ORAL ARGUMENT SCHEDULED FOR
SEPTEMBER 21, 2012

No. 11-1268
(consolidated with 11-1279)

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

CYTORI THERAPEUTICS, INC.,
Petitioner,

v.

FOOD AND DRUG ADMINISTRATION,
Respondent.

FINAL BRIEF OF PETITIONER CYTORI THERAPEUTICS, INC.

Consolidated Petitions for Review
of Orders of the Food and Drug Administration

FDA-06/27/2011 – Letter
FDA-07/29/2011 – Letter

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CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES

Pursuant to Circuit Rule 28(a)(1), counsel for Petitioner Cytori Therapeutics, Inc. certify as follows:

A. Parties and Amici

The Petitioner in this case, Cytori Therapeutics, Inc., is a publicly traded company which has no parent company, and no publicly-held company has a 10% or greater ownership interest of its shares. Cytori Therapeutics, Inc. is the manufacturer of the Cytori Celution 700/LAB device and the Stem Source 900/MB Processor System, the medical devices which are the subject of these consolidated Petitions.

The Respondent in this case is the United States Food and Drug Administration. There are no intervenors or amici.

B. Rulings Under Review

This case involves two Petitions for Review of Agency Orders which were consolidated by order of this Court on September 7, 2011.

The first Petition (Case No. 11-1268) concerns the review of Respondent's Order denying Petitioner's 510(k) submission for Petitioner's Celution 700/LAB medical device. This Order is dated June 27, 2011 and was signed by Maria M. Chan, Ph.D., on behalf of the Respondent in FDA matter K111198. Appendix A; JA 200-201.

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The second Petition (Case No. 11-1279) concerns the review of Respondent's Order denying Petitioner's 510(k) submission for Petitioner's Stem Source 900/MB Processor System medical device. This Order is dated July 29, 2011 and was signed by Celia M. Witten, Ph.D., M.D. on behalf of the Respondent in FDA matter BK110020. Appendix B; JA 384-385.

C. Related Cases

These consolidated Petitions were never previously before this or any other Court, and there are no related cases.

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CORPORATE DISCLOSURE STATEMENT

The Petitioner, Cytori Therapeutics, Inc., is a publicly traded company which has no parent company, and no publicly-held company has a 10% or greater ownership interest of its shares. The Petitioner is the manufacturer of the two medical devices which are the subject of these consolidated Petitions.

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TABLE OF AUTHORITIES[1]

Cases

[1] Authorities upon which we chiefly rely are marked with asterisks.

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GLOSSARY

FDCA	Federal Food Drug and Cosmetic Act codified at 21 U.S.C. § 301 *et seq*.
FDA	Food and Drug Administration
CDRH	FDA's Center for Devices and Radiological Health
CBER	FDA's Center for Biologic Evaluation and Research
PMA subject to premarket approval	Premarket Approval. Under 21 U.S.C. § 360(e), all devices placed into Class III are requirements. Premarket approval by FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices.
510(k)	21 U.S.C. § 360(k). Section 510(k) of the FDCA, codified at 21 U.S.C. § 360(k), requires device manufacturers to provide premarket notification to the FDA of their intent to market a medical device at least ninety (90) days prior to introducing their devices into interstate commerce for commercial distribution. The purpose of this notification is to allow FDA to classify every new device and determine the regulatory controls applicable to each.
Class I Medical Device	The Medical Device Amendments of 1976 grouped all medical devices into one of

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	three regulatory classes based on the controls necessary to provide reasonable assurance of each device's safety and effectiveness; *see* § 513(a)(1)(A) – (C) (21 U.S.C. § 360c(a)(1)(A)-(C)). Class I devices, which carry the least risk, are governed solely by the general misbranding and adulteration controls of the FDCA and its implementing regulations.
Class II Medical Device	Class II devices present a greater risk than Class I devices, and must comply with both the general controls governing Class I devices and special controls designed to assure safety and effectiveness.
Class III Medical Device	Class III devices present a greater risk than Class I and Class II devices, and require "premarket approval," a scientific review conducted by the FDA to ensure the device's safety and effectiveness.
"Least Burdensome" Standard	21 U.S.C. § 360c(i)(1)(D) requires the FDA when requesting additional information about a 510(k) notification from a device sponsor, to "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."

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JURISDICTIONAL STATEMENT

The Petitioner seeks review of two orders. In the first order, the FDA denied via letter dated June 27, 2011 Petitioner's 510(k) submission for Petitioner's Celution 700/LAB medical device. In the second order, the FDA denied via letter dated July 29, 2011 Petitioner's 510(k) submission for Petitioner's Stem Source 900/MB Processor System medical device.

Basis for Agency Jurisdiction: The Food and Drug Administration ("FDA") had jurisdiction over the two 510(k) submissions pursuant to 21 U.S.C. § 393(b)(2)(c) which vests the FDA with jurisdiction to regulate medical devices generally, and 21 U.S.C. § 360(k) and 21 U.S.C. § 360c which set forth the procedural pathway available to medical device manufacturers seeking FDA's approval of medical devices. This pathway is described in greater detail *infra*, at pp. 4-12.

Basis for this Court's Jurisdiction: It is the position of the Petitioner that this Court has jurisdiction over this case at this time pursuant to 21 U.S.C. § 360g(a)(8) which gives this Court immediate jurisdiction over FDA orders "pursuant to [21 U.S.C. § 360c(i)]

It is the position of the Respondent that this Court does not have jurisdiction over this case at this time, and accordingly the Respondent moved to dismiss this case on September 30, 2011.

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On December 29, 2011, this Court entered an Order referring the Respondent's motion to dismiss to the Merits Panel and instructing the parties "to address in their briefs the issues presented in the motion to dismiss rather than incorporate those arguments by reference." Accordingly, in Part I of the Petitioner's Argument, *infra*, Petitioner addresses the basis for the Court's jurisdiction to hear this case at this time.

STATUTES AND REGULATIONS

Copies of pertinent statutes and regulations are attached hereto as an addendum.

STATEMENT OF ISSUES PRESENTED FOR REVIEW

This appeal presents the following issues:

1. Whether this Court has the jurisdiction to hear this case at this time.

2. Whether the FDA's rejections of the Petitioner's 510(k) notifications were arbitrary and capricious.

STATEMENT OF THE FACTS

I. Introduction[2]

The Petitioner in this case, Cytori Therapeutics, Inc. ("Cytori"), is a medical device manufacturer headquartered in San Diego, California. The two medical devices which are the subject of these consolidated petitions are the Cytori

[2] Record citation will be in the following format: (R [Record Page Number]; Addendum [Addendum Number]; JA [Deferred Joint Appendix Page Number]).

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Celution 700/LAB device and the Stem Source 900/MB Processor System. These two devices, which are described in detail below, allow physicians to access their patients' adipose (fat) derived stem cells for non-clinical purposes. However, prior to describing the two devices and the reasons why FDA's refusal to clear them was arbitrary and capricious, we outline the regulatory scheme governing medical devices.

II. The FDA's Regulation of Medical Devices

Prior to 1976, the terms "drug" and "device" had "parallel" definitions. *United States v. Bacto-Unidisk*, 394 U.S. 784, 789 (1969). As stated by the Court, "the language of the statute is of little assistance in determining precisely what differentiates a 'drug' from a 'device': to the extent that both are intended for use in the treatment, mitigation and cure of disease, the former is an 'article' and the latter includes 'instruments,' 'apparatus,' and 'contrivances.'" *Bacto-Unidisk*, 394 U.S. at 799. According to the Court, "the [device] exception was created primarily for the purpose of avoiding the semantic incongruity of classifying as drugs (1) certain quack contraptions, and (2) basic aids used in the routine operation of a hospital…" *Id.*, at 800.

As a result of these parallel definitions, the FDA was able to regulate medical devices as drugs and subject medical devices to premarket review not permitted under earlier versions of the FDCA; *see e.g. Bacto-Unidisk*, 394 U.S.

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784, 798 (1969) (noting that the definitions of drug and device are "parallel" and permitting FDA to regulate screening test disc as a drug); *AMP Incorporated v. Gardner*, 389 F.2d 825, 829 (2d Cir. 1968) (noting that, as of 1968, there was "no practical significance to the distinction between 'drugs' and 'devices'…" and permitting the FDA to regulate nylon sutures as drugs.)

A. The 1976 Amendments

At least partially in an effort to draw a clearer distinction between devices and drugs, Congress enacted the Medical Device Amendments to the FDCA in 1976 ("the 1976 Amendments); Pub.L. No. 94-295, 90 Stat. 539 (codified at 21 U.S.C. §§ 360c-360k). The 1976 Amendments redefined the term "medical device" and created the system for classification and premarket clearance of medical devices which forms the procedural backdrop of these consolidated Petitions.

First, the 1976 Amendments grouped all medical devices into one of three regulatory classes based on the controls necessary to provide reasonable assurance of each device's safety and effectiveness; *see* § 513(a)(1)(A) – (C) (21 U.S.C. § 360c(a)(1)(A)-(C)). Class I devices, which carry the least risk, are governed solely by the general misbranding and adulteration controls of the FDCA and its implementing regulations. Class II devices present a greater risk than Class I devices, and thus Class II devices must comply with both the general controls

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governing Class I devices and special controls designed to assure safety and effectiveness. Class III devices present a greater risk than Class I and Class II devices, and therefore require "premarket approval," a scientific review conducted by the FDA to ensure the device's safety and effectiveness.

The 1976 Amendments also grouped all medical devices into one of two groups based on when each device was originally developed. The first category, "preamendment devices," were those devices which were introduced or delivered for introduction into interstate commerce before May 28, 1976, the enactment date of the 1976 Amendments. The second category, "postamendment devices," were introduced or delivered for introduction into interstate commerce on or after May 28, 1976. Whereas the FDA itself classified all preamendment devices in homogeneous groups via rulemaking, the 1976 Amendments provided that all postamendment devices would come into existence individually.

In the 1976 Amendments, at § 510(k) (21 U.S.C. § 360(k)), Congress created a premarket notification system to establish an initial classification for each postamendment device. Within this system, device manufacturers were now required to notify FDA at least ninety (90) days prior to introducing their devices into interstate commerce for commercial distribution. The purpose of this notification was to allow FDA to classify every new device and determine the regulatory controls applicable to each; *see* 21 U.S.C. § 360c(f)(1)).

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Today, pursuant to 21 U.S.C. § 360c(f)(1), if a manufacturer of a new device can establish that a device is "substantially equivalent" to a preamendment device, then the new device will take on the same classification status as the preamendment device. Similarly, pursuant to 21 U.S.C. § 360c(i), if a manufacturer of a new device can establish that a device is "substantially equivalent" to a postamendment Class I or II device, the new device will take on the same classification status as the postamendment Class I or II device to which it was compared.[3] Now, by statute, any legally marketed device may serve as a "predicate" for classifying new devices.

B. Substantial Equivalence

As previously stated, pursuant to 21 U.S.C. §§ 360c(f)(1) and 360c(i), if a manufacturer of a new device can establish that a device is "substantially equivalent" to a predicate device, then the new device will take on the same classification status as the predicate device. The meaning of the term "substantially equivalent" is critical to this case.

First, 21 U.S.C. § 360c(i)(1)(A) defines "substantial equivalence" as follows:

> …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—

[3] Congress wrote this amendment into the FDCA in 1990.

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> (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 360m of this title, 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.

Congress's intent in enacting the "substantial equivalence" provisions of the FDCA has been articulated as follows:

> The term "substantially equivalent" is not intended to be so narrow as to refer only to devices that are identical to marketed devices nor so broad as to refer to devices which are intended to be used for the same purposes as marketed products. The committee believes that the term should be construed narrowly where necessary to assure the safety and effectiveness of a device ***but not narrowly where differences between a new device and a marketed device do not relate to safety and effectiveness***. Thus, differences between "new" and marketed devices in materials, design, or energy source, for example, would have a bearing on the adequacy of information as to a new device's safety and effectiveness, and such devices should be automatically classified into class III. On the other hand, copies of devices marketed prior to enactment, or devices whose variations are immaterial to safety and effectiveness would not necessarily fall under the automatic classification scheme.

H.R. Rep. No. 94-853 pp. 36-37 (1976); (emphasis added); *see also*, Center for Devices and Radiological Health, FDA, *Guidance on the Center for Devices and*

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Radiological Health's Premarket Notification Review Program, (June 30, 1986)[4] ("If substantial equivalence were judged too narrowly, the marketing of devices that would benefit the public would be delayed; the device industry would be unnecessarily exposed to the greater burdens of premarket approval; new devices would not be properly classified; and new manufacturers of pre-Amendments type devices would not have marketing equity. If substantial equivalence were judged too broadly, the statutory purpose may not be served, i.e., devices with new uses or those presenting new or different risks would be marketed without adequate regulatory control.")

However, as Congress made clear in the statute, whether a device is substantially equivalent is not necessarily a black or white issue. Indeed, many devices fall into a grey zone of regulation, and Congress instructed the FDA via statute how to confront such circumstances. 21 U.S.C. § 360c(i)(1)(C) provides: "To facilitate reviews of reports submitted to the Secretary under [21 U.S.C. § 360(k)], the Secretary shall consider the extent to which reliance on postmarket controls may expedite the classification of devices…" The statute continues as follows:

> (E) (i) Any determination by the Secretary of the intended use of a device shall be based upon the

[4]http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm

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> proposed labeling submitted in a report for the device under [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.

21 U.S.C. § 360c(i)(E); *see also,* S. Rep. No. 105-43, at 81 (1997); ("In making determinations to approve or deny an application, ***the Secretary will be required to limit the evaluation of safety and effectiveness to those uses proposed in the product label if it is determined that the labeling is neither false nor misleading.*** For products claiming substantial equivalence with others having different technological characteristics, the Secretary will be required to request only that information that is necessary and corresponds to the least burdensome means of demonstration. ***The Secretary must also base this finding only on the intended uses in the proposed labeling in a report submitted under section 510(k).***") (emphasis added).

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The FDA has most recently explained its two-step approach to evaluating substantial equivalence in its draft guidance document titled *The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications*, (December 27, 2011). First, FDA must determine whether the "intended use" of the new device is substantially equivalent to that of the predicate, and does so by evaluating whether the indications of the new device "affect (or may affect) the safety and/or effectiveness of the new device as compared to the predicate device…" *Id.*, at 7. Second, the FDA must determine if the new device and the predicate have "different technological characteristics" which may raise "different questions of safety and effectiveness…" *Id.*

The evidentiary standard employed by the FDA in evaluating a 510(k) application is described as follows:

> In the 510(k) context, FDA generally relies, in part, on FDA's prior determination that a reasonable assurance of safety and effectiveness exists for the predicate device. Demonstrating basic similarities between a new device and a predicate device typically requires manufacturers to provide descriptive information such as a comparison of specifications, materials, and technology. In contrast, FDA generally evaluates differences between the new device and the predicate device to determine their effect on safety and effectiveness. It follows that the evidence necessary to show substantial equivalence will increase as differences between the new device and the predicate device increase, if those differences affect, or may affect, safety or effectiveness.

Id.

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C. FDA Responses to Premarket Notifications

If the FDA determines that a device manufacturer's 510(k) notification fails to establish that the new device is substantially equivalent to a predicate, the FDA has several options. First, if the FDA determines that the notification was simply insufficient to establish substantial equivalence, the FDA can request additional information about the device. *Id.*, at 9.[5] In that case, the device sponsor will have the opportunity to work with the FDA "in good faith" in an effort to "resolve [the identified deficiencies." *Id.* With the notification's deficiencies thus resolved, the FDA will determine whether the device is substantially equivalent to its predicates.

Alternatively, the FDA may determine that the 510(k) notification lacks a predicate device, presents a new intended use, or contains "different technological characteristics that raise different questions of safety or effectiveness when the new devices is compared to the cited predicate device." *Id.* If the FDA makes any of

[5] As part of the Food and Drug Administration Modernization Act of 1997 (FDAMA), Congress amended the FDCA at 21 U.S.C. § 360c(i)(1)(D) to require the FDA, when requesting additional information about a 510(k) notification from a device sponsor, to "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." This amendment was consistent with FDAMA's overarching purpose of ensuring "the timely availability of safe and effective new products that will benefit the public and to ensure that our Nation continues to lead the world in new product innovation and development." S.Rep. No. 105-43, at 2 (1997).

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these determinations, the FDA will classify the device as Class III and will require PMA approval or the filing and granting of a *De Novo* petition.[6] *Id.*

Additionally, the FDA can approve a premarket notification "if the application substantially meets the requirements of [21 C.F.R. Part 814] and the agency believes it can approve the application if specific additional information is submitted or specific conditions are agreed to by the applicant." 21 C.F.R. § 814.44(e). These additional conditions may include "[t]he submission of certain information identified in the approvable letter, e.g., final labeling or "[r]estrictions imposed on the device under section 515(d)(1)(B)(ii) or 520(e) of the [FDCA]." *Id.*[7]

In the two cases below, the FDA ruled that both devices were Class III and subjected both to the FDA's PMA process.

D. FDA's Regulation of Medical Devices "Utilized In or Indicated for the Collection, Processing or Administration of Biological Products."

In most cases, FDA's Center for Devices and Radiological Health (CDRH) is FDA's center responsible for the regulation of medical devices, while FDA's Center for Biologic Evaluation and Research (CBER) is FDA's center responsible

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[6] *De Novo* petitions are not applicable in this case; see 21 U.S.C. § 360c(f)(2)(A).

[7] As an example, we have attached as Addendum 8, the October 11, 2007 Approval Summary for the MarrowStim Concentration Kit manufactured by Biomet Manufacturing Corp.

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for the regulation of biological products for human use, including allergenics, blood and blood products, cellular and gene therapy products, and tissue and tissue products.[8]

However, as of 1991, the FDA recognized that many medical devices could potentially fall under the jurisdiction of both centers. Accordingly, on October 31, 1991, CBER and CDRH entered into an "Intercenter Agreement" *Intercenter Agreement Between [CBER] and [CDRH]*, October 31, 1991 setting forth the rules governing which center would regulate which devices.[9] Pursuant to this Agreement, CDRH maintained its prior role for regulating medical devices and radiation related medical devices to ensure their safety and effectiveness, and CBER was designated as the lead center in FDA for regulating medical devices utilized in or indicated for the collection, processing or administration of biological products to ensure their safety and effectiveness.

In this case, based on the Intercenter Agreement between CBER and CDRH and the intended use of each device, the Petitioner submitted the 700/LAB System to be reviewed by CDRH and the 900/MB Processor System to be regulated by CBER.

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[8] *See*, http://www.fda.gov/BiologicsBloodVaccines/default.htm

[9] http://www.fda.gov/combinationproducts/jurisdictionalinformation/ucm121175.htm

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III. The Petitioner's Medical Devices and 510(k) Notifications

The two medical devices which are the subject of these consolidated petitions are the Cytori Celution 700/LAB System and the Stem Source 900/MB Processor System. We discuss them, as well as the Petitioner's 510(k) notifications in support of them, below.

A. The Cytori Celution 700/LAB System

The Cytori Celution 700/LAB System is an automated centrifugation processor 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. (R 000009, 000848; JA 3, 21). The device consists of a push-button, menu-driven user interface used for the rapid preparation of a cell concentrate from adipose tissue (R 000849), as well as an automated centrifuge, single-use disposables, and a dissociation reagent called "Celase." (R 000009; JA 3).

The 700/LAB System works as follows:

> The Celution 700/LAB System is an automated cell extraction system that has been designed to dissociate connective tissue and subsequently wash and concentrate non-buoyant cells from connective tissues.
>
> The input material for the [700/LAB System] is connective tissue which is introduced into the collection container. Once the tissue has been added into the…collection container and washed, Celase 735/LAB reagent is added. The [700/LAB System] agitates the mixture to separate and release the individual cells from the connective tissue. The [700/LAB System] pumps the

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> digested cell suspension into the centrifuge processing chamber, adds processing fluid, and performs a series of centrifugation cycles to concentrate the non-buoyant cells. This cycle is repeated until the entire volume of input cell suspension has been processed and the non-buoyant cells have been localized into the processing chamber. The cells are washed with processing fluid and are then ready for use by clinical laboratory.

(R 000851; JA 23). In lay terms, the 700/LAB System is a liposuction device which allows a physician to access a patient's stem cells from the body fat in which the cells are stored, and then to study those cells in a clinical laboratory.

The Petitioner submitted its 510(k) Premarket Notification to CDRH on April 25, 2011, seeking to have CDRH classify the 700 LAB/System as a Class I device under 21 C.F.R. § 862.2050 (general purpose laboratory equipment labeled or promoted for a specific medical use) of a Class II device under 21 C.F.R. § 878.5040 (suction lipoplasty system). (R 000001; JA 1). In filing its 510(k) Premarket Notification, the Petitioner compared the 700 LAB/System to five predicate devices and three related devices, all of which showed that the 700 LAB/System was substantially equivalent to previously-cleared medical devices, and therefore safe and effective for its limited intended use. (R 000049-000053; JA 10-14).

More precisely, as detailed in its 510(k) notification, the Petitioner compared the 700/LAB device to three overlapping categories of predicates. The first category of devices included those which "provide and utilize a reagent that

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contacts and processes cells/tissue (sic) samples from the body in an ex vivo environment." (R 000059; JA 20). The second category included those which, like the 700/LAB device, are freestanding devices that perform the same function (collect, wash, and concentrate cells for laboratory use) through the use of like technology…" (R 000059; JA 20). The third and final category of predicate devices included, like the 700/LAB device's Celase enzyme, "enzyme reagents that share the same technology of cleaving specific amino sequences in a patient's sample tissue as a means to reduce the size of a targeted protein sequence." (R 000059; JA 20).The 700/LAB device, like its predicates, was designed to process bodily tissue for laboratory use without returning that tissue to the patient from whom it was removed.

Additionally, consistent with its description of the 700 LAB/System as "general purpose laboratory equipment," the Petitioner did not make any "specific diagnostic/disease claims," and instead focused "on the same indications for use of the predicate devices as a means to demonstrate substantial (sic) equivalence." (R 001773; JA 75).[10] This indication was also consistent with that of its predicates. *Id.* As the Petitioner made clear in a June 12, 2011 email to Dr. Gerald Marti of FDA:

[10] It is highly common for sponsors to submit medical devices to the FDA without clinical indications for use. As the FDA itself describes, "[f]or devices with general indications for use that do not specify a disease, condition, or population…, the indications for use and intended use are the same. Such indications for use are referred to as 'tool type' indications for use. Examples of

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> [W]e fully understand that the Celution 700/LAB device under your review is NOT a cell therapy product and will not be promoted for any other uses except for the approved indications for use. Our cell therapy products will be reviewed by CBER under a PMA with full clinical trials…We have multiple product lines with distinct market segments that we are trying to serve. We understand that a diagnostic device, such as the 700/LAB under your review, is not to be promoted for any indications beyond those sought and/or approved by FDA. We have no intentions of confusing or mixing our diagnostic products with our cell therapy products. This is why we have carefully named our products with distinct names and distinct numeric designations. We are simply trying to build a business with multiple products that service multiple and distinct customer needs.

(R 002115; JA 104-105).[11]

Via letter dated June 27, 2011, CDRH rejected the Petitioner's 510(k) Notification for the 700 LAB/System, and ruled that it was a Class III device requiring an approved premarket approval application before it can be legally

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devices with 'tool type' indications for use include devices such as scalpels, which are often indicated for cutting tissue, or imaging devices, which are often indicated for taking images of the body. A scalpel indicated for removing a particular type of cancerous cell, however, has indications for use specific to the identified disease, condition, or population and therefore are not 'tool type' indications for use." *Draft Guidance: The 510(k) Program: Evaluating Substantial Equivalence…*, at 14 (December 27, 2011).

[11] On December 16, 2011, the Petitioner submitted its investigational device exemption (IDE) application for its Celution One System, a medical device which will be marketed for the treatment of chronic myocardial ischemia. Petitioner's IDE was conditionally approved by FDA via letter dated January 26, 2012; IDE 14958. Unlike the two medical devices at issue in these consolidated petitions, the intended use of Petitioner's Celution One System assumes that the stem cells it processes will return to the patient from whom they were removed for the treatment of a disease.

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marketed. (R 002211; Addendum 6; JA 200). In its letter, CDRH based its decision on two factors. First, as of the time of its June 27, 2011 letter to the Petitioner, CDRH was "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." (R 002211; Addendum 6; JA 200). And second, according CDRH, "the intended use differs from the intended use of the predicate devices, and the performance data provided is inadequate to demonstrate substantial equivalence." (R 002211; Addendum 6; JA 200).

The substance of the reasoning behind the denial of the Petitioner's 510(k) Notification for the 700 LAB/System was not made apparent until after these consolidated petitions were filed, when the Respondent included in its Certified Index the FDA's "Summary Review Memorandum" dated June 21, 2011 (R 002196-002210; JA 185-199) and the Memorandum memorializing a June 10, 2011 telephone conference between CDRH and CBER. (R 002114; JA 103). These documents reveal the following critical points:

First, the intended use of the 700/LAB System is for the separation of fat cells from a stromal cell fraction, and that the resulting "concentrated, enriched stromal fraction is for clinical laboratory testing." (R 002114; JA 103).

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Second, there was no mention in the Petitioner's 510(k) Notification of the use of the resulting stromal cell fraction as a therapeutic product. (R 002114; JA 103).

Third, CDRH was concerned "about the potential therapeutic use" of the 700/LAB System's resulting "cellular product." (R 002202; JA 191).

Fourth, based on this concern, CDRH ruled that the Petitioner's 510(k) Notification for the 700 LAB/System was inadequate.

Fifth, CDRH could have approved the device and required that the Petitioner include labeling explicitly stating that "this product is not intended and may not be used (sic) for autologous in vivo or ex vivo use such as breast reconstitution," (R 002200; JA 189) or that the "safety and effectiveness of this device for in vitro indications for use has not been established." (R 002201; JA 190). Instead, without explaining why less drastic options were not available to the Petitioner, CDRH outright rejected the 510(k) notification.

B. <u>The Stem Source 900/MB Processor System</u>

As previously discussed, the Stem Source 900/MB Processor System itself is virtually identical to the 700 LAB/System. Like the 700 LAB/System, the 900/MB Processor System is composed of an electro-mechanical centrifuge, single use disposables, and Celase. (R 100002-100003; JA 203-204). However, while the two devices have similar physical attributes, the Petitioner submitted them separately to

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the FDA to be approved for different intended uses and indications.[12] Whereas the 700/LAB device was submitted to be approved for laboratory use, the 900/MB Processor System was submitted for use in banking/cryopreservation. (R 100124; JA 295).

The Petitioner submitted its 510(k) Premarket Notification for the Stem Source 900/MB Processor System to the FDA on April 28, 2011, seeking to have CBER classify it as a Class I device under 21 C.F.R. § 862.2050 (general purpose laboratory equipment labeled or promoted for a specific medical use) or a Class II device under 21 C.F.R. § 864.9900 (cord blood processing system and storage container). (R 100115; JA 292). In filing its 510(k) Premarket Notification, the Petitioner compared the Stem Source 900/MB Processor System to seven predicate devices, all of which showed that the Stem Source 900/MB Processor System was substantially equivalent to previously-cleared medical devices, and therefore safe and effective for its limited intended use. (R 100115; JA 292).

More precisely, as detailed in its 510(k) notification, the Petitioner compared the 900/MB device to nine overlapping categories of predicates. (R 100171-

[12] The Petitioner submitted multiple 510(k) notifications based on FDA's Guidance entitled, *Bundling Multiple Devices or Multiple Indications in a Single Submission*, (June 22, 2007), at p. 7 ("…devices with different indications for use in multiple medical specialties, which would require reviews by different divisions, should have separate submissions.") In this case, as previously stated, the two devices had different indications and intended uses and were thus reviewed by different divisions of the FDA. As such, submitting the two devices under separate 510(k) notifications was driven by FDA policy.

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100172; JA 298-299). However, unlike the 700/LAB device, many of these categories included predicate devices which process bodily tissue which will ultimately be returned to the patient from which it was returned. (R 100171-100172; JA 298-299). Of course, the Petitioner did not compare the 900/MB device to such predicates for purposes of establishing the safety and effectiveness of any particular therapy involving the use of a patient's own bodily tissue, and nor did its predicates upon the filing of their own 510(k) notifications. Instead, the Petitioner compared the 900/MB device to its predicates to establish that it was safe and effective for the intended use of banking and cryopreservation, which assumes that at some point in the future when compliant medical uses for the cells are available, the banked cells will be returned by someone other than the Petitioner to the person from whom they were removed. (R 100175; JA 302).

Via letter dated July 29, 2011, CBER rejected the Petitioner's 510(k) Notification for the Stem Source 900/MB Processor System, and ruled that it was a Class III device requiring an approved premarket approval application before it could be legally marketed. (R 102767; Addendum 7; JA 384). CBER's decision was based on two factors. First, as of the time of its July 29, 2011 letter to the Petitioner, CBER was "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 or cryopreservation." (R 102767; Addendum 7;

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JA 384). And second, according to CBER, "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." (R 102767; Addendum 7; JA 384).

The substance of the reasoning behind the denial of the Petitioner's 510(k) Notification for the Stem Source 900/MB Processor System was not made apparent until after these consolidated petitions were filed, when the Respondent included in its Certified Index the FDA's "Summary Review Memorandum" dated June 21, 2011 (R 002196-002210; JA 185-199) and the Memorandum memorializing a telephone conference between CDRH and CBER on June 10, 2011 (R 002114; JA 103). These documents reveal the following critical points:

First, the Petitioner submitted its 510(k) notification for the Stem Source 900/MB Processor System for use in banking and cryopreservation, and to be regulated under 21 C.F.R. § 862.2050 and/or 21 C.F.R. § 864.9900 as a cord blood processing system and storage container. (R 102759, 102760; JA 376-377).

Second, CBER refused to consider the Stem Source 900/MB Processor System under either § 862.2050 or § 864.9900, and deemed all of the device's proposed predicates invalid. (R 102760; JA 377).

Third, even though the Petitioner submitted its 510(k) notification for the Stem Source 900/MB Processor System for use in banking and cryopreservation,

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the FDA required the Petitioner to submit "a specific clinical indication for use…" (R 102760; JA 377). Furthermore, CBER required the Petitioner to establish through investigational studies the safety and effectiveness of the device for each proposed clinical indication. (R 102760; JA 377).

Fourth, the FDA could have approved the device and required that the Petitioner include labeling explicitly stating that "this product is not intended and may not be used (sic) for autologous in vivo or ex vivo use such as breast reconstitution," (R 002200; JA 189) or that the "safety and effectiveness of this device for in vitro indications for use has not been established." (R 002201; JA 190).

Fifth, CBER rejected the Petitioner's 510(k) Notification for the 900/MB Processor System without any explanation as to why less drastic alternatives were unavailable.

SUMMARY OF ARGUMENT

The Petitioner is a medical device manufacturer which submitted two devices – the 700/LAB device and the 900/MB device – to the FDA to be cleared for sale in the United States. At the time they were submitted to the FDA, the 700/LAB device was intended to be used in a clinical laboratory and the 900/MB device was intended to be used in the banking and cryopreservation of stem cells. However, upon their submission, the FDA raised "concerns" about the potential

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off-label therapeutic uses of each device, and based on those "concerns" completely rejected each submission.

In this Brief, the Petitioner argues the following points:

First, 21 U.S.C. § 360g(a)(8) unequivocally provides that this Court has jurisdiction to hear this case at this time. Moreover, even though the Court need not refer to the legislative history to discern the meaning of § 360g(a)(8), the legislative history nevertheless confirms the position of the Petitioner on this issue.

Second, the FDA's rejection of the Petitioner's submission for the 700/LAB device was arbitrary and capricious for a variety of reasons. Among other issues, even though the Petitioner submitted the 700/LAB device to be used in a laboratory, FDA evaluated it based on the ability of third parties' to use it in a clinical setting, and thus violated 21 U.S.C. § 360c(e)(i)(E). Moreover, in reviewing the submission, FDA failed to explain itself in numerous critical ways as required by *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

Finally, the FDA's rejection of the Petitioner's submission for the 900/MB device was also arbitrary and capricious for a host of reasons. As with the 700/LAB device, the FDA refused to review it based upon the intended use proposed by the Petitioner, and offered explanations for its choices which failed to meet the standards set forth in *Motor Vehicle Mfrs. Ass'n.*

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STATEMENT OF STANDING

The Petitioner's standing to seek review of the administrative actions at issue in this case is self-evident, and "no evidence outside the administrative record is necessary for the court to be sure of it." *Sierra Club* v. EPA, 292 F.3d 895, 900 (D.C. Cir. 2002). Indeed, the Petitioner is the manufacturer of the two medical devices which the FDA has refused to clear as safe and effective. By its actions, the FDA has dealt an ongoing injury to the Petitioner, and the Petitioner's standing is therefore clear; *see e.g. Dearth v. Holder*, 641 F.3d 499 (2011).

ARGUMENT

I. THIS COURT HAS JURISDICTION TO HEAR THIS CASE

On December 29, 2011, this Court entered an Order referring the Respondent's motion to dismiss to the Merits Panel and instructing the parties "to address in their briefs the issues presented in the motion to dismiss rather than incorporate those arguments by reference." The Petitioner argues the issue of whether the Court has the requisite subject matter to hear these consolidated petitions as follows:

A. 21 U.S.C. § 360g(a)(8) unambiguously provides for the direct review of NSE Orders in the United States Court of Appeals for the District of Columbia Circuit.

The FDCA "contains no single, overarching provision governing judicial review. Instead, discrete agency actions are subject to specialized review provisions." *See Cutler v. Hayes*, 818 F.2d 879, 887-888 n. 61 (D.C. Cir. 1987).

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As a result, only certain orders are directly reviewable by United States courts of appeals pursuant to the Act. *Id.*

The specialized jurisdictional provision applicable in this case is found at 21 U.S.C. § 360g. Section 360g(a) sets forth the categories of orders and regulations relating to medical devices for which direct review is available in United States Courts of Appeals. 21 U.S.C § 360g(a)(8) provides that any person adversely affected by "an order pursuant to section 513(i) [21 U.S.C. § 360c(i)]" may seek judicial review by filing a petition with the United States Court of Appeals for the District of Columbia within thirty days of the order.

21 U.S.C. § 360c(i) is entitled "Substantial Equivalence," and 21 U.S.C. § 360c(i)(1)(A) defines the terms "substantial equivalence" and "substantially equivalent" for the "purposes of ***determinations of substantial equivalence*** under subsection [21 U.S.C. § 360c(f)] and section 520(l) [21 U.S.C. § 360j(l)]."[13] (emphasis added). Thus, when §§ 360g(a)(8) and 360c(i)(1)(A) are read together, "an order pursuant to 21 U.S.C. § 360c(i)" is an order determining whether *or not* a device meets the definition of "substantial equivalence." The plain language of the statute does not distinguish between findings of substantial equivalence from

[13] 21 U.S.C. § 360j(l), entitled "[t]ransitional provisions for devices considered as new drugs" also grants the FDA the authority to make substantial equivalence determinations. However, § 360j(l) is not at issue in this matter.

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findings of not substantially equivalent.[14] Hence, regardless of whether the FDA finds a device in question to meet the definition of "substantially equivalent," the order is issued pursuant to § 360c(i) and thus directly reviewable in this Court.

Had Congress intended for direct review in federal Courts of Appeal to be limited to those in which FDA ruled that a device was substantially equivalent, Congress would have drafted the provisions of 21 U.S.C. § 360g(a)(8) similar to other jurisdictional provisions of the FDCA.[15] But Congress did not do so. Instead, Congress clearly provided that ***any*** order pursuant to § 360c(i) would be subject to direct review in this Court.[16] Therefore, this Court has jurisdiction to hear this case.

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[14] The regulatory scheme established by FDA for the premarket notification process supports the conclusion that "orders pursuant to § 360c(i)" include NSE orders. 21 C.F.R. § 807.100(a), entitled "FDA action on a premarket notification," states in pertinent part: "(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; [or] (2) Issue an order declaring the device to be not substantially equivalent to any legally marketed predicate device…"Additionally, §807.100(b) provides that the "FDA will determine that a device is substantially equivalent to a predicate device" using the criteria listed within the regulation. This criteria is identical to that found in the definition of "substantial equivalence" found at 21 U.S.C. § 360c(i)(1)(A). Thus, a determination of whether *or not* a device meets the definition of "substantial equivalence" pursuant to § 360c(i)(1)(A) can result in FDA issuing either an order finding substantial equivalence or an order finding that the device is not substantially equivalent.

[15] For example, in 21 U.S.C. § 360g(a)(3), Congress provided for the direct review of "the issuance of an order under section 514(b)(2) or 515(b)(2)(B) ***denying*** a request for reclassification of a device." (emphasis added).

[16] Direct review of substantial equivalence and NSE orders in the United States Courts of Appeals is consistent with the type of review provided for similar orders affecting food and drugs under the FDCA: "The [MDA] provide[s] for judicial review of final Agency orders concerning classification of devices, performance

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B. Legislative History supports the direct review of NSE Orders in this Court.

As previously shown, 21 U.S.C. § 360g(a)(8) unambiguously provides for the direct review of all final orders "pursuant to 21 U.S.C.§ 360c(i)," and the orders at issue in this case clearly fall within that category. Accordingly, the inquiry should end there, and the Court need not examine the legislative history; *see Performance Coal Co. v. Fed. Mine Safety and Health Review Comm'n*, 642 F.3d 234, 238 (D.C. Cir. 2011) ("Because congressional intent is best divined from the statutory language itself, resort to legislative history is inappropriate when the statute is unambiguous."). Nevertheless, to the extent that the Court perceives ambiguity in the statute, the legislative history, including prior draft versions of the Safe Medical Device Act of 1990, reveals that it was the intent of Congress to provide for direct review in this Court of both substantially equivalent and NSE Orders.

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standards, reclassification of devices, premarket approval, banded devices, good manufacturing practice regulations and investigational uses of devices. Such review must be made in the United States Circuit Court of Appeals...This provision is consistent with the review of similar types of orders affecting foods and drugs."*See* Jay H. Geller, *The Medical Device Amendments of 1976 – Major Features and Comparisons*, 31 Food Drug Cosm. L.J. 424, 433 (August 1976) (citing 21 U.S.C. §§ 346a(i) (providing direct review of orders and regulations regarding tolerances and exemptions for pesticide chemical), 348(g) (providing direct review of orders and regulations regarding food additives), 355(h) (providing direct review of an order of the Secretary refusing or withdrawing approval for a new drug application), 360b(h) (providing direct review of an order of the Secretary refusing or withdrawing approval for a new animal drug).

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On November 28, 1990, the Safe Medical Device Act of 1990 ("SMDA") was approved and became law. Pub. L. No. 101-629 (1990). However, prior to the SMDA's passage, the House and Senate versions of the bill differed as they related to which final actions would be directly reviewable in the United States Courts of Appeals. The SMDA is the bill resulting from the Conference between the House and Senate. H.R. Rep. No. 101-959, at 23 (1990) (Conf. Rep.).

Under the original version of the bill passed by the House, direct review of any order, substantially equivalent or not, pursuant to § 360c(i) was *not* provided for. SMDA, H.R. 3095, 101st Cong., § 4(c) (1990). However, the Senate amended the bill to provide for direct review in the United States courts of appeals of "the issuance of an order under § 513(f)(1) [21 U.S.C. 360c(f)(1)]…." Thus, the Senate bill expanded the potential orders and regulations for which direct review is available in this Court. *See* Amendment H.R. 3095, 101st Cong., §8 (October 12, 1990);[17] S. Rep. No. 101-513, at 37 (1990) (stating that "any order determining whether a product is substantially equivalent or not substantially equivalent to a market device will be heard in the United States Court of Appeals.").

[17] The original Senate version of the bill expressly provided for the direct review of "the issuance of an order under this subchapter that a device is substantially equivalent to another device." *See* Comprehensive Medical Device Improvement Act of 1990, S. 3006,101st Cong., § 9 (1990). However, this language was stricken by the Senate and replaced with "the issuance of an order under § 513(f)(1)." Thus, Congress considered and rejected the idea of providing for the direct review of only those orders in which substantial equivalence was found.

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At Conference, the direct review provision of the SMDA was amended once again, amending §517(a)(8) to read as it currently does to provide direct review of "an order pursuant to § 513(i)." However, this revision did not provide that only an FDA decision that a medical device is substantially equivalent is subject to direct review in the federal courts of appeals. Instead, the language of 21 U.S.C. § 360g(a)(8) was amended to make clear that direct review was available for all orders finding a product substantially equivalent or not substantially equivalent. Nowhere within the Conference Report does Congress state that the amendment was intended to exclusively provide for direct review of orders finding substantial equivalence. Rather, as explained above, this amendment was made in order to clarify and harmonize the differences between the House and Senate versions of the SMDA. H.R. Rep. No. 101-959, at 27 (1990) (Conf. Rep.).

Although the Court need not even consider the legislative history where, as here, the statute is unambiguous, the legislative history of the SMDA further strengthens Petitioner's argument that § 360g(a)(8) was intended to provide for direct review of orders finding substantial equivalence and NSE orders. Thus, this Court has jurisdiction to hear this case.

C. FDA's interpretation of 21 U.S.C. § 360g(a)(8) renders the statute meaningless.

In its motion to dismiss, the FDA argued that § 360g(a)(8) only applies to those orders finding that a device *is* substantially equivalent. This argument,

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however, raises a fundamental question: who would, and more importantly, who could, appeal such determinations? As will be demonstrated below, if the FDA's interpretation of § 360g(a)(8) is accepted, the judicial review provision would become a nullity.

To be sure, there are only four types of parties which could even conceivably appeal a determination that a device is substantially similar: 1) the applicant, 2) third parties such as the general public and consumer advocacy groups, 3) the manufacturer of a predicate device, and 4) competitors. The first potential appellant, the applicant, logically would never appeal the FDA's favorable ruling. Regarding the second potential appellant, in *Moms Against Mercury v. FDA*, 483 F.3d 824 (D.C. Cir. 2007), the Government argued before this Court that third parties lack standing to bring challenges to FDA orders finding substantial equivalence.[18]

This leaves only competitors and manufacturers of predicate devices as potential appellants. However, similar to third parties, these would-be litigants also face obstacles if they attempt to challenge a finding of substantial equivalence. First, predicate device manufacturers have no right to exclusivity in the production

[18] In *Moms Against Mercury*, multiple advocacy groups and individuals sought review under 21 U.S.C. § 360g(a)(8) of the FDA's failure to classify a material used for dental fillings, a medical device. 483 F.3d 824. In response, the Government filed a motion to dismiss claiming a lack of standing and lack of subject matter jurisdiction.

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of medical devices. Rather, the premarket approval process is a "pro-competition mechanism" designed so that companies whose devices "happened to be on the market before enactment of the [Medical Device Amendments of 1976] and . . . never subject to preclearance by the FDA should not enjoy a lengthy monopoly at expense of other firms and ultimately the consumer." *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 494 n. 14 (1996).

Second, competitors and predicate device manufacturers lack the information necessary to bring such a challenge. The FDA's substantial equivalence determination process is conducted entirely as an internal agency review without public participation. As such, there is no public record of any debate regarding a substantial equivalence determination. Additionally, FDA regulations make clear that the FDA has the authority to keep safety and effectiveness information regarding a premarket confidential for *30 days* after the FDA issues a determination of equivalency. 21 C.F.R. §807.95(d). Thus, given that § 360g(a)(8) provides that any and all challenges to an "order pursuant to section 513(i)" within the Circuit Court "not later than 30 days" of its issuance, competitors and predicate device manufacturers would have neither standing to challenge a substantial equivalence determination nor the information necessary to file such a challenge.

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Assuming *arguendo* that § 360g(a)(8) applies solely to orders finding a device substantially equivalent, the result would be highly curious: no party would have the standing or logical reason to challenge the determination. Although the Government argues that its interpretation of the law "likely reflects Congress's concern about protecting the public from 'dangerous health care products,'" the practical effect of the Government's position would make the jurisdiction provisions of 21 U.S.C. § 360g(a)(8) a nullity.

This Court has jurisdiction to hear this case.

II. THE FDA'S REJECTIONS OF THE PETITIONER'S 510(k) NOTIFICATIONS WERE ARBITRARY AND CAPRICIOUS.

A. Standard and Scope of Review

This Court's review of the FDA orders at issue in these consolidated petitions will involve the overlapping principles set forth in *Chevron U.S.A. Inc. v. NRDC*, 467 U.S. 837 (1984) and the Administrative Procedure Act; *see e.g. Warren v. E.P.A.*, 159 F.3d 616, 621 (D.C. Cir. 1998).

This Court reviews FDA orders to determine if they are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." *Mylan Labs, Inc. v. Thompson*, 389 F.3d 1272, 1279 (D.C. Cir. 2004); *Rhodia, Inc. v. Food and Drug Administration*, 698 F.2d 1376 (D.C. Cir. 1979). Questions of law are reviewed *de novo*. *Sherley v. Sebelius*, 644 F.3d 388, 393 (D.C. Cir. 2011);

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Sottera, Inc. v. Food and Drug Administration, 627 F.3d 891, 893 (D.C. Cir. 2010).

Whether FDA orders are contrary to the text of the FDCA also is reviewed *de novo*. *See generally, Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842 (1984); *see also Eagle Broad Group, Ltd. v. FCC*, 563 F.3d 543, 550 (D.C. Cir. 2009). Where "Congress has directly spoken to the precise question at issue," and where the agency's action conflicts with what Congress has said, the reviewing court must invalidate the agency's action. *Ranbaxy Labs, Ltd. v. Leavitt*, 369 F.3d 120, 124 (D.C. Cir. 2006); *Teva Pharms. U.S.A., Inc. v. Sebelius*, 595 F.3d 1303 (D.C. Cir. 2010).

Of course, as this Court has acknowledged, "[e]ven when an agency's construction of its statute passes muster under *Chevron*, a party may claim that the disputed agency action is 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.'" *Eagle Broadcasting Group Ltd. v. FCC*, 563 F.3d 543, 551 (D.C. Cir. 2009). The decisions of the FDA must be "the product of reasoned decisionmaking." *Alpharma, Inc. v. Leavitt*, 460 F.3d 1, 12 (D.C. Cir. 2006). FDA's factual findings must be supported by substantial evidence. *General Medical Co. v. United States Food and Drug Administration*, 770 F.2d 214 (D.C. Cir. 1985).

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To determine whether an agency action is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," reviewing courts are instructed to "consider whether the [agency's] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Marsh v. Oregon Natural Res. Council*, 490 U.S. 360, 378 (1989).

The Supreme Court has held that, "[a]t a minimum, the agency must have considered relevant data and articulated a satisfactory explanation establishing a 'rational connection between the facts found and the choice made.'" *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983); *see also Pub. Citizen, Inc. v. Fed. Aviation Admin.*, 988 F.2d 186, 197 (D.C. Cir. 1993) ("The requirement that agency action not be arbitrary or capricious includes a requirement that the agency adequately explain its result.")

Agency action will be found to be arbitrary or capricious if "the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Motor Vehicle*, 463 U.S. at 43.

Furthermore, it is well settled that agencies "must cogently explain why it has exercised its discretion in a given manner…" *Motor Vehicle Manuf. Ass'n v.*

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State Farm, 463, U.S. at 46-51; *see also PRHEAC v. DOE*, 10 F.3d 847, 852-53 (D.C. Cir. 1993) (DOE decision ruled to be arbitrary and capricious where denial letter failed to articulate the statutory interpretation upon which the decision was based.); *Int'l Ladies' Garment Workers Union v. Donovan*, 722 F.2d 795, 815 (D.C. Cir. 1983). An agency's failure to explain itself consistent with the directives of *Motor Vehicle Manuf. Ass'n* and its progeny will be deemed arbitrary and capricious.

B. The FDA's Rejection of the Petitioner's 510(k) Notification for The Cytori Celution 700/LAB System was Arbitrary and Capricious.

As previously discussed, the Petitioner presented this device to CDRH as "general purpose laboratory equipment labeled or promoted for a specific medical use," but made "tool type" claims for the device instead of "specific diagnostic/disease claims" because, like its predicates, the 700/LAB System was designed to be used in a clinical laboratory and its intended use did not involve a return of any cells to the patient.

However, as previously shown, CDRH rejected the 510(k) notification for the Petitioner's 700/LAB System based upon the FDA's "concern about the potential therapeutic use of this cellular product." (R 002114; JA 103). In other words, even though CDRH believed that the Petitioner's draft labeling was "appropriate" for general purpose laboratory equipment (R 002200; JA 189), CDRH rejected the notification due to the FDA's "concerns" about practitioners

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using the 700/LAB System in a manner not consistent with its labeling. (R 002200; JA 189). How CDRH addressed this concern was arbitrary and capricious in several material ways.

1. CDRH's rejection of the 510(k) notification for the 700/LAB device was arbitrary and capricious because CDRH failed to consider or explain why less drastic alternatives were unavailable.

First, even assuming that the "concerns" about off-label uses raised by FDA had any foundation at all, CDRH's rejection of the Petitioner's 510(k) notification nevertheless conflicted with 21 U.S.C. § 360c(e)(i)(E) because, rather than *even considering* clearing the device with labeling to control the risk of an off-label use, CDRH simply rejected the 510(k) notification altogether without explaining why less drastic alternatives contemplated by Congress were not available.

Indeed, 21 U.S.C. § 360c(e)(i)(E) provides that if the FDA determines 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 that such use could cause harm," the FDA may require the device sponsor to include "a statement in the device's labeling that provides appropriate information regarding a use of the device not identified in the proposed labeling…;" *see also* 21 C.F.R. § 814.44(e). However, in this case, CDRH simply rejected the Petitioner's 510(k) notification with no explanation as to why. This was arbitrary and capricious; *see e.g. Motor Vehicle Manuf. Ass'n v. State Farm*, 463, U.S. at 46-51; *PRHEAC v. DOE*, 10 F.3d

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847, 852-53 (D.C. Cir. 1993); *Int'l Ladies' Garment Workers Union*, 722 F.2d 795, 815.

2. CDRH's rejection of the 510(k) notification for the 700/LAB device was arbitrary and capricious because CDRH determined the intended use of the device based on something other than the 510(k) notification, and then rejected the 510(k) based on that newly written intended use.

Next, CDRH's rejection of the Petitioner's 510(k) notification ran contrary to 21 U.S.C. § 360c(e)(i)(E), which provides that "[a]ny determination by the Secretary of the intended use of a device shall be based upon the proposed labeling submitted" by a device sponsor in its 510(k) notification; *see also Draft Guidance: The 510(k) Program: Evaluating Substantial Equivalence…*, (December 27, 2011), at p.14.

In this case, the record reveals that CDRH simply dismissed the statement of intended use submitted by the Petitioner, and then evaluated the notification based upon an intended use never contemplated in the notification itself. (R 002202; JA 191) ("Questions: What are the indications for liposction? Cosmetic and not morbid obesity? When the reason is cosmetic, are there any comorbid medical or psychiatric conditions? One would assume that the patient population to be studied would be more than 12 individuals…") By rewriting the Petitioner's 510(k) notification in this way, CDRH licensed itself to determine that all of the predicates upon which the Petitioner had relied were invalid. Such a "straw man"

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dismissal was directly contrary to the plain language of the statute, and was therefore arbitrary and capricious. *Ranbaxy*, 369 F.3d at 124.

3. CDRH's rejection of the 510(k) notification for the 700/LAB device was arbitrary and capricious because CDRH failed to explain why the Petitioner's performance data was insufficient and why additional information would not cure the defect.

We also note that the FDA's June 27, 2011 letter rejecting the Petitioner's 510(k) notification reveals that the FDA believed that the Petitioner's "performance data [was] inadequate to demonstrate substantial performance." (R 002211; Addendum 6; JA 200). However, the FDA's correspondence with the Petitioner failed to offer any explanation as to why the data submitted by the Petitioner was insufficient, or why the FDA chose not to request additional information from the Petitioner as contemplated at § 360c(i)(1)(D). Given the availability of options less drastic than the outright rejection of the Petitioner's 510(k) notification, CDRH's failure to explain its conduct was arbitrary and capricious; *see e.g. Int'l Ladies' Garment Workers' Union*, 722 F.2d at 815.

4. CDRH's rejection of the 510(k) notification for the 700/LAB device was arbitrary and capricious because CDRH asserted a demonstrably incorrect position on what constitutes a Class I device.

Finally, although CDRH made no mention in its June 27, 2011 letter of the Petitioner's application to be classified as a Class I device under 21 C.F.R. §862.2050 as "general purpose laboratory equipment," the documents produced by

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FDA as part of its Certified Index in this case reveal the reason why the FDA refused to clear the 700/LAB device as Class I. In its Summary Review Memorandum, the FDA writes that the 700/LAB device could not be cleared as Class I because "the sponsor has indicated that they want to use this device (sic) at (sic) point of care in the operating room. This would remove the class I exemption…" (R 002203; JA 192). However, in reality, whether a device is used in the operating room has nothing to do with whether it may be classified as Class I; *see* 21 U.S.C. § 360c(a)(1)(A). In fact, FDA regularly classifies devices found in typical operating rooms as Class I.[19] Accordingly, FDA's position on this question of whether the 700/LAB device may qualify as a Class I device was arbitrary and capricious.

For all of these reasons, the FDA's rejection of the Petitioner's 510(k) notification for the Celution 700/LAB System was arbitrary and capricious and should not be endorsed by this Court.

C. The FDA's Rejection of the Petitioner's 510(k) Notification for The Stem Source 900/MB Processor System was Arbitrary and Capricious.

As previously discussed, the Petitioner presented the 900/MB device to CBER as a "general purpose laboratory equipment labeled or promoted for a

[19] Examples of operating room devices regulated as Class I include, without limitation, scalpels, operating tables, latex gloves, anesthesia masks, surgical microscopes, catheters, and the MarrowStim Concentration Kit manufactured by Biomet Manufacturing Corp.; *see* Addendum 8.

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specific medical use," but made "tool type" claims for the device instead of "specific diagnostic/disease claims" because the 900/LAB System was designed to be used for accessing and cryopreserving fat-derived tissue and cells, as opposed to being used as a medical therapy or for the treatment of any particular disease.

However, as previously shown, CBER rejected the 510(k) notification for the Petitioner's 900/MB device based upon the FDA's "concern about the potential therapeutic use of this cellular product." (R 002114; JA 103). In other words, even though the Petitioner submitted the device to CBER to be used in banking and cryopreservation, CBER rejected the notification due to the FDA's "concerns" about practitioners using the device in a manner not consistent with its labeling. (R 102760; JA 377). How CBER proceeded after raising this concern was arbitrary and capricious in several material ways.

1. **CBER's rejection of the 510(k) notification for the 900/MB device was arbitrary and capricious because CBER determined the intended use of the device based on something other than the 510(k) notification, and then rejected the 510(k) based on that newly written intended use.**

The administrative record of this device reveals that as long as the 900/MB device was submitted without specific disease claims, the FDA simply refused to clear it. First, CBER raised the same concerns about off-label uses of the 900/MB Processor as CDRH did about the 700/LAB processor described above. Having raised these concerns, CBER dealt with them as follows:

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> In order to gain marketing authorization for the StemSource System as a medical device, a specific clinical indication for use would be needed. The safety and effectiveness of the device for each proposed clinical indication for use will need to be established through investigational studies under an IND or IDE.

(R 102760; JA 377). As it did with the 700/LAB device, the FDA rejected the Petitioner's 510(k) notification based upon an intended use not even raised in the 510(k) notification. This rewriting of the 510(k) notification by CBER conflicted with 21 U.S.C. § 360c(e)(i)(E) and was arbitrary and capricious.

2. CBER's rejection of the 510(k) notification for the 900/MB device was arbitrary and capricious because CBER failed to consider or explain why less drastic alternatives were unavailable.

Next, as with the 700/LAB device, the FDA's rejection of the 510(k) notification for the 900/MB device based on "concerns" that the device would be used for off-label purposes was arbitrary and capricious as the FDA offered no explanation as to why less severe alternatives contemplated by Congress at 21 U.S.C. § 360c(i)(E) were not available to the Petitioner; *see e.g. Motor Vehicle Manuf. Ass'n,* 463 U.S. at 46-51; *PRHEAC,* 10 F.3d at 852-53; *Int'l Ladies' Garment Workers Union,* 722 F.2d at 815.

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3. CBER's rejection of the 510(k) notification for the 900/MB device was arbitrary and capricious because CBER's explanation of why the device was not substantially equivalent to its predicates was insufficient and conflicted with FDA's own guidance.

In its July 29, 2011 letter rejecting the Petitioner's 510(k) notification for the 900/MB device, as well as in its Premarket Notification Review, CBER raised an issue with the fact that the Petitioner had submitted the device pursuant to 21 C.F.R. § 864.9900 as a "cord blood processing system and storage container." According to the CBER, because the 900/MB device processes adipose (fat) tissue to obtain adipose-derived cells, the device could not be submitted under § 864.9900, and thus could not compare itself to any predicates which had been cleared under § 864.9900. (R 102760; JA 377).

How CBER dealt with this issue was arbitrary and capricious because, as FDA did throughout its reviews of the two devices at issue in these consolidated petitions, it failed to explain itself. In short, the FDA's July 29, 2011 letter offers no explanation whatsoever as to why the 900/MB device's predicates were insufficient, and the documents turned over to the Petitioner in this litigation do not cure that defect at all. While the Petitioner understands that its statement of intended use was not identical to that of its predicates (adipose tissue versus cord blood), the Petitioner still has no information as to why its predicates were insufficient. This problem is only aggravated by Congressional intent and FDA's

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own guidance documents, which state that the intended uses of new devices and their predicates may vary, and that the FDA will judge such variances based upon whether they present issues of safety and effectiveness; *see* H.R. Rep. No. 94-853 pp.36-37; *see also*, *Draft Guidance: The 510(k) Program: Evaluating Substantial Equivalence…*, at p.14 (December 27, 2011). If the differences between the intended use of the 900/MB and the intended uses of its predicates presented an issue of safety or effectiveness relating to the banking or cryopreservation of bodily tissue, CBER certainly never explained this to the Petitioner. CBER's failure to explain its reasoning on this critical issue was arbitrary and capricious; *see Motor Vehicle Manuf. Ass'n*; *PHREAC*; *Int'l Ladies' Garment Workers Union*.

4. CBER's rejection of the 510(k) notification for the 900/MB device was arbitrary and capricious because CBER determined the intended use of the device based on something other than the 510(k) notification, and then rejected the 510(k) based on that newly written intended use.

The next and final issue raised in the FDA's July 29, 2011 letter rejecting the Petitioner's 510(k) notification for the 900/MB device was that 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." (R 102767; Addendum 7; JA 384). However, like virtually every other issue raised by FDA

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regarding the Petitioner's medical devices, this issue stemmed directly from the FDA's refusal to clear the device without a specific clinical indication.

To be sure, as previously noted, the Petitioner readily acknowledged in its correspondence with FDA that it was not submitting the 700/LAB or 900/MB with clinical indications because the Petitioner had a variety of product lines and did not want these devices to be confused with its other devices that were designed to be marketed with specific clinical indications. (R 002115). Thus, rather than submitting the 900/MB device with specific clinical indications, the Petitioner submitted it with the "tool type" indications of banking and cryopreservation. However, rather than evaluating the device based on its tool claims as mandated by statute, CBER judged it based upon its lack of a specific clinical indication. As such, the FDA did not study the safety and effectiveness of the Celase for purposes of banking and cryopreservation, but instead studied and rejected it based on a straw man, i.e. whether it would be safe and effective for a specific medical treatment. This rewriting of the Petitioner's 510(k) notification was directly contradictory to statute and was arbitrary and capricious.

5. CBER's rejection of the 510(k) notification for the 900/MB device was arbitrary and capricious because CBER failed to explain why the device could not be classified as a Class I device.

Finally, neither CBER's July 29, 2011 letter nor the Premarket Notification Review produced by the FDA in this case make any mention of the fact that

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Petitioner sought approval of the 900/MB device as Class I under 21 C.F.R. § 862.2050. As such, the Petitioner has no way of knowing whether this was the result of a mere oversight or whether CBER actually denied that aspect of the Petitioner's 510(k) notification. In either case, CBER's silence on this critical issue was arbitrary and capricious; *Motor Vehicle Manuf. Ass'n*, 463 U.S. at 46-51; *PRHEAC*, 10 F.3d at 852-53; *Int'l Ladies' Garment Workers Union*, 722 F.2d at 815.

For all of these reasons, CBER's rejection of the Petitioner's 510(k) notification for the 900/MB device was arbitrary and capricious and should not be endorsed by this Court.

CONCLUSION AND PRAYER FOR RELIEF

For the foregoing reasons, Petitioner Cytori Therapeutics Inc. respectfully submits that the Court should declare the orders at issue in this case to be arbitrary and capricious and contrary to the mandates of the FDCA, and accordingly should vacate them in their entirety.

Petitioner further respectfully submits that the Court should either (1) enter an Order declaring that the Petitioner's medical devices are substantially equivalent to their predicates based upon their respective intended uses as determined by 21 U.S.C. § 360c(i)(E); (2) remand to FDA with instructions to enter orders declaring that the Petitioner's medical devices are substantially

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equivalent to their predicates based on their respective intended uses as determined by 21 U.S.C. § 360c(i)(E); or (3) remand to FDA with instructions to enter orders declaring that the Petitioner's medical devices are substantially equivalent to their predicates based on their respective intended uses as determined by 21 U.S.C. § 360c(i)(E), subject to limiting language in each device's labeling pursuant to 21 U.S.C. § 360c(i)(E).

Respectfully submitted,

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DESIGNATION PURSUANT TO FRAP 30(c)

Pursuant to Rule 30(c) of the Federal Rules of Appellate Procedure, Petitioner Cytori Therapeutics Inc. designates the following parts of the record to be included in the Deferred Appendix. References are to Record Item Nos. set out in FDA's "Certified Index to the Record" filed in this Court on or about January 27, 2012: Record Item Nos. 000001, 000009, 000049, 000050, 000051, 000052,

000053, 000059, 000848, 000849, 000851, 001773, 002114, 002115, 002196, 002197, 002198, 002199, 002200, 002201, 002202, 002203, 002204, 002205, 002206, 002207, 002208, 002209, 002210, 002211, 100002, 100003, 100115, 100124, 100171, 100172, 100175, 102759, 102760, 102767.

CERTIFICATION OF COMPLIANCE WITH FED. R. APP. P. 32(a)(7)(C) AND D.C. CIRCUIT RULE 32-1

I certify that pursuant to Federal Rule of Appellate Procedure 32(a)(7)(C) and D.C. Circuit Rule 32(a)(1), the attached opening brief is proportionately spaced, has a typeface of 14 points or more and contains 11,216 words.

/s/ Andrew S. Ittleman
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CERTIFICATE OF SERVICE

I hereby certify that on June 27, 2012, a true and correct copy of the foregoing was served electronically via CM/ECF to the opposing counsel:

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ADDENDUM: TABLE OF CONTENTS

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