous 510(k) submission. See JA 377-378.

2. Before making either of the 510(k) submissions at issue in this case, Cytori requested a formal meeting with CBER to discuss the appropriateness of its device for a 510(k) clearance. JA 202-205. CBER agreed to meet and asked for materials about the device. JA 205-206. Cytori sent a package describing its new device and the proposed predicate devices. JA 208-286.

CBER scientists met with Cytori to discuss a possible regulatory submission for its StemSource 900/MB. JA 377; see JA 287-290. CBER explained that it did not think the device is appropriate for a 510(k) or premarket notification. *Ibid.* Among other things, CBER explained that the proposed predicate devices were for processing and storing cord blood, which is a different intended use than processing adipose tissue. *Ibid.* In response to Cytori's question whether the device would be appropriate for de novo classification into Class I or Class II, see 21 U.S.C. §

360c(f)(2), CBER explained that it was premature to speculate on whether there could be adequate controls making the de novo process appropriate and Cytori would have to support its specific clinical indications with investigational studies to gain standard premarket approval. See JA 288-290.

B. Celution 700/LAB

1. On April 25, 2011, Cytori submitted a 510(k) notification to CDRH for the "Celution 700/Lab System," JA 1, as a system "intended to be used in the clinical laboratory or intraoperatively at point-of-care for the safe and rapid preparation of a cell concentrate from adipose tissue," JA 3, 21. Cytori submitted a package of information stating that the Celution 700 device is substantially equivalent to certain predicate devices. See JA 1, 10-14. Specifically, Cytori asserted that the Celution 700 "shares indications and design principles" with eight Class II devices that in some sense process or break down human tissue. JA 1, 10; see JA 14. These included two systems for processing blood and bone marrow, JA 27, 31, a device for performing liposuction, JA 35-38, enzymes used in certain blood and sputum testing, JA 39-56, a culture medium used to grow cells, JA 57-62, an enzyme used for assisted reproduction, JA 64-66, and a gelatin foam used to stop bleeding, JA 67-69.

Cytori also briefly stated that it believed the device is "classif[ied] * * * as a Class I device, under 21 C.F.R. 862.2050, 'General Purpose Laboratory Equipment, Labeled and Promoted for a Specific Medical Use.'" JA 1; see also JA 2, 18. Cytori

asked FDA to "confirm, in writing" if the agency "concur[s] with [that] assertion" and "if not" to review the 510(k) notification. JA 1.

2. CDRH asked Cytori additional questions and obtained from Cytori additional information. See, *e.g.*, JA 74-82, 83-85, 86-90, 91-95, 96-100, 101-102, 104-111, 112-119, 120-128, 129-184. CDRH also spoke with CBER, to discuss CBER's parallel review of "the same device [sent] to two different Centers." JA 103.

A CDRH scientist prepared a summary review memorandum containing his impressions and recommending that the Celution 700 be found not substantially equivalent. JA 188. The memo analyzed Cytori's 510(k) submission, described the device, and raised questions. JA 188-192. The memo noted the various devices that Cytori submitted as predicates and explained why certain devices have different intended uses than the Celution 700. See JA 189-190. It thus recommended that "there is no predicate device." *Ibid.*

The memo also reviewed the data submitted by Cytori about the effects of the device, including the [redacted] Celase enzyme. JA 189-191. The author noted various concerns with both the data itself and the results of Cytori's study. He explained that the system was tested on tissue from only 12 subjects, and Cytori did not submit information about the subjects' sex, age, or medical conditions. JA 189, 191. [redacted] JA 189-190. [redacted]

[redacted]. *Ibid.*

3. On June 27, 2011, the Division of Immunology and Hemotology Devices, Office of In Vitro Diagnostic Device Evaluation and Safety, a CDRH component, notified Cytori that it had determined that the Celution is not substantially equivalent to a valid predicate device. JA 200-201. The letter explained that FDA is "not aware of a legally marketed preamendments device labeled or promoted for the intended use in the clinical laboratory or intraoperatively at point-of-care for the safe and rapid preparation of a stromal cell concentrate from adipose tissue for further clinical testing." JA 200. "[T]he intended use of this device differs from the intended use of the predicate devices." *Ibid.* The letter also explained that "the performance data" is "inadequate to demonstrate substantial equivalence." *Ibid.* CDRH stated that the Celution 700 therefore "is classified by statute into class III" and must receive premarket approval. *Ibid.*

C. StemSource 900/MB

1. Three days after submitting the 510(k) notification to CDRH, on April 28, 2011, Cytori submitted a similar notification to CBER for the StemSource 900/MB. Under the heading"indications for use," the notification stated that it is "an adipose tissue processing system intended for laboratory use" for "rapid and reproducible

separation of adipose derived cells in a closed and sterile environment." JA 294, 307. The notification and attached draft labeling made clear that the StemSource 900 is used to produce cells "for banking/cryopreservation." JA 295, 312 [redacted] see JA 298-299 (urging that the StemSource "shares indication for use principles" with predicates because the cellular output is "intended for re-implantation into a donor" and "cryopreservation"); JA300, 305 (charts listing StemSource "intended use" as including "Ex Vivo Processing for Re-implanted," "Ex Vivo Processing for Cryopreservation," and "Autologous Cells for Re-implanted."); see also JA 298 (positing that the StemSource 900 and predicates "share the same intent of delivering minute amounts of residual reagent back to the donor"). Cytori's notification asserted that its StemSource 900 should be classified as a Class II Cord Blood Processing System, JA 293, 308, and asserted that it is substantially equivalent to seven Class II devices, including cord blood processing systems, an autotransfusion device for surgery, cell growth media, and a foam used to help stop bleeding. JA 292, 298-305, 313-375.

As with the Celution 700, Cytori's cover letter briefly asserted that the StemSource 900 was Class I "General Purpose Laboratory Equipment, Labeled and Promoted for a Specific Medical Use." JA 292. Cytori asked FDA to "confirm, in writing" if they agree with that "assertion," and "if not" to review the 510(k)

notification. *Ibid.*.

2. A CBER scientist prepared a review memorandum, recommending that the StemSource 900 be found not substantially equivalent. JA 376-383. The memo described the device's components and operation. JA 380-381. It discussed several of Cytori's proposed predicate devices, and explained that the only three predicates that were systems at all have different intended uses than the StemSource 900. JA 379-380, 381-383. Two of the systems are for processing cord blood, and one is an autotransfusion device. *Ibid.* As had been noted in FDA's pre-510(k) answers to Cytori's questions, "processing adipose tissue to obtain adipose-derived cells" is a "different intended use" than "cord blood processing and storage." JA 377. The third device, the reviewer commented, "is an Autotransfusion Apparatus," which similarly has a "different intended use." JA 380. The memo further explained that the Celase enzyme is a "new technology that raises new questions of safety." JA 381, 383. The memo also referred back to CBER's pre-510(k) communication with Cytori, which reminded Cytori that it would need to support its specific medical indications with investigational studies to gain premarket approval. JA 383.

3. On July 29, 2011, the Office of Cellular, Tissue, and Gene Therapies, an office in CBER, informed Cytori that it had determined that the StemSource is not substantially equivalent. JA 384-385. The letter explained that FDA is "not aware of a legally marketed preamendments device labeled or promoted for laboratory use for

processing of adipose tissues to separate adipose-derived cells for banking and cryopreservation." JA 384. "Furthermore," the decision explained, "the device has new technological characteristics that could affect the safety and effectiveness and raise new types of safety questions related to the potential effects the Celase reagent may have on tissue that may be returned to the patient." *Ibid.* The device, therefore, "is classified by statute into class III." *Ibid.*

D. Petitions for Review

Cytori filed petitions for review on July 27, 2011, and August 10, 2011. Pursuant to agreement by the parties, this Court consolidated the petitions.

SUMMARY OF ARGUMENT

I. This Court lacks jurisdiction over Cytori's petitions. "[T]he normal default rule is that persons seeking review of agency action go first to district court rather than to a court of appeals." *Watts* v. *SEC*, 482 F.3d 501, 505 (D.C. Cir. 2007) (internal quotation marks omitted). Thus, "[i]f judicial review of an FDA action or inaction is not provided for [by statute], challenges to such actions may be brought only in the district court." *Moms Against Mercury* v. *FDA*, 483 F.3d 824, 826 (D.C. Cir. 2007).

Cytori mistakenly invokes 21 U.S.C. § 360g(a)(8) as a basis for jurisdiction. As this Court has explained, however, § 360g(a)(8) authorizes direct review only of an FDA decision "determining that a post-amendment device *is* substantially equivalent

to a pre-amendment device under subsection (a)(8)." *Moms Against Mercury*, 483 F.3d at 827 (emphasis added). Section 360g(a)(8) provides for direct review of "an order pursuant to [21 U.S.C. § 360c(i)]," which, in turn, authorizes and defines only an "order" in which FDA "has found that the device" is substantially equivalent to a predicate device.

This review provision facilitates Congress's goal that 510(k) notifications concerning substantial equivalence would not serve as a "loophole" through the standard process of premarket approval for safety and efficacy. See *Medtronic* v. *Lohr*, 518 U.S. 470, 479-80 & n.4 (1996); H.R. Rep. No. 101-808, at 14 (1990); S. Rep. No. 101-513, at 15 (1990). Thus, as the legislative history of this judicial review provision makes clear, only an order "*finding* substantial equivalence * * * will be reviewable in the United States court of appeals." H.R. Rep. No. 101-959, at 27 (1990) (Conf. Rep.) (emphasis added).

II. Even if this Court should address Cytori's petitions for review, they are meritless. FDA's determinations were correct, thorough, and reasoned. To be "substantially equivalent" to a predicate device, a new device must meet two requirements. Cytori's devices met neither.

First, a new device must have "the same intended use as the predicate device." 21 U.S.C. § 360c(i). Yet, as FDA concluded, Cytori did not submit any predicate device with the same intended use as the Celution 700 or StemSource 900. Cytori

wrongly urges that the intended uses need not be the same but must only be similar. This is plainly at odds with the statutory text and legislative history, and FDA's interpretation is therefore reasonable.

Second, a new device must either (i) "ha[ve] the same technological characteristics as the predicate device"; *or* (ii) if it has different technological characteristics there must be "information submitted that the device is substantially equivalent to the predicate device * * * including appropriate clinical or scientific data" demonstrating "that the device is as safe and effective," *and* it must "not raise different questions of safety and effectiveness than the predicate device." 21 U.S.C. § 360c(i)(1)(A); see also 21 C.F.R. § 807.100(b)(2). After examining the predicate devices, the new technology, and Cytori's limited data, FDA concluded that the new devices do not satisfy this requirement. In particular, the effects of the new enzyme Celase were not known, and standard premarket approval was necessary.

STANDARD OF REVIEW

FDA's decisions may be disturbed only if they were arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. *Contact Lens Mfrs. Assn*, 766 F.2d at 597. FDA's interpretation of the statute it is charged with administering is entitled to deference under *Chevron, U.S.A., Inc.* v. *Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), and its interpretations of its own regulations receive deference "unless plainly erroneous or inconsistent with the regulations." *Novartis*

Pharms. Corp. v. *Leavitt*, 435 F.3d 344, 349 (D.C. Cir. 2006).

ARGUMENT

I. No Statute Gives This Court Jurisdiction Over the Petitions for Direct Review.

"[T]he normal default rule is that persons seeking review of agency action go first to district court rather than to a court of appeals." *Watts* v. *SEC*, 482 F.3d 501, 505 (D.C. Cir. 2007) (internal quotation marks omitted). "Initial review occurs at the appellate level only when a direct-review statute specifically gives the court of appeals subject-matter jurisdiction to directly review agency action." *Ibid.* Thus, "[i]f judicial review of an FDA action or inaction is not provided for [by statute], challenges to such actions may be brought only in the district court." *Moms Against Mercury* v. *FDA*, 483 F.3d 824, 827 (D.C. Cir. 2007). Cytori bears the burden of establishing jurisdiction. *Id.* at 828. It cannot meet that burden here.

1. Cytori invokes 21 U.S.C. § 360g(a)(8) as a basis for jurisdiction over FDA's letters concerning Cytori's 510(k) notifications. As this Court has explained, however, § 360g(a)(8) authorizes direct review only of an FDA decision "determining that a post-amendment device *is* substantially equivalent to a pre-amendment device under subsection (a)(8)." *Moms Against Mercury*, 483 F.3d at 826 (emphasis added). Because the devices at issue here "ha[ve] not been * * * the subject of any order deeming [them] substantially equivalent" to a valid predicate device, there is no

jurisdiction. *Id.* at 827; see also Order, *ReGen Biologics, Inc.*, v. *FDA*, No. 11-1123 (D.C. Cir. Sept. 1, 2011) (per curiam).[5]

This is a clear application of the statutory text. Section 360g(a)(8) provides for direct review of "an order pursuant to [21 U.S.C. § 360c(i)]." The cross-referenced § 360c(i), in turn, authorizes and defines a determination in which FDA "by order has found that the device" meets the requirements of being substantially equivalent to a predicate device. 21 U.S.C. § 360c(i)(1)(A). Section 360c(i) does not authorize or define any other "order."[6] In other words, the only order that may be made "pursuant to" § 360c(i) is an order finding that a device is substantially equivalent. And § 360g(a)(8), therefore, authorizes direct review only of such an order. See *Moms Against Mercury,* 483 F.3d at 827 (no jurisdiction under § 360g(a)(8) because the device at issue "ha[d] not been * * * the subject of any order deeming it substantially

---

[5] In *ReGen*, a device manufacturer sought direct review of an FDA decision that its device was not substantially equivalent to a predicate device. FDA moved to dismiss on the same grounds presented here. The petitioner in *ReGen* agreed with FDA that the proper forum for review is the district court but urged that this Court maintain jurisdiction pending a district court action. This Court granted FDA's motion and dismissed the case, although it did not explain the basis for its order. See Order, *ReGen Biologics, Inc.*, No. 11-1123 (D.C. Cir. Sept. 1, 2011) (per curiam).

[6] Section 360c(i)(2) refers collaterally to "a judicial order" which "determined" that a device is "misbranded or adulterated," but that judicial order is not the type of "order" at issue here, nor is it made "pursuant to" § 360c(i).

equivalent to a pre-amendment device").[7]

This reading is also consistent with the judicial review framework. As noted, a premarket notification seeking a determination that a device is substantially equivalent is submitted to request that a device should not be initially classified as Class III. See 21 U.S.C. § 360c(f)(1). A determination that a new device is not substantially equivalent therefore results in an initial classification as Class III. And initial classifications in Class III are not directly reviewable in courts of appeals. *Moms Against Mercury*, 483 F.3d at 827.[8]

Even if there were any ambiguity in the statute's text, the legislative history of the jurisdictional provision confirms that this Court lacks jurisdiction. Congress added § 360g(a)(8) in the Safe Medical Devices Act of 1990, Pub. L. No. 101-629, 104 Stat. 4511, 4524. In passing that Act, Congress was particularly concerned that the vast majority of medical devices entering the market were doing so based on substantial equivalence orders, thereby avoiding the standard premarket approval for safety and efficacy. See *Medtronic* v. *Lohr*, 518 U.S. 470, 479-80 & n.4 (1996); H.R.

---

[7] Moreover, § 360c(i) refers to "determinations of substantial equivalence under [§ 360c](f) and [§ 360j(*l*)], which, in turn, both refer to a device that "*is* substantially equivalent to another device." 21 U.S.C. §§ 360c(f)(1)(A)(ii), 360j(*l*)(1)(D) (emphasis added).

[8] If FDA deems a medical device Class I, and thus subject to the lowest category of government evaluation, that classification is directly reviewable in the courts of appeals. See 21 U.S.C. § 360g(a)(1).

Rep. No. 101-808, at 14; S. Rep. No. 101-513, at 15. There was a concern that these substantial equivalence orders "provide little protection to the public," *Medtronic*, 518 U.S. at 493. "[T]o the extent" that such orders had "perpetuated a loophole," the 1990 amendments were intended to "close the loophole and assure that all devices are regulated consistent with the expectations of Congress." S. Rep. No. 101-513, at 15; see also *Medtronic*, 518 U.S. at 480 n.4 ("In 1990, Congress enacted amendments * * * to reduce the FDA's reliance on the § 510(k) process while continuing to ensure that particularly risky devices received full PMA [premarket approval] review.").

In the 1990 Act, Congress thus added a provision that would facilitate direct review of what had become a substantial path for bypassing FDA's standard premarket approval. The initial House and Senate versions differed as to whether there would be direct review of decisions concerning substantial equivalence. The House version had no provision for direct review. See H.R. Rep. No. 101-808, at 6. The Senate initially proposed a version providing direct review only of decisions finding substantial equivalence. See Comprehensive Medical Device Improvement Act of 1990, S. 3006.IS, 101st Cong., § 9 (1990). But the final Senate bill provided for review of any such determination, "whether a product is substantially equivalent or not substantially equivalent to a market device." S. Rep. No. 101-513, at 37. In conference, the two houses reached a compromise. "Under the conference agreement," it was "made clear in the new [21 U.S.C. § 360g(a)(8)] that an order

pursuant to [21 U.S.C. § 360c(i)], *finding* substantial equivalence * * * will be reviewable in the United States court of appeals." H.R. Rep. No. 101-959, at 27 (1990) (Conf. Rep.), reprinted in 1990 U.S.C.C.A.N. 6327, 6332 (emphasis added).

This compromise adds substantial equivalence orders, which allow medical devices to bypass premarket approval, to the very limited set of FDA actions that are directly reviewable. The compromise is fully consistent with Congress's concern that substantial equivalence orders may have "perpetuated a loophole" in the premarket approval system, S. Rep. No. 101-513, at 15; see also *Medtronic,* 518 U.S. at 479-80; H.R. Rep. No. 101-808, at 14, and Congress's intent "to reduce the FDA's reliance on the § 510(k) process while continuing to ensure that particularly risky devices received full PMA [premarket approval] review." *Medtronic*, 518 U.S. at 480 n.4.

2. a. Cytori's primary contention is that § 360c(i) is titled "Substantial Equivalence" and "defines the terms 'substantial equivalence' and 'substantially equivalent' for the 'purposes of determinations of substantial equivalence.'" Br. 26-27 (quoting § 360c(i), emphasis omitted). Cytori ignores the key text. As noted, § 360g(a)(8) authorizes direct review only of "an order pursuant to" § 360c(i). And § 360c(i) authorizes and defines only one type of "order," in which "the Secretary by order has found that the device" is substantially equivalent. 21 U.S.C. § 360c(i)(1)(A); see also H.R. Rep. No. 101-959, at 27 (Conf. Rep.) (explaining that "an order pursuant to [21 U.S.C. § 360c(i)], *finding* substantial equivalence * * * will be

reviewable in the United States court of appeals") (emphasis added).

If anything, Cytori's textual argument cuts against jurisdiction here. In § 360c(i)(1)(A), Congress distinguished between the general category of "determinations of substantial equivalence" — the category that Cytori urges is reviewable — and the specific "order [that] has found that the device" is substantially equivalent — the category incorporated into the judicial review provision's cross reference to "an order pursuant to" § 360c(i).[9]

Cytori is on no firmer ground in noting that another judicial review provision, § 360g(a)(3), states more clearly that it authorizes direct review only of one type of decision, a decision "denying a request for reclassification of a device." See Br. 27-28 & n.15. "[T]he mere possibility of clearer phrasing cannot defeat the most natural reading of a statute." *Caraco Pharm. Labs., Ltd.* v. *Novo Nordisk A/S*, 132 S. Ct. 1670,

---

[9] It is of no matter that one of FDA's regulations concerning premarket notification (21 C.F.R. § 807.100) uses the word "order" when referencing any final decision concerning substantial equivalence. See Br. 27, n.14. Section 360g(a)(8) authorizes direct review of "an order pursuant to [§ 360c(i)]," not an order as referenced by FDA regulations. Indeed, when Congress added this direct review provision in 1990 (Pub. L. No. 101-629), the regulation that Cytori identifies did not even exist. See 57 Fed. Reg. 58,400-01, 58,403 (Dec. 10, 1992) (adding the language in question). FDA cannot by regulation expand the jurisdiction of an Article III court. Nor, in FDA's view, does its regulation attempt to do so here. 21 C.F.R. § 807.100(a) merely lists the five possible FDA actions after review of a premarket notification. FDA's use of the word "order" simply distinguishes those two courses of action in which FDA makes a decision from the other three options, such as requesting additional information.

1682 (2012). "Nor does Congress's use of more detailed language in another provision, enacted years earlier,"[10] alter the meaning of this provision. *Ibid.*; see also *Field* v. *Mans*, 516 U.S. 59, 75 (1995) (reasoning from a negative pregnant is of "limited" use, especially where the contrast is not "apparently deliberate" or the result is "at odds with other textual pointers").

Moreover, in addition to the fact that the two subsections, § 360g(a)(3) and § 360g(a)(8), were added in different statutes, (compare Pub. L. No. 101-629, 104 Stat. 4511, 4524 (1990) with 94 Pub. L. No. 295; 90 Stat. 539, 560 (1976)), they cross-reference statutory provisions that are written differently. Section 360g(a)(8) cross-references § 360c(i), which provides for only one type of "order." In contrast, § 360g(a)(3) cross-references § 360d(b)(2) and § 360e(b)(2)(B), which provide that FDA shall "*either* deny the request or give notice of an intent to initiate such change." (emphasis added). Indeed, if anything, § 360g(a)(3) shows that Congress was careful in § 360g(a) to echo the appropriate language in the cross-referenced sections — "deny" in (a)(3) and "order" in (a)(8).

b. Cytori's argument concerning legislative history is merely a repackaged version of its textual argument that Congress was not clear enough. Br. 28-31. Cytori asserts that "[n]owhere within the Conference Report does Congress state that the

---

[10] See Pub. L. No. 94-295; 90 Stat. 539, 560 (1976) (adding § 360g(a)(3)).

amendment was intended to exclusively provide for direct review of orders finding substantial equivalence." Br. 30. But the Conference Report said exactly that: "an order pursuant to [21 U.S.C. § 360c(i)], *finding* substantial equivalence * * * will be reviewable in the United States court of appeals." H.R. Rep. No. 101-959, at 27 (Conf. Rep.) (emphasis added). Cytori concedes that the final version "harmonize[d] the differences between the House and Senate versions," Br. 30, yet urges that in substance the final bill adopted the Senate's substantive version wholesale.

c. Cytori is wrong in asserting that Congress must have authorized direct review of decisions that devices are not substantially equivalent, because otherwise § 360g(a)(8) would be "a nullity." Br. 31. As an initial matter, Cytori's assertion rests on various assumptions about who, in practice, can successfully challenge a substantial equivalence order. There is no reason to believe that Congress could or did foresee certain practical obstacles to judicial review, that are not part of the statute itself. And even if Congress had some sense of these obstacles, it still may have left open the possibility of future changes in law or practice rendering petitions for review easier. Cf. *Abbott* v. *United States*, 131 S. Ct. 18, 30-31 (2010).

In any event, the plain textual reading of § 360g(a)(8) does not render it a nullity. Orders finding substantial equivalence can be challenged by competitors who do not want their existing products to compete against new ones and manufacturers who do not want their products that are awaiting FDA approval to fall behind

devices that avoided FDA's premarket approval process through substantial equivalence orders.[11] And in appropriate cases, petitions could be brought by insurance companies, public interest groups, doctors, or patients who want devices to undergo standard premarket approval for safety and efficacy.[12] The requirements for Article III standing are broad and fact based. And the only statutory requirement is that the petitioner be "adversely affected." 21 U.S.C. § 360g(a). In appropriate cases, third parties may have standing to challenge substantial equivalence orders.

Cytori is mistaken in asserting that anyone who might petition for review would, by definition, lack the information to do so. Br. 32-33. Premarket notifications do not involve public participation, but in many circumstances, parties other than the manufacturer have information about the devices and FDA's decision. In various circumstances — such as when a device is already on the market, a

---

[11] Cytori is mistaken when it posits that because competitors have "no right to exclusivity," they could not challenge an FDA decision. Br. 32. The requirement of being "adversely affected" is a broad one and, in appropriate circumstances, allows for suits by competitors. See, *e.g.*, *NCUA* v. *First Nat'l Bank & Trust Co.*, 522 U.S. 479, 487-88 (1998); *Teva Pharms. USA, Inc.* v. *Sebelius*, 595 F.3d 1303, 1312 (D.C. Cir. 2010).

[12] Cytori mistakenly asserts that in *Moms Against Mercury*, FDA argued that third parties lack standing. Br. 31-32 & n.18. FDA argued only that the particular petitioners in *Moms Against Mercury* had neither alleged a concrete injury nor that their purported injury would be redressed by the requested agency action. See Brief for Respondent at 18-31, *Moms Against Mercury* v. *FDA*, 483 F.3d 824 (D.C. Cir. 2007) (No. 06-1147). As far as FDA is aware, no court has categorically held that all third-parties lack standing to seek review of substantial equivalence determinations.

manufacturer has told market analysts, exporters, or scientists about it, or a manufacturer otherwise does not comply with FDA requirements concerning confidentiality — FDA discloses publically that a premarket submission has been made as well as certain data and information about the device. See 21 C.F.R. § 807.95(a) & (e). Moreover, FDA publishes orders finding devices substantially equivalent, along with a variety of the supporting documentation. See 21 C.F.R. § 807.95(d) & (e).[13] While FDA may take up to 30 days after issuing a substantial equivalence order to publish certain data concerning the device, that data are not necessary for filing a petition for review. Although some substantial equivalence orders may be difficult to challenge, § 360g(a)(8) is not a nullity, and Congress did not provide for direct review of all such determinations. Cf. *Mohamad* v. *Palestinian Authority*, 132 S. Ct. 1702, 1710 (2012) (interpretation resulting in practical limitations on a statute's use required by statutory text and legislative history).

II. FDA's Decisions Were Not Arbitrary or Capricious or Otherwise Inconsistent with Law.

FDA's decisions may be disturbed only if they were arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. *Contact Lens Mfrs. Ass'n*,

---

[13] See, *e.g.*, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/default.htm (CDRH); http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/SubstantiallyEquivalent510kDeviceInformation/ucm063708.htm (CBER).

766 F.2d at 597. "[A]gency determinations based upon highly complex and technical matters are entitled to great deference." *Domestic Securities, Inc.* v. *SEC*, 333 F.3d 239, 248 (D.C. Cir. 2003) (internal quotation marks omitted). Whether a medical device is substantially equivalent to a predicate device is "a classic example of a factual dispute the resolution of which implicates substantial agency expertise," *Marsh* v. *Or. Natural Res. Council*, 490 U.S. 360, 376 (1989). Thus, "FDA has broad discretion in implementing the definition of 'substantial equivalence.'" *Gen. Medical Co.* v. *FDA*, 770 F.2d 214, 217 n.1 (D.C. Cir. 1985); see also *Baltimore Gas & Electric Co.* v. *Nat. Resources Defense Council, Inc.*, 462 U.S. 87, 103 (1983) (when examining an expert "scientific determination" a "reviewing court must generally be at its most deferential"). This Court must deny the petitions if FDA "ruled in a manner at least arguably consistent with the statutory scheme, and it considered the matter in a detailed, adequately reasoned fashion." *Contact Lens Mfrs. Ass'n*, 766 F.2d at 597.

To be "substantially equivalent" to a predicate device, a new device must meet two requirements. First, it must have "the same intended use as the predicate device." 21 U.S.C. § 360c(i)(1)(A); see also 21 C.F.R. § 807.100(b)(1). Second, it must either (i) "ha[ve] the same technological characteristics as the predicate device"; *or* (ii) if it has different technological characteristics there must be "information submitted that the device is substantially equivalent to the predicate device * * * including appropriate clinical or scientific data" demonstrating "that the device is as

safe and effective" *and* it must "not raise different questions of safety and effectiveness than the predicate device." 21 U.S.C. § 360c(i)(1)(A); see also 21 C.F.R. § 807.100(b)(2).

Both of these requirements must be met. Here, FDA reasonably concluded that Cytori's devices met neither. To prevail, Cytori must demonstrate that both determinations were arbitrary and capricious. See *Casino Airlines, Inc.* v. *NTSB*, 439 F.3d 715, 717-18 (D.C. Cir. 2006). Cytori has not and cannot do so.

A. FDA Properly Concluded that Cytori's New Devices Do Not Have the Same Intended Uses as the Predicate Devices.

For a new medical device to be substantially equivalent to a predicate device, it must have "the same intended use as the predicate device." 21 U.S.C. § 360c(i)(1)(A); see also 21 C.F.R. § 807.100(b)(1). Neither of the devices at issue here had the same intended use as the predicate devices that Cytori identified.

1. FDA was within its discretion in concluding that the Celution 700 does not have the same intended use as the predicate devices. The Celution 700 was intended for "rapid preparation of a cell concentrate from adipose tissue." JA 3, 16. Yet, as FDA concluded, this "differs from the intended use of the predicate devices," and FDA was not aware of any predicate device with the intended use of "rapid preparation of a stromal cell concentrate from adipose tissue." JA 200; see also JA 189-190 (CDRH review memo).

As FDA concluded, none of Cytori's eight predicate devices[14], JA 10-14, had that intended use. See JA 14 (Cytori's chart of intended uses); JA 24-72 (Cytori's submitted literature on the predicate devices). Indeed, Cytori did not seriously contend otherwise, merely notifying CDRH that the Celution 700 "shares indications and design principles" with Cytori's proposed predicate devices. JA 1; see also JA 10.

Thus, the two Harvest Technologies SmartPReP2 Centrifuge Systems had the

---

[14] In its premarket notification, Cytori actually refers to three of these eight devices as "related devices." Although a sponsor may use multiple predicates to show substantial equivalence, there must be at least one predicate that meets all of the statutory requirements. FDA has explained this in recent recommendations and has included an explanation of this in its recently-circulated Draft Guidance. See 510(k) and Science Report Recommendations 14-15 (*available at,* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM239449.pdf?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=); Draft Guidance, The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications 10-11 (2011) ("Draft Guidance") (*available at*, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf); see also Guidance on the Center for Devices and Radiological Health's Premarket Notification Review Program (1986) (*available at*, http://www.fda.gov/ Medical Devices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=) (explaining that "[a] new device is a so-called 'combination' device when it claims to have the same intended uses as two or more different types of predicate devices" and that "the Center will subject [a] combination device to the same sorts of questions and documentation requirements that are applied to a single device"). If there is an appropriate primary predicate, "FDA may use one or more additional devices proposed by the manufacturer in certain circumstances to help support substantial equivalence" (*e.g.,* to address specific scientific questions for a new device). Draft Guidance 10-12. Although it is not entirely clear what for what purpose Cytori submitted these "related devices," whether considered predicates or not, they do not help Cytori demonstrate substantial equivalence.

intended use of processing blood and bone marrow, not adipose tissue. JA 27, 31. The Cytori Lipoplasty System was not intended for creating a cell concentrate at all, but instead for "fragmentation, emulsification, and aspiration of soft tissue" in surgery. JA 35-38. The remaining predicates were not even systems. The Flow Laboratories Trypsin and Oxoid USA Sputasol are merely enzymes intended for different uses — clumping red blood cells to test for Rubella and liquefying sputum for microbial testing. JA 190; see also JA 39-56; 21 C.F.R. § 864.4400 (classification of enzyme preparations). The StemPro MSC SFM is "a liquid tissue culture media" used to grow cells in an ex-vivo tissue culture. JA 57-62. The Medi-Cult AlS Medi-Cult Hyaluronidase is an enzyme "[f]or use in assisted reproduction techniques," such as in vitro fertilization. JA 64-66. And ThrombiGel is a gelatin foam used to stop bleeding. JA 67-69.

Cytori's 510(k) notification wrongly sought to use these as predicates by characterizing the intended use of the Celution 700 and eight predicates at an artificially high level of generality, such as "processing of a donor's tissue sample with a reagent," without regard to the type of processing, type of tissue, or type of reagent. JA 10; see also JA 14 (Cytori's chart comparing the devices). Viewed at such a high level of generality, the requirement that a substantially equivalent device have "the same intended use as the predicate device," 21 U.S.C. § 360c(i), would provide little assurance that devices are equivalent in the ways that warrant avoiding premarket

approval. FDA did not abuse its discretion in concluding that Cytori had not met its burden of showing that the Celution and its predicates had the same intended use. JA 200; see also JA 190 ("none of these intended uses are in anyway related to the proposed testing of a Celution® 700/LAB System cell concentrate[,] [a]nd therefore there is no predicate device for Celution® 700/LAB System"); see generally Guidance on the Center for Devices and Radiological Health's Premarket Notification Review Program (1986)[15] ("Guidance on Premarket Notification") (explaining that, for the purposes of determining whether a new device has the same intended use as a predicate device, the Center considers such points as "physiological purpose," "parts of the body," and "types of tissue involved").

2. Similarly, FDA was well within its discretion in concluding that the StemSource 900 does not have the same intended use as the predicate devices. Cytori's stated intended use was "laboratory use" for "separation of adipose derived cells," JA 294, 307, which Cytori clarified would produce a cellular product for banking or cryopreservation, JA 295; see JA 298-300, 305, 312. Yet, as FDA concluded, they were "not aware of a legally marketed" predicate device labeled or promoted for this use. JA 384; see also JA 379-380 (CBER scientist review memo).

---

[15] *Available at*, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=.

As FDA concluded, none of Cytori's predicate devices[16] has the same intended use. See JA 298-305 (Cytori's proposed equivalence); JA 313-375 (Cytori's submitted literature on the predicate devices). Indeed, Cytori did not seriously contend otherwise, merely notifying FDA that the StemSource 900 "shares indications and design principles" with Cytori's proposed predicate devices. JA 298.

Thus, the ThermoGenesis AXP AutoXpress and Biosafe Sepax System are for processing and storing cord blood. JA 300, 305, 317-322, 325-335; see also JA 287, 289. The Cytori Celution Cell Concentration Device is for the collection of autologous cells to obtain concentrated blood cells for reinfusion during various surgical procedures. JA 300, 305, 338-343. Cytori's other purported predicates — LifeGlobal Protein Supplement, StemPro MSC SFM Medium, Medi-Cult A/S Medi-Cult Hyaluronidase, and Thrombigel Thrombin/Gelatin Foam — are not systems at all, but rather are substances. See JA 289 ("It is impossible to answer the question regarding the applicability of a predicate for a component of the StemSource System without having an acceptable predicate for the entire system."); see *supra* p. 28, n.14 (describing FDA Guidance on use of multiple and "split" predicates); Guidance on Premarket Notification ("the Center will subject [a] combination device

---

[16] As with its submission to CDRH, Cytori identified one of the devices as a "related device," not a predicate device. Regardless of moniker, none of the devices identified in Cytori's submission had the same intended use.

to the same sorts of questions and documentation requirements that are applied to a single device"). And the stated uses for these substances was entirely different from the use of the StemSource 900 System. LifeGlobal Protein Supplement and Medi-Cult Hyaluronidase are intended for use in assisted reproductive procedures, such as in vitro fertilization. JA 356, 363. StemPro MSC is a liquid tissue culture medium, used to grow human cells ex vivo. JA 370. And Thrombigel is used "as a trauma dressing for temporary control of moderate to severely bleeding wounds." JA 352, 347-349.

As with the Celution 700, Cytori tried to reconceptualize the intended uses at such a high level of generality that nearly any device involved in processing or growing human cells could be used as a predicate for its specific system. See JA 298 (asserting that StemSource 900 "and all of the predicate devices * * * are all indicated for use in the processing of cells/tissue with a reagent"). FDA was well within its discretion to evaluate the intended use more specifically.

Before this Court, Cytori argues that FDA abused its discretion by concluding that the StemSource 900 — a device that Cytori submitted with an intended use of "separation of adipose derived cells," JA 294, 307 — does not have "the same intended use," 21 U.S.C. § 360c(i), as the cord blood processing systems that Cytori submitted. See Br. 43-44. Fat is not blood. And adipose tissue, *i.e.*, fat tissue, is not cord blood. The intended use of processing and separating fat tissue is different from

processing and separating cord blood. They are different tissues that will react differently in a device, and differently still when a [redacted] enzyme is used. Cells are the basic building blocks of life. Not every cell is the same. See generally Guidance on Premarket Notification (explaining that, for the purposes of determining whether a new device has the same intended use as a predicate device, the Center considers "types of tissue involved"); cf. *United States* v. *Caputo*, 517 F.3d 935, 940 (7th Cir. 2008) (finding that promotion of a device "as suitable for use with all medical instruments is a major change in intended use, compared with using it for solid stainless-steel instruments alone").

Cytori urges that the new device and predicate device need not have "the same intended use," 21 U.S.C. § 360c(i), but instead "the intended uses of new devices and their predicates may vary" and "FDA will judge such variances based upon whether they present issues of safety and effectiveness." Br. 44; see also Br.10.[17] Cytori's interpretation of the statute is flatly wrong. Cytori points to a 1976 House Report, H.R. Rep. No. 94-853. Br. 44. But "the same intended use" requirement was added fourteen years after that report, in the 1990 amendments. See Safe Medical Devices Act, Pub. L. No. 101-629 § 12, 104 Stat. 4511, 4523 (1990). The legislative history of

[17] Cytori appears to make this argument only with regard to CBER's decision about the StemSource 900, see Br. 43-44, but describes the background law in this manner elsewhere in the brief, see Br. 10.

the 1990 Act indicates that Congress meant what it said. See H.R. Rep. 101-808, at 24-25 (stating six times that the new device must have the "same intended use"); S. Rep. No. 101-513, at 28 ("Generally speaking, a device is substantially equivalent to its predicate device if it has the *same* intended use, and is as safe and effective as the predicate device.") (emphasis added).[18]

Cytori also misunderstands a draft guidance document about the 510(k) process.[19] Br. 44. The draft guidance makes clear that the new and predicate device must have "the same intended use." *E.g.*, Draft Guidance, The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications 7, 14 (2011)[20] ("Draft Guidance"); see also Guidance on Premarket Notification ("Devices which do not have the same intended use cannot be substantially equivalent."); *ibid.*("[S]light modifications in intended use can be significant to the claimed effect or purpose of

---

[18] In any event, we note that the language in H.R. Rep. No. 94-853, to which Cytori points, see Br. 44, 7, would itself support FDA's finding here, insofar as the "differences" between the new and predicate devices, *e.g.*, processing entirely different kinds of cells, and using a brand new [redacted] enzyme, likely "relate to safety and effectiveness." H.R. Rep. 94-853, at 36.

[19] We note that the draft guidance document was not even circulated for public comment until December 27, 2011, months after CBER issued its decision, see JA 384. It also is not a binding statement of FDA's interpretation of the Act. The Draft Guidance states clearly that it was distributed "for comment purposes only," (p.1), and the top of every page states that it "[c]ontains [n]onbinding [r]ecommendations" and is a "[d]raft - [n]ot for [i]mplementation."

[20] *Available at*, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf.

the predicate device. If a device has a different intended use, there is no reason to proceed further to decide whether the devices are substantially equivalent.").

Cytori appears to have conflated the "intended use" — the term at issue, with the"indications for use." Cytori's brief thus asserts that a new device must only have an "intended use" that is "substantially equivalent," meaning that it may have a different intended use so long as "'the indications of the new device'" do not "'affect'" the "'safety and/or effectiveness of the new device as compared to the predicate device.'" Br. 10 (quoting Draft Guidance 7). But in fact, the draft guidance states that "FDA must find that the intended use of the device and its predicate are '*the same.*'" Draft Guidance 7 (emphasis added). The language from which Cytori draws excerpts explains: "As discussed in the Intended Use Section of this guidance, differences in the indications of use such as the population for which a device is intended * * * do not necessarily result in a new intended use." *Ibid.* "Such differences [in indications for use] result in a new intended use when they affect (or may affect) the safety and/or effectiveness of the new device as compared to the predicate device * * * ." *Ibid.* The very page of the draft guidance that Cytori cites in its argument section makes clear that a device's "intended use" is different from the "indication for use" of a device. See Draft Guidance 14 ("For purposes of substantial equivalence, the term *intended use* means the general purpose of the device — or what the device does — and encompasses the indications for use. The term *indications for*

use describes the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended.").[21]

B. FDA Properly Concluded that Cytori's New Devices Do Not Have the Same Technological Characteristics and Cytori Had Not Submitted Appropriate Data Demonstrating that the New Devices Are Safe and Effective and Do Not Raise Different Questions of Safety and Effectiveness.

Even if Cytori's devices had the same intended use as the predicate devices, Cytori also was required to show that its new devices either (i) "ha[ve] the same technological characteristics as the predicate device[s]"; *or* (ii) if it has different technological characteristics there must be "information submitted that the device is substantially equivalent to the predicate device * * * including appropriate clinical or scientific data" demonstrating "that the device is as safe and effective" *and* it must

[21] Cytori complains that CBER "failed to explain" why the StemSource 900 has a different intended use than the predicate devices that Cytori submitted. Br. 44. Yet curiously, Cytori concedes "that its statement of intended use was not identical to that of its predicates." *Ibid.* Presumably, Cytori's desire for a more detailed explanation may result from Cytori's mistaken belief that the intended uses do not have to be the same. In any event, FDA's "path may reasonably be discerned." *Motor Vehicle Mfrs. Ass'n of U.S., Inc.* v. *State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983); see *Casino Airlines, Inc.*, 439 F.3d at 717-18. CBER's decision stated that it was "not aware" of a predicate device "labeled or promoted for laboratory use for processing of adipose tissues to separate adipose-derived cells for banking and cryopreservation." JA 384. The CBER memo also makes clear that CBER's scientists reviewed the predicate devices and noted that cord-blood processing is a different intended use. See JA 379-380.

"not raise different questions of safety and effectiveness than the predicate device." 21 U.S.C. § 360c(i)(1)(A); see also 21 C.F.R. § 807.100(b)(2).

FDA properly concluded that both devices have "new technological characteristics that could affect safety and effectiveness and raise new types of safety questions." JA 384 (CBER decision about StemSource 900); accord JA 200 (CDRH decision about Celution 700) ("the performance data provided is inadequate to demonstrate substantial equivalence").

As noted, Cytori's new systems process adipose tissue and separate adipose-derived cells from such tissue. As FDA's scientific memos explained, the new devices operate by taking advantage of the greater buoyancy of fat cells, JA 188 (CDRH memo); JA 380-381 (CBER memo); JA 4, 296 (510(k) submissions) — a different mechanism than the predicate devices. Moreover, as FDA noted, the new devices use a [redacted] enzyme, Celase, that [redacted] JA 188 (CDRH memo); accord JA 380 (CBER memo), see JA 4, 295, 297, 309. Cytori did not demonstrate that its [redacted] enzyme has the same technological characteristics as the enzymes used in their predicates. See JA 11-14 (asserting that Celase and certain predicates "share design and material characteristics" and share the "technology of cleaving" protein); JA 301-303 (same); see also Guidance on Premarket Notification ("Technological differences may include modifications in design, materials, or energy sources; for example, changes in

the power levels of electrical surgical instruments, the use of new reagents in in vitro diagnostic devices, the use of new materials in orthopedic implants, and the use of new battery designs in implanted pacemakers.")

Thus, the question was whether Cytori submitted information, "including appropriate clinical or scientific data" demonstrating that the new devices are "as safe and effective" as the predicate devices *and* do "not raise different questions of safety and effectiveness than the predicate device[s]." 21 U.S.C. § 360c(i)(1)(A); see also 21 C.F.R. § 807.100(b)(2). FDA reasonably concluded the Cytori has not done so.

With regard to the Celution 700, a CDRH scientist explained that the submitted data were based on a study of only 12 donors, without any information concerning sex, age, or medical conditions. JA 189; see JA 5. And the FDA scientist expressed concerns about Cytori's data, [redacted] JA 189; see JA 6-9.

[redacted]. JA 189; see JA 7-8. [redacted]

Public Copy -- Sealed Material Deleted

See JA 189. [redacted] *Ibid.*; see JA 8-9. [redacted] JA 189.

A CBER scientist expressed similar concerns about the StemSource 900, specifically stating that "the enzyme, Celase" "is a new technology that raises new questions of safety of the subject device." JA 381. The scientist referenced CBER's earlier letter to Cytori, which had concluded that a similar device was not substantially equivalent, in part because of the same Celase enzyme. *Ibid.*, see also JA 377-378 (explaining that another Cytori device was determined not to be substantially equivalent because, among other things, the same Celase enzyme raised "new types of safety questions").

Cytori does not appear to dispute the substance of FDA's decision. With regard to the Celution 700, Cytori makes a passing comment that CDRH's decision letter did not explain "why the data * * * was insufficient." Br. 39. Because the device did not have the same stated intended use as any of the predicates, this Court need not address CDRH's decision concerning Cytori's insufficient data. See *Casino Airlines, Inc.*, 439 F.3d at 717-18. But in any event, FDA's "path may reasonably be discerned." *Motor Vehicle Mfrs. Ass'n* v. *State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43

(1983) (internal quotation marks omitted); see *Casino Airlines, Inc.*, 439 F.3d at 717-18. As noted, the CDRH memo about the Celution 700 explained the various deficiencies in Cytori's data. See JA 189. [redacted] See *ibid.* While Cytori can argue whether the device is, in fact, safe and effective despite the different questions of safety and effectiveness raised by their new technology, that determination must be made as part of a premarket approval.[22] FDA had ample basis for its finding that Cytori had not met the burden of showing that the device is as safe and effective as the identified predicates. 21 U.S.C. § 360c(i)(1)(A); see also H.R. Rep. No. 101-959, at 27 (Conf. Rep.) ("a device will not be found to be as substantially equivalent if the device *raises questions* of safety and effectiveness that are different from the predicate device") (emphasis added); S. Rep. No. 101-513, at 28 (1990) ("[T]he agency will not find a device substantially equivalent to a predicate device where the newer device raises different safety or effectiveness considerations"); H.Rep. No. 101-808, at 24

[22] See generally 21 U.S.C. § 360e; 21 C.F.R. part 814; Draft Guidance 19 (explaining that if a device is not substantially equivalent, a manufacturer may apply for premarket approval or, if appropriate, a de novo petition); *id.* at 6 (the 510(k) review of safety and effectiveness is "comparative whereas the PMA standard relies on an independent demonstration of safety and effectiveness"); Guidance on Premarket Notification ("Data in a 510(k) should show comparability of a new device to a predicate device, whereas demonstration, in an absolute sense, of a device's safety and effectiveness, is reserved for PMAs.").

(1990) (similar).[23]

C. Cytori's Remaining Objections Are Meritless.

Other than Cytori's misinterpretation of the "same intended use" requirement, Cytori does not seriously argue that either of its devices meet the statutory prerequisites for substantial equivalence. Instead, Cytori seizes on a few comments from the two review memos, urging that improper considerations infected the ultimate determinations. Each of the two statutory prerequisites is an independent and valid ground for FDA's decisions. See *Casino Airlines, Inc.*, 439 F.3d at 717-18. Cytori has not offered a basis to disturb either one.

1. FDA Did Not "Rewrite" Cytori's Statements of Intended Use.

Cytori's primary argument is that FDA treated its devices as having different intended uses than Cytori submitted. Br. 37-39, 41-42, 45-46. This set of arguments takes aim at strawmen, taking comments in FDA review memos out of context.

a. The CDRH review memo properly stated Cytori's intended use. JA 188, 191. And in commenting on the proposed predicate devices, and the deficiencies in the safety-related data, the CDRH memo did discuss any other intended use. See JA

---

[23] Cytori also suggests that FDA was required to request additional information. Br. 39. But while FDA may choose to request more information, see 21 U.S.C. § 360c(i)(1)(D), it is not obligated to do so, and certainly not if the request would be fruitless. Here, FDA concluded that the new device did not have the same intended use as any predicate device. Thus, no additional data could change the ultimate decision.

189-190. CDRH's decision letter also accurately described the stated intended use. JA 200; see JA 21 (Cytori's stated intended use).

Cytori is thus wrong that "CDRH simply dismissed the statement of intended use," or "rewr[ote]" the 510(k) submission. Br. 38-39. Cytori's primary basis for this assertion is that in the CDRH review memo, the reviewing scientist posed certain questions about a patient population of 12 people, why they had liposuction, and what medical conditions they had. See Br. 38-39 (quoting JA 190). No such comments appear in FDA's final decision, but only in the review memo from a scientist describing the device and data to a decisionmaker. In any event, the comments do not suggest that the reviewing scientist "simply dismissed" Cytori's intended use. The reviewing scientist described Cytori's intended use accurately in the memo, including in the paragraph after the one that Cytori quotes. JA 188, 191. The questions about liposuction concludes the discussion of Cytori's data and are plainly questions relating to Cytori's data, which involve testing on cells drawn from 12 donors who had liposuction, from whom there was no information about other medical conditions. See JA 189.

Cytori is on no firmer ground noting that during a phone conversation between CBER and CDRH, the offices expressed "concern about the potential therapeutic use of this cellular product." Br. 37 (quoting JA 103). As noted, CDRH did not rely on this concern in making its decision. See JA 200-201 (CDRH

decision). The comment appears in the CDRH review memo only as a memorialization of the phone conversation. See JA 188-191. Further, it was an appropriate matter for discussion between CDRH and CBER to determine jurisdiction, because a device producing a therapeutic biologic product must be reviewed by CBER. See *supra*, p. 6.; JA 306 (citing jurisdictional document in explaining to Cytori that "[d]evices intended to process HCT/Ps ex vivo to create a therapeutic article * * * have been assigned to CBER"). The fact that CDRH continued reviewing the device and issued a decision, instead of transferring the submission to CBER or telling Cytori to resubmit it to CBER, shows that CDRH did not analyze the device as one used to create a therapeutic cellular product. See *ibid.* And, as Cytori itself notes, these concerns are relevant to CDRH's determination because possible off-label use may justify requiring labeling modifications. See Br. 37-38; 21 C.F.R. § 814.44(e). Because that was not CDRH's ultimate reason for finding that the device is not substantially equivalent, however, see JA 200-201 (CDRH decision), CDRH's not requiring such a label was not an error. See Br. 37-38.

b. The CBER review memo also properly stated Cytori's intended use. JA 379. The review memo accurately reported Cytori's stated "indications for use," see *ibid.*, and accurately noted that Cytori's submission clarified that the intended use was to produce a cellular product "for banking [and] cryopreserving." JA 376; see JA 295,

298-300, 305, 312 (Cytori's 510(k) notification and accompanying draft product labeling). In commenting on the proposed predicate devices, and the deficiencies in the safety-related data, the CBER memo did not rely on any other intended use. See JA 380-381, 383.[24] CBER's decision letter thus accurately described the intended use as "laboratory use for processing of adipose tissues to separate adipose-derived cells for banking and cryopreservation." JA 384.

Cytori is wrong that "FDA rejected [its] 510(k) notification based upon an intended use not even raised in the 510(k) notification" or "rewr[ote] the 510(k) notification." Br. 42. Cytori's primary basis for this assertion is that the CBER review memo commented that "to gain marketing authorization * * * a specific clinical indication for use would be needed." Br. 42 (quoting JA 377). But a comment about the lack of a clinical *indication* is not a rewrite of the *intended use* — the matter relevant to the first part of FDA's determination. As noted, intended use and

---

[24] Cytori suggests that CBER's concerns about the cellular product being returned to patients could have been addressed by requiring a statement in the device's labeling prohibiting "off-label" use for return to a patient. See Br. 43. But as noted, Cytori's labeling and various statements of the StemSource's intended use specifically referred to banking and preservation, which includes an eventual return to a patient. Indeed, in its brief here, Cytori concedes as much. See Br. 21. And without return to patients, the device would be before CDRH. Moreover, any discussion of labeling was premature because Cytori had not identified any acceptable predicate devices, for even a narrower intended use. See Determination of Intended Use for 510(k) Devices 2-3 (2002), *available at*, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082166.pdf.

indications for use are different. See *supra*, p. 35-36.

In any event, no such comments appear in CBER's decision letter. See JA 384-385. And the CBER scientist's comments in the review memo are entirely appropriate. The language that Cytori quotes in the review memo was the author's recitation of the pre-510(k) process — that is, what occurred *before* Cytori's 510(k) submission. See JA 377. That summary of the pre-510(k) process makes clear that FDA had told Cytori that the 510(k) process was inappropriate because there was no valid predicate device, mentioning the need for a clinical indication separately, as part of the next step for conducting investigational studies and seeking standard premarket approval. See JA 377; see also JA 290, 288 (pre-510(k) communications).[25]

Cytori similarly posits that FDA abused its discretion when evaluating the technological characteristics and "'safety questions related to the potential effects the Celase reagent may have on tissue that may be returned to the patient.'" Br. 45 (quoting JA 384). Cytori urges that FDA was required to analyze the data with "'tool type' indications" without considering that the banked or preserved cells may be

[25] Moreover, there are other reasons that a reviewing scientist may believe that indications for use are necessary. First, indications for use confirm that the device is a medical device covered by the Act. See 21 U.S.C. § 321(h) (defining "device"). Second, indications for use are relevant when evaluating whether Cytori's "clinical or scientific data" demonstrates "that the device is as safe and effective" as the predicate. 21 U.S.C. § 360c(i)(1)(A).

returned to patients. Br. 41-42, 45-46.[26] But the predicates that Cytori identified did not have the same tool-type claim that Cytori now desires. Moreover, Cytori reported in, *inter alia*, its draft labeling and comparisons to predicate devices, that the StemSource 900 was intended to create a cellular product to be preserved and eventually returned to patients. See JA 295 ("banking/cryopreservation"); JA 298 (positing that the StemSource 900 and predicates "share the same intent of delivering minute amounts of residual reagent back to the donor"); JA 298-299 (urging the StemSource "shares indication for use principles" with predicates because the cellular output is "intended for re-implantation into a donor" and "cryopreservation"); JA 300, 305 (charts listing StemSource "intended use" as including "Ex Vivo Processing for Re-implanted," "Ex Vivo Processing for Cryopreservation," and "Autologous Cells for Re-implanted."); JA 312 [redacted]

Thus, Cytori concedes that it told FDA that the StemSource 900 is

[26] We note that a portion of Cytori's argument here concerning CBER's decision about the StemSource 900 actually draws on statements from the CDRH record. See Br. 41 (quoting JA 103). To be sure, those statements are CDRH's summary of a phone conversation with CBER about what is the same physical device. But CBER did not include the conversation in its record. CDRH and CBER's joint concerns about therapeutic use of the cellular product are relevant both to how Cytori's data must be viewed and to determine which center should properly be reviewing the device(s), since CBER is charged with devices that produce a biologic product used in patients. See *supra*, p. 6.

substantially equivalent to "devices which process bodily tissue * * * [to] be returned to the patient." Br. 21; see *ibid.* (Cytori's "intended use of banking and cryopreservation" "assumes that at some point in the future * * * the banked cells will be returned by someone other than the Petitioner to the person from whom they were removed"). As noted, if the device were not producing such a product (*e.g.,* being used for clinical diagnostic testing), it would be reviewed by CDRH, not CBER. See *supra*, p. 6. Cytori's 510(k) notification urged that the StemSource 900 and predicates "share the same intent of delivering minute amounts of residual reagent back to the donor." JA 298. It is reasonable for FDA to consider as relevant what effects the Celase reagent may have when returned to the patient.[27]

Cytori wants to have it both ways. Cytori wants to say that the intended use did not include return to a patient, so as to undermine CBER's second ground concerning risks of the Celase reagent.[28] But if their intended use is not to create a

---

[27] In any event, Cytori does not argue that FDA's considering the banking/cryopreservation use improperly affected that determination whether the StemSource has the "same intended use" as a predicate device. Nor could Cytori do so, as it is clear that Cytori's predicate devices differed substantially in intended use, for reasons unrelated to banking/cryopreservation. See 5 U.S.C. § 706; *PDK Labs. Inc.* v. *United States DEA*, 362 F.3d 786, 799 (D.C. Cir. 2004) (even if an agency makes a mistake, if it did "not affect the outcome, if it did not prejudice the petitioner, it would be senseless to vacate and remand for reconsideration"). And the difference in stated intended use is an independent basis for FDA's decision. See *Casino Airlines, Inc.,* 439 F.3d at 717-18.

[28] Of course, there can still be safety-type concerns with a device even if the device's output is not returned to patient. A device used diagnostically, for example,

product that will be returned to patients, it only further reinforces CBER's first ground that the device did not have the same intended use as the predicates, because Cytori's predicate devices had intended uses of returning products to patients.

2. Cytori Cannot Complain Here that its Devices Should Be Treated as General Purpose Laboratory Equipment.

a. At several points in its brief, Cytori suggests that FDA somehow erred by not classifying and/or treating its devices as Class I "General Purpose Laboratory Equipment," under 21 C.F.R. § 862.2050. See Br. 40-41, 46. But even assuming that 21 U.S.C. § 360g(a)(8) creates jurisdiction to review FDA's decisions here about substantial equivalence, § 360g(a)(8) does not authorize direct petitions for review concerning Cytori's objections concerning Class I general laboratory equipment. See 21 U.S.C. § 360g(a)(8).

Cytori's arguments concerning Class I general laboratory equipment are distinct from FDA's decisions concerning substantial equivalence. Cytori "notifie[d] CDRH of its intent to introduce" the Celution 700 as "substantially equivalent" to eight "Class II devices." JA 1. Thus, the section of Cytori's 510(k) notification about "equivalence to marketed product[s]" referenced "Class II medical devices." JA 10;

---

poses safety concerns if it does not produce accurate results. Here, the Celase enzyme [redacted]. Questions about how the Celase affects, for example, cell integrity, cell death, or quality of preservation, may affect whether diagnostic use of the cellular product is scientifically valid. And a false negative on a diagnostic lab test, for example, can pose safety-type concerns.

see also JA 14 (chart concerning proposed equivalence); JA 25-72 (510(k) notification exhibits concerning proposed predicates). Likewise, Cytori notified CBER that the StemSource 900 is substantially equivalent only to certain "Class II medical devices." JA 292. Thus, the 510(k) notification mentioned only classification under Class II as a Cord Blood Processing System, JA 293, and offered Class II devices as predicates, see JA 298-300; see also JA 308, 313-375.

Without reference to the rest of the application or to the standards for substantial equivalence, Cytori briefly stated that it believed that each device is "classif[ied] * * * as a Class I device, under 21 C.F.R. [§] 862.2050, 'General Purpose Laboratory Equipment, Labeled and Promoted for a Specific Medical Use.'" JA 1 (Celution 700); JA 292 (StemSource 900); see also JA 2, 18. Cytori asked FDA to "confirm, in writing" if the agency "concur[s] with [that] assertion" and "if not" to review the 510(k) notification concerning substantial equivalence. JA 1 (Celution 700); JA 292 (StemSource 900).

Manufacturers sometimes place such statements at the beginning of a 510(k) notification, inviting FDA to "[a]dvise" them "that the premarket notification is not required." 21 C.F.R. § 807.100(a)(5); see 21 U.S.C. § 360(*l*) & (m); 21 C.F.R. § 862.9 (certain Class I and II devices exempt from premarket notification). But as noted, even if the substantial equivalence decisions are properly before this Court, any decisions concerning exemption from premarket notification are not properly before

this Court. And if Cytori is now complaining that it wants to have been initially classified as a Class I device, that matter also is not properly before this Court. See *Moms Against Mercury*, 483 F.3d at 827 ("Classifications of devices into classes II or III * * * are directly reviewable only in district court because the FDCA does not provide for their review in the courts of appeals.").

b. In any event, FDA correctly acted on Cytori's comments about being a Class I general laboratory equipment. As noted, manufacturers sometimes place such statements at the beginning of a 510(k) notification, so that FDA can "[a]dvise" them "that the premarket notification is not required." 21 C.F.R. § 807.100(a)(5); see 21 U.S.C. § 360(*l*) & (m); 21 C.F.R. § 862.9. That appears to have been the case here. See JA 1, 292 (inviting FDA to "confirm" Cytori's assertion and "if not" to review the premarket notification).

Even were Cytori's new devices Class I general laboratory equipment,[29] the devices would not be exempt from premarket notification because the exemption is inapplicable if a "device is intended for a use different from the intended use of a

---

[29] We note that Cytori's suggestion to CBER that the StemSource 900, is a Class I device under 21 C.F.R. § 862.2050 is on its face incorrect. 21 C.F.R. § 862.2050 is covered under Part 862, entitled"Clinical chemistry and Clinical Toxicology Devices," and Subpart C, entitled "Clinical Laboratory Instruments." See 21 C.F.R. Part 862. These are devices used to analyze samples in a clinical laboratory or prepare samples for such analysis. Thus, 21 C.F.R. § 862.2050, is not an appropriate classification for devices like the StemSource, which are submitted to CBER and used to prepare materials for therapeutic products. See *supra*, p. 6.

legally marketed device in that generic type of device" or if "device operates using a different fundamental scientific technology than a legally marketed device in that generic type of device." 21 C.F.R. § 862.9(a) & (b). Processing adipose tissue and using a [redacted] enzyme are not "characteristics of commercially distributed devices within that generic type." 21 C.F.R. § 862.9. Cytori has not pointed to a single device within the type covered by 21 C.F.R. § 862.2050 with the same intended use or with same technology as its devices. Therefore, the same reasons that justify FDA's decisions concerning substantial equivalence mean the devices are not exempt under this regulation.[30]

Thus, it is inconsequential that FDA's letters did not explicitly state that the devices are not exempt from a premarket notification (an issue that is not subject to direct review). See Br. 46. Exactly as Cytori requested, FDA reviewed the premarket notifications concerning substantial equivalence. See JA 1, 292. By determining that the devices are not substantially equivalent, FDA necessarily rejected Cytori's

---

[30] Cytori criticizes a comment made during the telephone call between CBER and CDRH scientists, that its device is not "Class I exempt" because Cytori "want[s] to use [it] at point of care in the operating room." Br. 40-41 (quoting JA 192). This comment is only a report of a scientist's thought during an early telephone call. In any event, Cytori is wrong that point of care use "has nothing to do" with the matter at issue. Br. 40 & n.19. The exemption from premarket notification excludes "an in vitro device that is intended" for "near patient testing (point of care)." 21 C.F.R. § 862.9(c)(9). Thus, Cytori's desire "to use [it] at point of care," meant it was not "Class I exempt." JA 192.

suggestion that it need not submit any premarket notification at all. See 21 C.F.R. § 807.100(a) (listing mutually exclusive actions that FDA can take, including declaring a device not substantially equivalent and advising a manufacturer that the premarket notification is not required).

3. Cytori Cannot Ask This Court to Make Its Own Determination of Substantial Equivalence.

In the conclusion of its brief, Cytori asks that this Court itself declare that Cytori's devices are substantially equivalent to the submitted predicates. Br. 47. Because FDA's decisions were not arbitrary and capricious, this Court need not address Cytori's demand for such an extraordinary remedy.

In any event, the appropriate remedy for improper agency action is remand. "Generally speaking, a court of appeals should remand a case to an agency for decision of a matter that statutes place primarily in agency hands." *INS* v. *Orlando Ventura*, 537 U.S. 12, 16 (2002) (per curiam); see *Florida Power & Light Co.* v. *Lorion*, 470 U.S. 729, 744 (1985). "The reviewing court is not generally empowered to conduct a de novo inquiry into the matter being reviewed and to reach its own conclusions based on such an inquiry." *Ibid.* All the more so here, where the matter at issue is a specialized, scientific determination entrusted to experts, and Cytori has not seriously disputed FDA's ultimate conclusion that the new medical devices do not satisfy the statutory requirements for substantial equivalence.

CONCLUSION

The petitions for review should be dismissed or, in the alternative, denied.

Respectfully submitted,

STUART F. DELERY
Acting Assistant Attorney General

SCOTT R. MCINTOSH
(202) 514-4052
ADAM C. JED */s/ Adam Jed*
(202) 514-8280
Attorneys, Appellate Staff
Civil Division, Room 7280
U.S. Department of Justice
950 Pennsylvania Avenue, N.W.
Washington, D.C. 20530

JUNE 2012

CERTIFICATE OF COMPLIANCE

This brief is set in a 14-point proportional typeface, and contains 13,231 words, as counted by WordPerfect X5.

/s/ Adam C. Jed

CERTIFICATE OF SERVICE

On June 27, 2012, I filed and served a public, redacted version of this brief using the CM/ECF system, and caused an original plus six copies of a sealed, unredacted version to be delivered to the Court by FedEx, and two copies of a sealed, unredacted version to be delivered by FedEx to opposing counsel.

/s/ Adam C. Jed

ADDENDUM

ADDENDUM TABLE OF CONTENTS

21 U.S.C. § 360c

* * *

(i) Substantial equivalence.

(1) (A) For purposes of determinations of substantial equivalence under subsection (f) and section 520(l) [21 U.S.C. § 360j(l)], the term "substantially equivalent" or "substantial equivalence" means, with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that the Secretary by order has found that the device--

(i) has the same technological characteristics as the predicate device, or

(ii) (I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data if deemed necessary by the Secretary or a person accredited under section 523 [21 U.S.C. § 360m], that demonstrates that the device is as safe and effective as a legally marketed device, and (II) does not raise different questions of safety and effectiveness than the predicate device.

(B) For purposes of subparagraph (A), the term "different technological characteristics" means, with respect to a device being compared to a predicate device, that there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device.

(C) To facilitate reviews of reports submitted to the Secretary under section 510(k) [21 U.S.C. § 360(k)], the Secretary shall consider the extent to which reliance on postmarket controls may expedite the classification of devices under subsection (f)(1) of this section.

(D) Whenever the Secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such request, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly.

(E) (i) Any determination by the Secretary of the intended use of a device shall be based upon the proposed labeling submitted in a report for the device under section 510(k) [21 U.S.C. § 360(k)]. However, when determining that a device can be found substantially equivalent to a legally marketed device, the director of the organizational

unit responsible for regulating devices (in this subparagraph referred to as the "Director") may require a statement in labeling that provides appropriate information regarding a use of the device not identified in the proposed labeling if, after providing an opportunity for consultation with the person who submitted such report, the Director determines and states in writing--

(I) that there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device; and

(II) that such use could cause harm.

(ii) Such determination shall--

(I) be provided to the person who submitted the report within 10 days from the date of the notification of the Director's concerns regarding the proposed labeling;

(II) specify the limitations on the use of the device not included in the proposed labeling; and

(III) find the device substantially equivalent if the requirements of subparagraph (A) are met and if the labeling for such device conforms to the limitations specified in subclause (II).

(iii) The responsibilities of the Director under this subparagraph may not be delegated.

(F) Not later than 270 days after the date of the enactment of the Food and Drug Administration Modernization Act of 1997 [enacted Nov. 21, 1997], the Secretary shall issue guidance specifying the general principles that the Secretary will consider in determining when a specific intended use of a device is not reasonably included within a general use of such device for purposes of a determination of substantial equivalence under subsection (f) or section 520(l) [21 U.S.C. § 360j(l)].

(2) A device may not be found to be substantially equivalent to a predicate device that has been removed from the market at the initiative of the Secretary or that has been determined to be misbranded or adulterated by a judicial order.

(3) (A) As part of a submission under section 510(k) [21 U.S.C. § 360(k)] respecting a device, the person required to file a premarket notification under such section shall provide an adequate summary of any information respecting safety and effectiveness or state that such information will be made available upon request by any person.

(B) Any summary under subparagraph (A) respecting a device shall contain detailed information regarding data concerning adverse health effects and shall be made available to the public by the Secretary within 30 days of the issuance of a determination that such device is substantially equivalent to another device.

21 U.S.C. § 360g

(a) Petition; record. Not later than thirty days after–

(1) the promulgation of a regulation under section 513 [21 U.S.C. § 360c] classifying a device in class I or changing the classification of a device to class I or an order under subsection (f)(2) of such section [21 U.S.C. § 360c(f)(2)] reclassifying a device or denying a petition for reclassification of a device,

(2) the promulgation of a regulation under section 514 [21 U.S.C. § 360d] establishing, amending, or revoking a performance standard for a device,

(3) the issuance of an order under section 514(b)(2) or 515 (b)(2)(B) [21 U.S.C. § 360d(b)(2) or 360e(b)(2)(B)] denying a request for reclassification of a device,

(4) the promulgation of a regulation under paragraph (3) of section 515(b) [21 U.S.C. § 360e(b)(3)] requiring a device to have an approval of a premarket application, a regulation under paragraph (4) of that section [21 U.S.C. § 360e(b)(4)] amending or revoking a regulation under paragraph (3), or an order pursuant to section 515(g)(1) or 515(g)(2)(C) [21 U.S.C. § 360e(g)(1) or (2)©],

(5) the promulgation of a regulation under section 516 [21 U.S.C. § 360f] (other than a proposed regulation made effective under subsection (b) of such section [21 U.S.C. § 360f(b)] upon the regulation's publication) making a device a banned device,

(6) the issuance of an order under section 520(f)(2) [21 U.S.C. § 360j(f)(2)],

(7) an order under section 520(g)(4) [21 U.S.C. § 360j(g)(4)] disapproving an application for an exemption of a device for investigational use or an order under section 520(g)(5) [21 U.S.C. § 360j(g)(5)] withdrawing such an exemption for a device,

(8) an order pursuant to section 513(i) [21 U.S.C. § 360c(i)], or

(9) a regulation under section 515(i)(2) or 520(l)(5)(B) [21 U.S.C. § 360e(i)(2) or 360j(l)(5)(B)],

any person adversely affected by such regulation or order may file a petition with the United States Court of Appeals for the District of Columbia or for the circuit wherein such person resides or has his principal place of business for judicial review of such regulation or order. A copy of the petition shall be transmitted by the clerk of the

court to the Secretary or other officer designated by him for that purpose. The Secretary shall file in the court the record of the proceedings on which the Secretary based his regulation or order as provided in section 2112 of title 28, United States Code. For purposes of this section, the term "record" means all notices and other matter published in the Federal Register with respect to the regulation or order reviewed, all information submitted to the Secretary with respect to such regulation or order, proceedings of any panel or advisory committee with respect to such regulation or order, any hearing held with respect to such regulation or order, and any other information identified by the Secretary, in the administrative proceeding held with respect to such regulation or order, as being relevant to such regulation or order.

* * *

21 C.F.R. § 807.95

(a) The Food and Drug Administration will disclose publicly whether there exists a premarket notification submission under this part:

(1) Where the device is on the market, i.e., introduced or delivered for introduction into interstate commerce for commercial distribution;

(2) Where the person submitting the premarket notification submission has disclosed, through advertising or any other manner, his intent to market the device to scientists, market analysts, exporters, or other individuals who are not employees of, or paid consultants to, the establishment and who are not in an advertising or law firm pursuant to commercial arrangements with appropriate safeguards for secrecy; or

(3) Where the device is not on the market and the intent to market the device has not been so disclosed, except where the submission is subject to an exception under paragraph (b) or (c) of this section.

(b) The Food and Drug Administration will not disclose publicly the existence of a premarket notification submission for a device that is not on the market and where the intent to market the device has not been disclosed for 90 days from the date of receipt of the submission, if:

(1) The person submitting the premarket notification submission requests in the submission that the Food and Drug Administration hold as confidential commercial information the intent to market the device and submits a written certification to the Commissioner:
(i) That the person considers his intent to market the device to be confidential commercial information;
(ii) That neither the person nor, to the best of his knowledge, anyone else, has disclosed through advertising or any other manner, his intent to market the device to scientists, market analysts, exporters, or other individuals, except employees of, or paid consultants to, the establishment or individuals in an advertising or law firm pursuant to commercial arrangements with appropriate safeguards for secrecy;
(iii) That the person will immediately notify the Food and Drug Administration if he discloses the intent to market the device to anyone, except employees of, or paid consultants to, the establishment or individuals in an advertising or law firm pursuant to commercial arrangements with appropriate safeguards for

secrecy;
(iv) That the person has taken precautions to protect the confidentiality of the intent to market the device; and
(v) That the person understands that the submission to the government of false information is prohibited by 18 U.S.C. 1001 and 21 U.S.C. 331(q); and

(2) The Commissioner agrees that the intent to market the device is confidential commercial information.

(c) Where the Commissioner determines that the person has complied with the procedures described in paragraph (b) of this section with respect to a device that is not on the market and where the intent to market the device has not been disclosed, and the Commissioner agrees that the intent to market the device is confidential commercial information, the Commissioner will not disclose the existence of the submission for 90 days from the date of its receipt by the agency. In addition, the Commissioner will continue not to disclose the existence of such a submission for the device for an additional time when any of the following occurs:

(1) The Commissioner requests in writing additional information regarding the device pursuant to § 807.87(h), in which case the Commissioner will not disclose the existence of the submission until 90 days after the Food and Drug Administration's receipt of a complete premarket notification submission;

(2) The Commissioner determines that the device intended to be introduced is a class III device and cannot be marketed without premarket approval or reclassification, in which case the Commissioner will not disclose the existence of the submission unless a petition for reclassification is submitted under section 513(f)(2) of the act and its existence can be disclosed under § 860.5(d) of this chapter; or

(3) [Removed. See 59 FR 18067, April 28, 1992.]

(d) FDA will make a 510(k) summary of the safety and effectiveness data available to the public within 30 days of the issuance of a determination that the device is substantially equivalent to another device. Accordingly, even when a 510(k) submitter has complied with the conditions set forth in paragraphs (b) and (c) of this section, confidentiality for a premarket notification submission cannot be granted beyond 30 days after FDA issues a determination of equivalency.

(e) Data or information submitted with, or incorporated by reference in, a premarket

notification submission (other than safety and effectiveness data that have not been disclosed to the public) shall be available for disclosure by the Food and Drug Administration when the intent to market the device is no longer confidential in accordance with this section, unless exempt from public disclosure in accordance with Part 20 of this chapter. Upon final classification, data and information relating to safety and effectiveness of a device classified in class I (general controls) or class II (performance standards) shall be available for public disclosure. Data and information relating to safety and effectiveness of a device classified in class III (premarket approval) that have not been released to the public shall be retained as confidential unless such data and information become available for release to the public under § 860.5(d) or other provisions of this chapter.

21 C.F.R. § 807.100

(a) After review of a premarket notification, FDA will:

(1) Issue an order declaring the device to be substantially equivalent to a legally marketed predicate device;

(2) Issue an order declaring the device to be not substantially equivalent to any legally marketed predicate device;

(3) Request additional information; or

(4) Withhold the decision until a certification or disclosure statement is submitted to FDA under part 54 of this chapter.

(5) Advise the applicant that the premarket notification is not required. Until the applicant receives an order declaring a device substantially equivalent, the applicant may not proceed to market the device.

(b) FDA will determine that a device is substantially equivalent to a predicate device using the following criteria:

(1) The device has the same intended use as the predicate device; and

(2) The device:

(i) Has the same technological characteristics as the predicate device; or

(ii)(A) Has different technological characteristics, such as a significant change in the materials, design, energy source, or other features of the device from those of the predicate device;

(B) The data submitted establishes that the device is substantially equivalent to the predicate device and contains information, including clinical data if deemed necessary by the Commissioner, that demonstrates that the device is as safe and as effective as a legally marketed device; and

(C) Does not raise different questions of safety and effectiveness than the predicate device.

(3) The predicate device has not been removed from the market at the initiative of the Commissioner of Food and Drugs or has not been determined to be misbranded or adulterated by a judicial order.