UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

ISTA PHARMACEUTICALS, INC.,	:	CASE NO. 1:11-CV-0907
Plaintiff,	:	
vs.	:	OPINION & ORDER
	:	[Resolving Doc. Nos. 36; 40]
FOOD AND DRUG ADMINISTRATION, *et al.*,	:	
Defendants.	:	

JAMES S. GWIN,[1/] UNITED STATES DISTRICT JUDGE:

Plaintiff ISTA Pharmaceuticals, Inc., brings this action against the Defendants, the Food and Drug Administration, the Commissioner of Food and Drugs, Margaret A. Hamburg, and the Secretary of Health and Human Services, Kathleen Sebelius (collectively, "FDA"). Plaintiff ISTA alleges that the FDA unlawfully approved a generic version of an ISTA eye-drop drug. [Doc. 1.] Coastal Pharmaceuticals, the manufacturer and marketer of the generic eye-drops, intervened as a Defendant.[2/] [Doc. 7.] The parties filed cross motions for summary judgment. [Docs. 36; 40.] For the following reasons, the Court finds that the FDA acted lawfully, **DENIES** ISTA's motion for summary judgment, and **GRANTS** the FDA's motion for summary judgment.

[1/]The Honorable James S. Gwin of the United States District Court for the Northern District of Ohio, sitting by designation.

[2/]Two companies—Mylan Pharmaceuticals Inc., and Metrics, Inc.—do joint business as Coastal Pharmaceuticals. In 2009, Mylan and Coastal agreed to develop and market a generic version of ISTA's bromfenac ophthalmic solution ("bromfenac").

I. Background

1. Statutes and Regulations

The Federal Food, Drug, and Cosmetic Act ("FDCA") requires all pharmaceutical companies wishing to market "pioneer" or "innovator" drugs to first obtain FDA approval through a New Drug Application. ("NDA"). The NDA must contain sufficient data to demonstrate the safety and effectiveness of the product. 21 U.S.C. §355. In addition, the FDCA permits manufacturers that wish to produce a generic version of an approved drug product to submit an abbreviated new drug application ("ANDA"). *Id.* at § 355(j). An ANDA applicant can rely on the FDA's prior finding of safety and effectiveness for a previously-approved NDA—the " reference listed drug"—as long as the ANDA is the same as, bioequivalent to, and references the currently approved labeling of an innovator drug. *Id.*; 21 C.F.R. § 314.94(a)(8)(i).

2. Administrative Record

In March 2005, the FDA approved ISTA's NDA for Xibrom, a bromfenac ophthalmic solution (eyedrops prescribed to reduce pain and inflamation following cataract surgery). The FDA approved Xibrom in a 2.4ml bottle size sufficient for use twice-a-day on one or both eyes. In October 2010, the FDA approved ISTA's supplement to Xibrom labeling—including a change to the dosing regimen (from twice-a-day to once-a-day) and name change (from "Xibrom" to "Bromday")—and ISTA received three years of exclusivity for the new Bromday.[3/] [Doc. 36-1 at 3-5.] For the next few months, ISTA marketed both Xibrom and Bromday and also requested approval of a Bromday 2.4ml bottle (like that utilized by Xibrom), capable of treating two eyes. The FDA rejected the request to approve the 2.4ml bottle. [Doc. 40 at 6-7.]

[3/] That is, for three years the FDA may not approve an ANDA that relies on Bromday's labeling.

Meanwhile, on December 18, 2009, Coastal Pharmaceuticals submitted an ANDA relying on Xibrom's twice-a-day labeling as the reference-listed drug. [Doc. 40 at 8.] In response, on March 1, 2011, ISTA submitted a Citizen's Petition requesting that the FDA refrain from issuing approval of any ANDAs referencing Xibrom, claiming that Bromday and Xibrom are the same product, and arguing that Bromday's once-a-day labeling was the "currently approved" label, thus the three-year exclusivity agreement banned such approval. In the alternative, ISTA urged the FDA to decline Coastal's ANDA until there was a determination that Xibrom was not removed from the market for issues of safety and efficacy. [Doc. 36-1 at 7-8.]

On May 11, 2011, the FDA simultaneously approved Coastal's ANDA and denied ISTA's Citizen's Petition. In denying ISTA's Petition, the FDA explained that Xibrom and Bromday were two separate drugs and that the Bromday once-a-day labeling was not the "currently approved" labeling for Xibrom. Moreover, the FDA determined that Xibrom was not withdrawn for safety or effectiveness reasons. [Doc. 40 at 9-10.]

Two days later, ISTA filed this suit and sought a temporary restraining order against the approval of Coastal's ANDA. [Docs. 1, 3.] The Court denied the motion for a temporary restraining order. [Doc. 36-1 at 14.] On May 18, 2011, the Parties agreed to consolidate the motion for a preliminary injunction with proceedings on the merits, and ISTA later filed an Amended Complaint to include additional information regarding the FDA's safety concerns of bromfenac solutions. [Doc. 27.] The Parties then submitted revised cross-motions for summary judgment on whether the FDA acted lawfully. [Docs. 36, 40.]

Generally, ISTA complains that the FDA unlawfully approved Coastal's generic bromfenac ANDA for two reasons: (1)Xibrom's twice-a-day labeling is obsolete and not "currently approved

labeling"; and (2) the FDA determined that the 2.4ml bottle size is unsafe, thus Coastal's generic is unsafe. [Doc. 36-1 at 17, 30.] The Court rejects each in turn.

II. Legal Standard

The FDA's administrative decisions are subject to review under the Administrative Procedure Act ("APA"), 5 U.S.C. § 706, which requires the reviewing court to set aside an agency action that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." In making this inquiry, the reviewing court "must 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. Or. Natural Res. Council*, 490 U.S. 360, 378 (1989) (internal quotation marks omitted). The FDA "is entitled to summary judgment if the path of its reasoning is sufficiently discernable in light of the record." *Settles v. U.S. Parole Comm'n*, 429 F.3d 1098, 1108 (D.C. Cir. 2005). And although "the Court's review is limited to the administrative record[,] . . . [s]ummary judgment is an appropriate procedure for resolving a challenge to a federal agency's administrative decision." *Fund for Animals v. Babbitt*, 903 F.Supp. 96, 105 (D.D.C. 1995).

III. Analysis

1. Currently Approved Labeling

ISTA first argues that the FDA's approval of Coastal's generic bromfenac was arbitrary and capricious because, ISTA claims, Xibrom's label was not "currently approved" and therefore unavailable to serve as a reference drug. But ISTA's position is, at best, disingenuous—at worst, intentionally misleading.

Under 21 C.F.R. § 314.94(a)(8)(i), an abbreviated-new-drug applicant (e.g., Coastal) must submit a"copy of the currently approved labeling . . . for the listed drug referred to in the abbreviated

new drug application, if the abbreviated new drug application relies on a reference listed drug." Likewise, 21 U.S.C. § 355(j)(2)(A)(v) requires an ANDA applicant to submit "information to show that the labeling proposed for the new drug is the same as the labeling approved for the [previously approved] listed drug . . . ." And if the ANDA applicant fulfills that requirement—along with many other requirements—"the Secretary *shall approve* [the] application." *Id.* at § 355(j)(4).

The FDA first approved Xibrom's twice-a-day label back in 2005. In October 2010, the FDA approved Bromday, which has the same drug formulation and indication as Xibrom: only the dosing and name are different. Then, for the next four-and-a-half months, ISTA continued to market both Xibrom and Bromday. In this case, ISTA says that Xibrom and Bromday are a single product, and thus, the argument goes, Bromday's label is the only "currently approved" label. But ISTA fails to offer any substantial basis for its contention that Xibrom's label was (and is) not currently approved. The list of arguments, while extensive, is wholly unpersuasive.

First, as the FDA points out, ISTA could have revised Xibrom's labeling and sold Xibrom as twice-a-day product. Rather, as ISTA's President/CEO demonstrates, the company chose to tout its revolutionary new Bromday product:

> Having the first and only once-a-day [eyedrop] for postoperative inflammation and reduction of ocular pain in patients . . . has proven to be a major differentiation in the eyes of our customers and their patients. We look forward to gaining even wider acceptance of BROMDAY throughout the prescribing ophthalmic community in the years to come.

[Doc. 39-2 at 3.] Then, ISTA pulled Xibrom from the market only the day before it filed its Citizen's Petition arguing against approval of Coastal's generic.

Moreover, ISTA does not cite a single authority for its notion that Xibrom was not, and is not, a currently approved label, or that discontinued drugs cannot serve as reference label drugs.

Simply put, there was no statutory or regulatory bar to the FDA's approval of Coastal's generic version of Xibrom. To the contrary, FDA only "remove[s] a previously approved new drug product from the list [of approved drugs]" under certain circumstances, most of them involving "safety or effectiveness reasons." 21 C.F.R. § 314.162(a). Moreover, FDA regulations explicitly anticipate that ANDAs will rely upon drugs that the manufacturer no longer sells:

> An abbreviated new drug application that refers to, or a petition under section 505(j)(2)(C) of the act and § 314.93 that relies on, a listed drug that has been voluntarily withdrawn from sale in the United States must be accompanied by a petition seeking a determination whether the listed drug was withdrawn for safety or effectiveness reasons. . . .

21 C.F.R § 314.122.

Likewise, the FDA is required to "determin[e] whether a listed drug that has been voluntarily withdrawn from sale was withdrawn for safety or effectiveness reasons . . . prior to approving an abbreviated new drug application that refers to the listed drug . . . ." 21 C.F.R. § 314.161. And here, the FDA did just that. ISTA voluntarily stopped selling Xibrom. Then the FDA approved Coastal's generic after making the determination Xibrom—the listed drug—had not been withdrawn from sale for safety or effectiveness reasons. But throughout the entire process, the FDA never removed Xibrom from the list and ISTA never indicated—until Coastal's ANDA came along—that Xibrom and Bromday were one product.

In fact, ISTA itself always treated Xibrom and Bromday as two products (apparently until realizing it wouldn't have the bromfenac market cornered). For example, in its Securities and Exchange Commission filings, ISTA noted that it "currently ha[s] five products for sale in the U.S. and Puerto Rico: BROMDAY (bromfenac ophthalmic solution) 0.09% for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract

extractions[, and] . . . XIBROM (bromfenac ophthalmic solution) 0.09% for the treatment of inflammation and pain following cataract surgery." [Doc. 40-3 at 6.] ISTA's now-inconsistent assertion is a poorly-disguised gambit to avoid competition, game the drug-approval system, and maintain a monopoly over the bromfenac eyedrop market.

In sum, ISTA fails to show that Bromday and Xibrom are one product, and the FDA properly concluded that Xibrom's label is "currently approved." Therefore, the FDA also properly approved Coastal's ANDA and rejected ISTA's Citizen's Petition. Accordingly, the Court generally rejects ISTA's arguments in their entirety. The FDA did not act arbitrarily or capriciously; it did not fail to follow its own regulations or controlling statutes. The FDA's website, approval letter, and response to the Citizen's Petition were neither arbitrary or capricious.

2. Xibrom was not removed for safety reasons

ISTA next claims that the FDA violated 21 C.F.R. § 314.127(a)(11) and 21 U.S.C. § 355(j)(7)(C) when the FDA approved Coastal's ANDA referencing an innovator drug—Xibrom—that ISTA says was withdrawn for reasons of safety or effectiveness. [Doc. 36-1 at 34.] ISTA says that the FDA's conclusion that Xibrom was not withdrawn for reasons of safety or effectiveness is contradicted by the Administrative Record. And as ISTA argues this claim, the FDA cited safety concerns when denying ISTA's request to change Bromday's bottle to a larger size like that of Xibrom and FDA has requested that ISTA modify Xibrom's labeling to take safety concerns into account. [Doc. 30-1 at 32-34.] Again, the Court disagrees.

While the FDA is required to evaluate all NDA submissions and supplements for safety and effectiveness, *see* 21 U.S.C. § 355(a), (b), the agency does not have the same obligation when reviewing an ANDA. Instead, the FDA is to determine whether the generic product is the "same as"

the innovator drug it seeks to reference. 21 U.S.C. § 355 (j). If an ANDA relies on an innovator drug that has been withdrawn from the market, the FDA must determine whether the innovator drug was withdrawn for safety or effectiveness reasons, 21 C.F.R. § 314.161(a)(1), and if it has, the ANDA will not be approved. 21 C.F.R. § 314.127(a)(11).

First, the Administrative Record shows that Xibrom was not removed from the market for safety or effectiveness reasons. Rather, ISTA voluntarily removed Xibrom from the market and ISTA never indicated that Xibrom was unsafe or ineffective. [*See* Doc. 9-3 at 13, 15, 45, 92-93.]

Second, the Court finds that the FDA did not act inconsistently when it denied ISTA's request for a larger bottle size while approving Coastal's ANDA. The Administrative Record shows that the FDA remains confident of the safety of bromfenac sodium solution generally, and Xibrom specifically—despite some ongoing concerns of improper consumer usage and cross-contamination of post-operative eyes. [Doc. 30-2 at 47.] The FDA has admittedly asked some sponsors to *voluntarily* change their labeling to address these concerns, but has *not required* any changes thus far. [Doc 40 at 31, 32.] Furthermore, the FDA denied ISTA's NDA supplemental request for a 2.4mL Bromday fill-size due to emerging safety concerns; Xibrom, on the other hand, was approved before these concerns. [Doc. 9-4 at 5.] Until the FDA reaches a final conclusion on the safety of the fill-size and requires Xibrom to change its label, any generic—such as Coastal's ANDA—can reference the current label.[4/] *See* 21 U.S.C. § 355(j)(2)(A)(v).

In the end, the FDA properly concluded (1)that the larger fill size on the Xibrom label was

[4/]Interestingly enough, ISTA only needs to change Xibrom's label, a supposedly obsolete product, to prevent Coastal's ANDA from referencing it. It is ironic—and quite a bit revealing—that on one front ISTA is continuing to urge the FDA to approve a larger bottle for Bromday, but on a different front petitioning the Court to overturn such an approval for Coastal.

currently approved; (2) that Xibrom was not removed for safety or effectiveness concerns; and (3) that Coastal's ANDA was the same as that Xibrom label. Those steps—and not a new review of safety or effectiveness—are all that was required by 21 U.S.C. § 355(j).

IV. Conclusion

The Court concludes that the FDA did not act unlawfully in approving Coastal's generic-bromfenac ANDA. Accordingly, the Court **DENIES** ISTA's motion for summary judgment and **GRANTS** the FDA's motion for summary judgment.

IT IS SO ORDERED.

Dated: July 9, 2012

s/ *James S. Gwin*
JAMES S. GWIN
UNITED STATES DISTRICT JUDGE