

United States Court of Appeals
FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued September 21, 2012

Decided March 22, 2013

No. 11-1268

CYTORI THERAPEUTICS, INC.,
PETITIONER

v.

FOOD & DRUG ADMINISTRATION,
RESPONDENT

Consolidated with 11-1279

On Petitions for Review of Orders
of the Food & Drug Administration

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

Adam C. Jed, Attorney, U.S. Department of Justice, argued the cause for respondent. With him on the brief were *Stuart F. Delery*, Acting Assistant Attorney General, and *Scott R. McIntosh*, Attorney. *Douglas N. Letter*, Attorney, entered an appearance.

Before: BROWN and KAVANAUGH, *Circuit Judges*, and SENTELLE, *Senior Circuit Judge*.

Opinion for the Court filed by *Circuit Judge* KAVANAUGH.

KAVANAUGH, *Circuit Judge*: In Administrative Procedure Act cases alleging arbitrary and capricious agency action, courts must be careful not to unduly second-guess an agency's scientific judgments. That basic principle of administrative law controls this case.

The Food and Drug Administration must approve certain medical devices before they are marketed. Here, Cytori Therapeutics applied to FDA to market two new medical devices, the Celution 700 and the StemSource 900. Those two devices use adipose tissue – that is, fat – as a source of stem cells that could later be used in lab analysis or, potentially, in regenerative medicine. The most similar devices on the market extract stem cells from blood or bone marrow.

Federal law establishes two basic paths for FDA approval of new medical devices. One is the “premarket approval” process. *See* 21 U.S.C. § 360e. That process generally requires extensive clinical research on a new device to ensure the device's safety, and it often takes significant time. The other is the streamlined “premarket notification” process, which simply requires that the new device be “substantially equivalent” to another device already on the market. *See* 21 U.S.C. §§ 360(k), 360c(i).

Here, FDA concluded that the Celution and the StemSource were not substantially equivalent to any device already on the market. The FDA reasoned, in essence, that using fat rather than blood as a source of cells made those new devices different from existing devices. Therefore, FDA ruled that Cytori must go through the extensive premarket approval process.

Cytori argues that FDA's decision was arbitrary and capricious under the Administrative Procedure Act. Cytori contends in particular that FDA acted unreasonably in rejecting Cytori's substantial equivalence application and that, in any event, FDA did not reasonably explain its decision. In response, FDA first raises a jurisdictional argument: that Cytori must file its petition in the district court rather than in this Court. On the merits, FDA argues that it reasonably determined and explained that the Celution and the StemSource were not substantially equivalent to any device already on the market, meaning that Cytori must go through the more extensive premarket approval process.

On the threshold jurisdictional issue, we conclude that this Court is the proper forum for direct review of FDA's substantial equivalence determination. On the merits, we conclude that FDA's determination was reasonable and reasonably explained for purposes of the Administrative Procedure Act. We therefore deny the petitions for review.

I

Cytori Therapeutics manufactures medical devices, including devices for use in cell therapy and other forms of regenerative medicine. In a typical cell therapy treatment, doctors introduce stem cells¹ or other regenerative cells into the patient's body to treat a disease. The cells may come from the patient or from a donor. For example, there are several devices on the market that draw and concentrate blood or bone marrow in order to treat leukemia and blood-borne diseases, among other things. The healthy donor cells are

¹ Stem cells are a cellular "blank slate" that can change into a variety of other kinds of cells and generate additional stem cells. Those cells can be used to regenerate and repair damaged tissue.

used to replace the diseased or damaged cells and regenerate new tissue.

Cytori is anticipating a major breakthrough in regenerative medicine: the expanded use of adipose tissue – that is, fat – as a source of stem cells for therapy and other medical uses. Cytori recently developed technology to harvest and concentrate stem and regenerative cells from fat via its Celution system. The Celution and the StemSource are two versions of this broader Celution system.

But before a new medical device such as the Celution or StemSource may be marketed in the United States, the manufacturer must obtain approval from FDA. In many cases, premarket clearance is obtained by submitting a “premarket notification.” The premarket notification process requires that FDA find the new device “substantially equivalent” to a device that is currently on the market. *See* 21 U.S.C. § 360c(i). Once FDA makes that finding, the device may be marketed.

Some devices – in recent years, a low percentage of all devices marketed in the United States – are not “substantially equivalent” to existing devices and must go through FDA’s more extensive “premarket approval” process. Premarket approval entails scientific review of a device and often requires clinical studies.

Cytori recently submitted premarket notifications for two of its cell-harvesting devices. Although the notifications both referred to virtually identical physical devices, each notification corresponded to a different marketing version of the device that would be sold for different medical purposes. One version of the device, labeled as the Celution 700, is intended to harvest and prepare stem cells for clinical

laboratory analysis. The other, labeled as the StemSource 900, is also intended to harvest stem cells but for storage, so they can be used or analyzed in the future, potentially for therapeutic purposes. Neither version of the device is expressly intended for a specific cell therapy treatment, at least not yet.

In general, federal law requires a new device to meet two criteria to be considered “substantially equivalent” to a previously marketed device. First, the new device must have the same intended use as the predicate device. Second, the new device must use the same basic technology as the predicate device – or, if not, the materials submitted must establish that the devices are equally safe and effective, and the technological differences must not raise any different questions of safety and effectiveness.

In its premarket notifications, Cytori claimed that the Celution and StemSource were substantially equivalent to currently marketed devices, including devices that harvest cells from blood and bone marrow. FDA’s basic response was simple: Fat is not blood. And a device meant to derive cells from fat does not have the same intended use as a device meant to derive cells from blood. FDA also determined (as an alternative basis for the “not substantially equivalent” finding) that the devices had different technological characteristics or posed different safety concerns. In particular, FDA highlighted risks posed by an enzyme that the Celution and the StemSource use to separate the useful cells from other tissue. FDA stated that this enzyme posed new safety questions based on its effect on the harvested cells.²

² Cytori correctly notes that its devices are not yet labeled for use in cell therapy. However, because the StemSource 900 is designed for cell banking and cryopreservation – that is, for storing

Moreover, FDA said that the testing data for the Celution were based on a study of only 12 donors and thus not sufficient to demonstrate substantial equivalence. Therefore, FDA concluded that Cytori's devices would need to complete the more extensive premarket approval process.

Cytori contests FDA's "not substantially equivalent" determination. Cytori claims that the Celution and the StemSource share an intended use with other predicate devices already on the market: They all process tissue samples and isolate cells. In addition, according to Cytori, the devices share basic technological characteristics. Cytori therefore claims that FDA acted unreasonably in rejecting its premarket notification.

FDA contends that this Court does not have jurisdiction to hear Cytori's petitions and, alternatively, defends its determination on the merits.

II

As a preliminary matter, FDA asserts that this Court lacks jurisdiction to hear Cytori's petitions. In particular, FDA argues that the relevant statutes establish the district court as the proper forum for initial review of Cytori's petitions.

In general, 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." *Watts v. SEC*, 482 F.3d 501, 505 (D.C. Cir. 2007). The medical device section of the Food, Drug, and Cosmetic Act contains such a direct-review provision. *See*

cells – those cells could foreseeably be used for treatment at a later date.

21 U.S.C. § 360g. That provision allows “any person adversely affected by” a specified regulation or order to file a petition in the U.S. Court of Appeals for the D.C. Circuit. 21 U.S.C. § 360g(a). The specified orders in Section 360g include “an order pursuant to section 360c(i) of this title” – that is, an order determining whether a new device is substantially equivalent to an existing device. 21 U.S.C. § 360g(a)(8).

This Court may therefore review an “order” that is made “pursuant to section 360c(i)” of Title 21. We thus must decide (i) whether a “not substantially equivalent” determination is an “order” for purposes of the Act’s direct-review provision; and, if so, (ii) whether such an order is “pursuant to” Section 360c(i).

First, a “not substantially equivalent” determination is plainly an “order” for purposes of the direct-review provision. Because the Food, Drug, and Cosmetic Act does not define an “order,” we look to the Administrative Procedure Act’s definition. *See Watts*, 482 F.3d at 505. The APA provides that an “order” is “the whole or a part of a final disposition, whether affirmative, *negative*, injunctive, or declaratory in form.” 5 U.S.C. § 551(6) (emphasis added).

In this case, FDA’s decision was the “final disposition” of the issue. FDA’s letter to Cytori stated that, after consideration, FDA had determined that the devices were not substantially equivalent to any device currently on the market and would need to go through the premarket approval process. The letter did not state that FDA was still considering the applications or that the decision was preliminary. FDA said that the devices were not substantially equivalent. End of story. And as the APA’s definition makes clear, a final

disposition may be either affirmative or negative. The disposition here was negative.

Second, a “not substantially equivalent” order is made pursuant to Section 360c(i). Section 360c(i) sets forth the criteria for determining whether a new medical device is substantially equivalent to a predicate device already on the market.

FDA contends that findings of equivalence – but not findings of *non*-equivalence – are made “pursuant to” Section 360c(i). According to FDA, Section 360c(i) explicitly refers to only one kind of order, in which “the Secretary by order has found that the device” *is* substantially equivalent. 21 U.S.C. § 360c(i). Based on that passing reference to an affirmative order, FDA concludes that negative, non-equivalence orders are not made pursuant to Section 360c(i) because negative, non-equivalence orders are not specifically mentioned.

We do not read the statute that way. Section 360c(i) sets criteria for determining whether a device is substantially equivalent to another device already on the market. As a natural consequence of Section 360c(i)’s criteria, some orders will confirm substantial equivalence, and some will not. As the APA puts it, some orders may be “affirmative,” and others may be “negative.” Either way, the order is “pursuant to” Section 360c(i) because the criteria of that section – and that section alone – guide the determination.

A non-equivalence determination, then, is an “order” made “pursuant to” Section 360c(i). Under the text of the Food, Drug, and Cosmetic Act, this Court therefore has jurisdiction to directly review Cytori’s petitions.

III

Applying the arbitrary and capricious standard of the Administrative Procedure Act, we next must determine whether FDA's non-equivalence decision was reasonable and reasonably explained. *See Motor Vehicle Manufacturers Assn. v. State Farm Mutual Auto. Insurance Co.*, 463 U.S. 29 (1983).

Under Section 360c(i), a device must meet two core criteria to be substantially equivalent to a currently marketed device. First, the device must have "the same intended use as the predicate device." 21 U.S.C. § 360c(i)(1)(A). Second, the new device must also have "the same technological characteristics as the predicate device" or, if not, the submitted data must establish that the new device is *both* equally "safe and effective as a legally marketed device" *and* "does not raise different questions of safety and effectiveness than the predicate device." *Id.*

Here, FDA reasonably determined – and reasonably explained its determination – that the Celution and the StemSource met neither the "intended use" criterion nor the "technological characteristics" criterion.

First, FDA concluded that the intended uses of the Celution and the StemSource are not the same as the intended uses of the most similar predicate devices. The Celution and the StemSource are designed to derive stem cells from fat tissue. But the most similar devices currently on the market are designed to derive cells from blood and bone marrow. Extracting cells from fat, FDA reasoned, is different from extracting cells from blood. Cytori, however, argues that deriving cells and preparing cell concentrate – whether from fat or blood – is the same intended use.

One of the factors FDA routinely considers regarding intended use concerns the “types of tissue involved.” FDA, *Guidance on the Center for Devices and Radiological Health’s Premarket Notification Review Program* (1986). To illustrate how different kinds of tissue can lead to different intended uses, FDA’s guidance document offered the example of (i) a device meant to process fat and (ii) a device meant to process blood and other tissue. *Id.* A device designed specifically to process fat, FDA explained, is not intended for the same use as a device designed to process some other form of tissue.

Here, using that same logic, FDA concluded and explained that fat is not blood and that the difference matters. A court is ill-equipped to second-guess that kind of agency scientific judgment under the guise of the APA’s arbitrary and capricious standard. After careful review, we find FDA’s assessment both reasonable and reasonably explained.

Second, FDA concluded that, in any event, the Celution and the StemSource did not meet the substantial equivalence criteria for another, independent reason: They did not pass the separate “technological characteristics” test for a substantial equivalence determination.

To pass this prong of the substantial equivalence test, a device ordinarily must have the same technological characteristics as a predicate device. But as FDA explained, the Celution and the StemSource use different technology than blood processing devices use. The Celution and the StemSource required new technology both to break down the fat tissue and to harvest the useful cells. For example, the Celution and the StemSource take advantage of the particular buoyancy of fat cells to separate heavier stem cells from fat tissue. In this way, the technology of the Celution and

StemSource differs from the technology of blood processing devices.

Alternatively, even if it does not have the same technological characteristics, a device may still satisfy the technological characteristics component of the substantial equivalence test if it is equally “safe and effective as a legally marketed device” and does not raise different “questions of safety.” However, FDA concluded that the Celution and StemSource did not meet this prong of the test. As to the StemSource, the FDA focused on one component, the enzyme used to aid the separation of stem cells from fat tissue. The enzyme, which is called Celase, was previously approved by FDA for one particular use: After liposuction, it is used to liquefy fat waste to simplify disposal. Because the enzyme has been approved only for that use, the scientists at FDA identified “different questions of safety” – and reasonably raised concerns about the impact the Celase enzyme might have on cells that may be reintroduced into the human body.

Regarding the Celution, FDA also reasonably determined that the only safety study Cytori submitted – which had merely a dozen participants – was insufficient to show that the device was equally “safe and effective” as a “legally marketed device.”

In short, FDA reasonably concluded and reasonably explained that the Celution and StemSource did not meet either the “intended use” requirement or the “technological characteristics” requirement for a substantial equivalence determination.

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We have considered all of Cytori's arguments. We deny the petitions for review.

So ordered.