UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

CUMBERLAND PHARMACEUTICALS INC.,	
Plaintiff,	
v.	Civil Action No. 12-01842 (RBW)
	UNDER SEAL
FOOD & DRUG ADMINISTRATION, et al.,	
Defendants.	

MEMORANDUM OPINION

Plaintiff Cumberland Pharmaceuticals Inc. ("Cumberland") brings suit against the Food & Drug Administration ("FDA"), FDA Commissioner Margaret A. Hamburg, and Department of Health and Human Services Secretary Kathleen Sebelius (collectively "FDA"), alleging that the FDA's denial of Cumberland's May 18, 2012 citizen petition and simultaneous approval of InnoPharma, Inc.'s ("InnoPharma") abbreviated new drug application for acetylcysteine injection was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law in violation of the Administrative Procedure Act ("APA"), 5 U.S.C. § 706(2)(A) (2012). Complaint ("Compl.") ¶¶ 32–38. The FDA's Motion to Dismiss Or, In the Alternative, for Summary Judgment ("Defs.' Mot.") and Cumberland's Cross-Motion for Summary Judgment ("Pl.'s Mot.") are currently before the Court. After careful consideration of the parties' submissions and the administrative record ("A.R."),[1] the Court concludes that it must grant summary judgment to the FDA.

[1] In addition to the filings already referenced, the Court considered the following documents in rendering its decision: (1) the Defendants' Memorandum in Support of Motion to Dismiss Or, In the Alternative, for Summary Judgment ("Defs.' Mem."); (2) the Memorandum of Points and Authorities in Opposition to Defendants' Motion to Dismiss and In Support of Plaintiff's Cross-Motion for Summary Judgment ("Pl.'s Mem."); (3) the Federal

(continued . . .)

I. STATUTORY AND REGULATORY BACKGROUND

The Food, Drug, and Cosmetic Act ("FDCA") provides that "[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to . . . this section is effective with respect to such drug." 21 U.S.C. § 355(a) (2012). In order to obtain approval, a new drug application ("NDA") must include, among other things, "full reports of investigations which have been made to show whether or not [the] drug is safe for use and whether [the] drug is effective in use." Id. § 355(b)(1)(A). Because this process is "costly and time[-]consuming," Congress amended the FDCA in 1984 to "permit[] a manufacturer of a generic alternative to a pioneer drug to seek FDA approval by submitting an abbreviated new drug application ("ANDA")," Serono Labs., Inc. v. Shalala, 158 F.3d 1313, 1316 (D.C. Cir. 1998), which references and relies on the prior approval of the pioneer drug, Astellas Pharma US, Inc. v. FDA, 642 F. Supp. 2d 10, 13–14 (D.D.C. 2009). So "[r]ather than requiring the [ANDA] applicant to make an independent showing that the proposed generic is itself safe and effective, the amended statute requires a showing that the proposed generic operates in the same manner as the pioneer drug on which it is based." Id.

To that end, FDA regulations require that an ANDA include information comparing, among other things, the proposed drug's active ingredients, route of administration, dosage form, and strength to the "reference listed drug." 21 C.F.R. §§ 314.94(a)(5), (6) (2012). For injectable ANDA drugs in particular, there are additional regulations regarding the inactive ingredients in the drug, which require that the proposed drug "[g]enerally . . . contain the same inactive ingredients and in the same concentration as the reference listed drug." Id. § 314.94(a)(9)(iii).

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Defendants' Reply Memorandum in Support of Motion to Dismiss Or, In the Alternative, for Summary Judgment and Opposition to Plaintiff's Cross-Motion for Summary Judgment ("Defs.' Reply"); and (4) the Reply Memorandum in Support of Plaintiff's Cross-Motion for Summary Judgment ("Pl.'s Reply").

Nonetheless, "an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product." Id. An ANDA applicant may also ask the FDA to waive any regulatory requirement governing the submission of ANDAs. Id. § 314.99(b). The FDCA unequivocally prohibits the FDA from approving an ANDA, however, if

> information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.

21 U.S.C. § 355(j)(4)(H).

If an ANDA applicant wishes to rely on a reference listed drug that has been voluntarily withdrawn from the market in the United States, the applicant must include with its application a petition "seeking a determination whether the listed drug was withdrawn for safety or effectiveness reasons . . . and must contain all evidence available to the petitioner concerning the reasons for the withdrawal from sale." 21 C.F.R. § 314.122(a). The petition may be in the form of a "citizen petition" under 21 C.F.R. § 10.30 or another petition form specified in FDA regulations. Id. The FDA "consider[s] the evidence in the petition and any other evidence before the agency" to determine whether the reference listed drug was withdrawn for safety or effectiveness reasons. Id. § 314.122(b).

In conducting this inquiry, the FDA "rel[ies] upon circumstantial evidence and logical inference to determine the actual intent of those who decided to withdraw the product from the market" and "focus[es] on whether there were sufficient concerns about safety and effectiveness to make a withdrawal from sale likely and reasonable." 54 Fed. Reg. 28,872-01, 28,907 (July

10, 1989). While the FDA considers a manufacturer's stated reasons for withdrawing a product, it does "not consider the NDA holder's stated reasons for withdrawing a drug to be determinative because such remarks could be biased." 57 Fed. Reg. 17,950-01, 17,971 (Apr. 28, 1992). Recognizing that a drug manufacturer may have business reasons to disclaim concerns about the safety or effectiveness of a withdrawn product, the FDA employs a rebuttable presumption that a withdrawal was for safety or effectiveness reasons "[i]f a drug manufacturer withdraws a drug from the market which accounted for significant sales to that manufacturer, and there is no evidence to the contrary." 54 Fed. Reg. 28,872-01 at 28,907. To determine whether a withdrawal was for reasons of safety or effectiveness, the FDA also considers "other factors . . . such as increases in the number of adverse drug reactions reported on the drug and published or unpublished studies of the drug questioning its safety or effectiveness." Id. If it concludes that the reference listed drug was withdrawn from sale for safety or effectiveness reasons, the FDA must disapprove the ANDA referencing the withdrawn drug. See 21 C.F.R. §§ 314.93(e)(1)(v), 314.127(a)(11).

II. FACTUAL BACKGROUND

Acetylcysteine injection, marketed by Cumberland under the brand name Acetadote, is an intravenous drug administered to treat acetaminophen overdose. A.R. at 000456. Cumberland first submitted an NDA for Acetadote to the FDA on June 27, 2002. See A.R. at 001723. The original formulation of Acetadote contained the inactive ingredient disodium edetate ("edetate"), which Cumberland believed to be necessary to stabilize the drug. A.R. at 000282. In a letter dated December 30, 2002, the FDA informed Cumberland that it found the information submitted in the NDA to be inadequate to approve Acetadote, and identified a number of deficiencies for Cumberland to address in an amendment to its application if it wished to continue seeking approval for Acetadote. See A.R. at 001723–27. Among other things, the FDA

requested that Cumberland provide "scientific and regulatory justification for the inclusion of [e]detate as a component of the drug product" and "a description of the pharmacological properties for [e]detate in this drug product." A.R. at 001724.

Following additional submissions by Cumberland, the FDA approved Acetadote on January 23, 2004. A.R. at 001540–43. In its approval letter, the FDA noted that Cumberland had agreed, at the FDA's request, to conduct postmarketing studies to "further evaluate the incidence of anaphylactoid[2] reactions after administration of Acetadote" and to "evaluate the potential benefit of [e]detate disodium on the stability of the drug product," including "a comparison of the current concentration of [e]detate to a formulation with a lower concentration and no concentration of [e]detate." A.R. at 001541. Cumberland completed its commitment to evaluate the inclusion of edetate, A.R. at 000932–33, finding that edetate was not, in fact, necessary to ensure the stability of Acetadote, A.R. at 001355. Cumberland sent its final report on the inclusion of edetate to the FDA on August 13, 2008, A.R. at 001349–61, and then in September 2010, sought approval to market a new formulation of Acetadote that did not contain edetate, A.R. at 001147–56. The FDA approved the application supplement containing the new formulation, A.R. at 001081–82, and Cumberland withdrew the original formulation from the market ten days thereafter, A.R. at 000282. Cumberland issued a press release announcing the new formulation and the withdrawal of the prior version of Acetadote, stating that the new formulation was the result of a postmarketing commitment to the FDA, under which Cumberland "initiated a program to develop the new formulation and determined that it could be prepared and scaled in a commercial manufacturing setting without compromising the potency, solubility or

[2] Anaphylaxis is "[a]n immediate (and often unpleasant) hypersensitivity reaction produced by the body's . . . antibodies to a foreign substance" in which "the affected tissues release histamine which causes local or systemic attack." Black's Medical Dictionary 31 (Gordon Macpherson ed., 40th ed. 2004). In rare cases, anaphylaxis may cause shock and lead to death unless the individual receives medical attention. Id.

stability of the product." A.R. at 000006. Neither the FDA nor Cumberland initiated a recall of the original formulation of Acetadote that was already on the market after the new formulation was approved. See A.R. at 000519.

Several months after the introduction of the new formulation of Acetadote, the FDA received a citizen petition from the law firm Leydig, Voit & Mayer, Ltd. ("Leydig") on behalf of an unnamed client, seeking a determination that the edetate-containing formulation was not withdrawn for safety and effectiveness reasons. A.R. at 000001–03. Cumberland then submitted a citizen petition to the FDA requesting that the agency not approve any ANDA based on the edetate-containing formulation of Acetadote as the reference listed drug. A.R. at 000280–89. During this same time period, an ANDA using the edetate-containing formulation that had been initially filed in 2009 by InnoPharma remained pending before the FDA. See A.R. at 001851.

Following receipt of Leydig's citizen petition, FDA's Office of Regulatory Policy requested the opinion of FDA's Division of Gastroenterology and Inborn Errors Products ("the Gastroenterology Division" or "the Division") on the issues raised by the petition. A.R. at 000563. The Division issued a four-page opinion on July 1, 2011. See A.R. at 000563–66. The opinion noted that the amount of edetate in the original formulation of Acetadote was comparable to that contained in "[o]ther injectable acetylcysteine products used worldwide," discussed two studies "showing that [edetate] is associated with allergic reactions when used in other drug product formulations," and compared the amount of edetate in Acetadote to the amount of the substance in another drug, Leukine, which was withdrawn from the market by the manufacturer due to an increase in the number of adverse reactions following the addition of edetate to the drug's formula. See A.R. at 000564. In response to the Office of Regulatory Policy's question regarding why the FDA originally requested a postmarketing study from Cumberland concerning edetate, the Division determined without further discussion that

"[a]lthough early documentation concerning the postmarketing commitment is sparse, it is clear from subsequent discussions with the company that the FDA had concerns about allergic reactions and syncope." A.R. at 000565. It therefore recommended that the agency "not accept ANDAs for acetylcysteine injection based on the discontinued formulation." Id.

The Office of Regulatory Policy subsequently asked the Office of Surveillance and Epidemiology ("Surveillance Office") for its opinion regarding the safety of Acetadote containing edetate. See A.R. at 000664. The Surveillance Office conducted a search of the Adverse Event Reporting System, but concluded that "safety concerns regarding the use of the preservative [edetate] in Acetadote[] cannot be reliably ascertained using available [adverse event report] data" because "[t]he lack of control prevents the attribution of the adverse events in question to either of the co-present ingredients." A.R. at 000665. The Surveillance Office offered a similar opinion concerning reports of adverse events involving other drug products containing edetate. See A.R. at 000665–66.

After the Surveillance Office issued its report, individuals from various divisions within the FDA met twice to discuss the ongoing review of the safety of Acetadote containing edetate. See A.R. at 000515. During the initial meeting, findings regarding edetate in another drug product, Diprivan, were also discussed. Id. At the conclusion of this meeting, the individuals representing the Gastroenterology Division "agreed to reassess, in light of additional information, whether they [should] conclude that Acetadote with [edetate] was discontinued for reasons of safety or effectiveness." Id. During the second meeting, representatives from the FDA's Office of Generic Drugs and Office of New Drugs raised concerns that the Gastroenterology Division's initial opinion "appears inconsistent with Agency precedent and potentially unsupportable" because (1) there was no recall of the original formulation, (2) the amount of edetate in Acetadote is comparable to that in approved and currently-marketed

propofol products, (3) the FDA allows both propofol products that contain and do not contain edetate, (4) there are a number of other products containing edetate in various amounts on the market, and (5) "[t]here are concerns about drug shortages and the potential problems of having a single supplier of this product." Id. Based on these concerns, the Gastroenterology Division "was asked to reconsider its position taking into account these concerns." A.R. at 000516.

The Gastroenterology Division ultimately issued a twenty-eight page report reconsidering its initial opinion. A.R. at 000513–40. First, with respect to the motivation for the FDA's request for a postmarketing commitment to study the benefit of edetate on the stability of the drug, the Division concluded that, "[o]n re-examination of the electronic records of letters and reviews for this NDA, there is no definitive evidence that this [postmarketing commitment] was prompted by specific safety concerns." A.R. at 00516. The report reviewed the FDA's internal documentation regarding the postmarketing commitment, which focused primarily on whether it was actually necessary to include edetate in the formulation. See A.R. at 000534–37. Second, regarding whether the original formulation of Acetadote was withdrawn for safety reasons, the Division ultimately concluded that while "[t]here are potential safety concerns . . . associated with [edetate,] . . . none of these concerns rises to the level that would enable us to conclude that the old formulation of Acetadote[] (with [edetate]) was withdrawn for reasons of safety." A.R. at 000539–40. The report considered the chelation[3] potential of edetate, reports of adverse events involving Acetadote, studies and safety information on other edetate-containing products, and the FDA's review of a propofol product that contains edetate. See A.R. at 000517–34. In addition, the memorandum considered information submitted by InnoPharma supporting its

[3] Edetate "is a molecule that functions as a chelator," A.R. at 000514, which is a "compound[] that will render an ion (usually a metal) biologically inactive," thereby "ridding the body of toxic metals such as mercury," Black's Medical Dictionary, supra, n.2, at 107. Edetate's chelating ability is used to rid the body of an excess of elements (continued . . .)

ANDA application. See A.R. at 000519, 000526, 000528–32. After reviewing the above considerations and concluding that the original formulation of Acetadote was not withdrawn for reasons of safety, the Division acknowledged that "exclusively marketing a non-[edetate] containing product would be preferable because it would eliminate even the potential for risk from [edetate]," but reasoned that "there is a risk to the U.S. population in having only a single source of Acetadote[] available for treating [the] life[-]threatening condition of acetaminophen poisoning (i.e., concerns about future drug shortages, which could be devastating in this case)." A.R. at 000539–40.

On November 7, 2012, the FDA issued a joint decision on the citizen petitions submitted by Leydig and Cumberland, finding that the formulation of Acetadote which contained edetate was not discontinued for safety and effectiveness reasons and that the original formulation of Acetadote is therefore an appropriate reference listed drug for an ANDA. A.R. at 000456–63. In reaching this conclusion, Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research, discussed the Gastroenterology Division's findings regarding the chelation potential of edetate, the Surveillance Office's conclusions regarding adverse reports involving Acetadote, the inclusion of edetate in comparable or higher amounts in other approved and currently-marketed products, and the recent withdrawal of another edetate-containing drug, Leukine, for safety reasons. A.R. at 000460–61. Dr. Woodcock determined that "[a]lthough there is a theoretical safety concern with [edetate] in Acetadote based on its potential to contribute to anaphylactic reactions, we have insufficient data to conclude that the original formulation was withdrawn for reasons of safety." A.R. at 000461.

(. . . continued)
such as lead and calcium, but can present a safety concern if the amount of edetate "would be expected to cause major electrolyte changes" when edetate is not being used for its chelating abilities. A.R. at 000514.

Concerning the use of the edetate-containing formulation of Acetadote as the reference listed drug in an ANDA, Dr. Woodcock first notes that pursuant to 21 C.F.R. § 314.99(b), the FDA may waive the regulatory requirement that the inactive ingredients in an injectable drug proposed in an ANDA be the same as those in the reference listed drug "as long as the statutory requirement [of 21 U.S.C. § 355(j)(4)(H)] regarding safety of inactive ingredients has been met." A.R. at 000462. She then concludes that "experience with Cumberland's original Acetadote formulation and FDA's recent analysis have not shown that the original [edetate]-containing Acetadote formulation is unsafe," and therefore, a waiver of the regulatory requirements to permit ANDAs based on the original formulation of Acetadote is appropriate. A.R. at 000462. The same day when Dr. Woodcock issued her decision, the FDA approved InnoPharma's ANDA using the edetate-containing version of Acetadote as its reference listed drug. A.R. at 001851–55.

Cumberland subsequently commenced this litigation, alleging that both the FDA's denial of its citizen petition and its approval of InnoPharma's ANDA violated the FDCA and its regulations, and therefore was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the APA, 5 U.S.C. § 706(2)(A). See Compl. ¶¶ 32–38. In response, the FDA has filed a motion to dismiss, or in the alternative, for summary judgment, and Cumberland then cross-moved for summary judgment. Specifically, Cumberland argues that (1) the FDA's conclusion that the edetate-containing formulation of Acetadote was not withdrawn for safety reasons relies in part on improper considerations and is not supported by the administrative record and, (2) the FDA violated its own regulations by waiving the requirements that InnoPharma's generic drug contain the same inactive ingredients as the reference listed drug on which its ANDA is based and that InnoPharma demonstrate that the inclusion of edetate in its

formulation does not render the drug less safe than the reference listed drug. See Pl.'s Mem. at 1–2.

III. STANDARD OF REVIEW

The FDA moves for dismissal under Federal Rule of Civil Procedure 12(b)(6), or, in the alternative, for summary judgment under Federal Rule of Civil Procedure 56. Defs.' Mot. at 1. Because a claim under the APA presents only questions of law, the claim may be considered on its merits pursuant to either a motion to dismiss under Rule 12(b)(6) or a motion for summary judgment under Rule 56. Marshall Cnty. Health Care Auth. v. Shalala, 988 F.2d 1221, 1226 (D.C. Cir. 1993). While "there is no real distinction in this context between the question presented on a 12(b)(6) motion and a motion for summary judgment," id., "[i]t is probably the better practice for a district court always to convert to summary judgment," id. at 1226 n.5. Accordingly, the Court will consider the parties' motions under the summary judgment standard of review.

"Summary judgment is the proper mechanism for deciding, as a matter of law, whether an agency action is supported by the administrative record and consistent with the APA standard of review." Loma Linda Univ. Med. Ctr. v. Sebelius, 684 F. Supp. 2d 42, 52 (D.D.C. 2010) (citing Stuttering Found. of Am. v. Springer, 498 F. Supp. 2d 203, 207 (D.D.C. 2007), aff'd, 408 F. App'x 383 (D.C. Cir. 2010)); see also Richards v. INS, 554 F.2d 1173, 1177 & n.28 (D.C. Cir. 1977). But due to the limited role of a court in reviewing the administrative record, the typical summary judgment standards set forth in Federal Rule of Civil Procedure 56 are not applicable. Stuttering, 498 F. Supp. 2d at 207. Rather, "[u]nder the APA, it is the role of the agency to resolve factual issues to arrive at a decision that is supported by the administrative record, whereas 'the function of the district court is to determine whether or not as a matter of law the evidence in the administrative record permitted the agency to make the decision it did.'" Id.

(quoting Occidental Eng'g Co. v. INS, 753 F.2d 766, 769–70 (9th Cir. 1985)). In other words, "when a party seeks review of agency action under the APA, the district judge sits as an appellate tribunal," and "[t]he 'entire case' on review is a question of law." Am. Bioscience, Inc. v. Thompson, 269 F.3d 1077, 1083 (D.C. Cir. 2001) (footnote and citations omitted).

IV. ANALYSIS

The APA requires courts to "hold unlawful and set aside agency action, findings, and conclusions found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). "The 'arbitrary and capricious' standard of review as set forth in the APA is highly deferential," and the Court must "presume the validity of agency action." Am. Horse Prot. Ass'n v. Yeutter, 917 F.2d 594, 596 (D.C. Cir. 1990). Nonetheless, a reviewing court must ensure that the agency "examine[d] the relevant data and articulate[d] a satisfactory explanation for its action including 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) (citations and quotation marks omitted). An agency's decision will be considered arbitrary and capricious if

> the agency has relied on factors which Congress has not intended for 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.

Id. However, a "court is not to substitute its judgment for that of the agency," and will "uphold a decision of less than ideal clarity if the agency's path may reasonably be discerned." Id. (citations and quotation marks omitted).

Moreover, when a court reviews an agency's evaluation of "'scientific data within its technical expertise,'" the arbitrary and capricious standard of review is "'extreme[ly] deferential.'" Nuclear Energy Inst., Inc. v. EPA, 373 F.3d 1251, 1289 (D.C. Cir. 2004) (citation

omitted). This is because courts "review scientific judgments of the agency 'not as the chemist, biologist, or statistician that we are qualified neither by training nor experience to be, but as a reviewing court exercising our narrowly defined duty of holding agencies to certain minimal standards of rationality.'" Troy Corp. v. Browner, 120 F.3d 277, 283 (D.C. Cir. 1997) (citation omitted). It is well-established that the FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference." Schering Corp. v. FDA, 51 F.3d 390, 399 (D.C. Cir. 1995).

A. Determination that Original Formulation of Acetadote Was Not Withdrawn for Safety Reasons

The FDA's decision in response to the Leydig and Cumberland citizen petitions easily meets the minimum standards of rationality required by the APA. The decision responded point-by-point to the arguments made in Cumberland's citizen petition regarding edetate's association with adverse events, Bayer HealthCare Pharmaceuticals' withdrawal of Leukine, the purported inconsistency of the FDA's requested postmarketing commitment on the removal of edetate, and the FDA's prior determinations concerning original formulations of drugs for which a safer alternative was later developed. Compare A.R. at 000285–88 (Cumberland Citizen Petition), with A.R. at 460–61, 460 n.11 (FDA Response to Leydig and Cumberland Citizen Petitions). In addition, the FDA's response also considered and relied on Cumberland's stated reasons for withdrawing the original formulation of Acetadote, a comment to Cumberland's citizen petition filed by the Rocky Mountain Poison and Drug Information Center and the Pittsburgh Poison Center, additional safety concerns potentially associated with edetate, a comparison of the warnings and precautions included in both the new and original formulations of Acetadote, and the fact that other approved and currently-marketed drug products contain edetate, some at even higher quantities than the original formulation of Acetadote. See A.R. at 460–61, 460 n.14, 461

n.15, 16, 17. In further support of its conclusion, the decision incorporated the independent analyses conducted by the Surveillance Office and the Gastroenterology Division. See A.R. at 460–61.

None of Cumberland's attacks on the reasoning of the FDA's decision or the factors it considered are persuasive. Cumberland contends that the agency's consideration of other drugs that include edetate was improper because "[t]he only issue for FDA to determine was whether the original formulation of Acetadote was withdrawn for safety reasons," and "not whether all [edetate]-containing products are or are not safe." Pl.'s Mem. at 17 (emphasis added). The Court disagrees with Cumberland's premise. That numerous other products containing edetate are currently on the market, a fact which Cumberland was undoubtedly aware of when it decided to withdraw the original formulation of Acetadote from the market, is clearly relevant to the FDA's determination regarding whether Cumberland discontinued edetate-containing Acetadote for safety reasons. The FDA's consideration of this fact does not convert its decision into an exploration of the safety of all drugs containing edetate, but rather serves only as circumstantial evidence from which to divine Cumberland's reasons for withdrawing the original formulation of Acetadote.

Cumberland also argues that the FDA improperly relied on "inconclusive data" regarding adverse event reports involving Acetadote without "explain[ing] . . . why, if the data were 'inconclusive,' that would not lead to the opposite conclusion; that is, that the original formulation was withdrawn for reasons of safety." Pl.'s Mem. at 18–19. But Cumberland mischaracterizes the FDA's discussion of the adverse events data. After noting that the relevant adverse event reports showed that "the original formulation of Acetadote, which contained [edetate], was associated with allergic reactions, including anaphylaxis, in some patients," the FDA's decision continues:

> However, these data did not demonstrate that these adverse reactions were attributable to the [edetate] in the formulation. These adverse events could alternatively be attributed to the active ingredient, acetylcysteine, or to the multisystem organ pathology associated with the underlying acetaminophen overdose. Therefore, the [adverse event reports] data do not provide a reasonable basis upon which to conclude that the original, [edetate]-containing formulation of Acetadote was unsafe.

A.R. at 000460–61 (emphasis added). Accordingly, the data do not show that edetate caused the adverse reactions, and therefore offer no support for the conclusion urged by Cumberland that edetate-containing Acetadote is unsafe. Nor do the data support the conclusion that edetate-containing Acetadote is safe. Cumberland attempts to undermine this conclusion by pointing out that an opposite inference is appropriate because "the data indicated that the incidence of allergic reactions in patients had decreased once the [edetate]-containing formulation had been withdrawn." Pl.'s Mem. at 18. The FDA's reasoning here, however, is consistent with logic and sufficiently explained. And, even if the data arguably supports an opposing inference, the FDA does not rely solely on this data to explain its decision,[4] and so any deficiency in this single aspect does not render the decision arbitrary and capricious. See Mail Order Ass'n of Am. v. U.S. Postal Serv., 2 F.3d 408, 434 (D.C. Cir. 1993) ("When an agency relies on multiple grounds for its decision, some of which are invalid, we may nonetheless sustain the decision as long as one is valid and the agency would clearly have acted on that ground even if the other were

[4] For this reason, Earth Island Institute v. Hogarth, 494 F.3d 757 (9th Cir. 2007), cited by Cumberland in support of its argument regarding the adverse events data, Pl.'s Mem. at 19, is inapposite. In that case, the agency relied primarily on inconclusive data to support its conclusion. See Earth Island Inst., 494 F.3d at 763–64 ("[B]ecause most of the data the government relied upon was inconclusive, the district court correctly held that the [agency's final decision] was not rationally connected to the best available scientific evidence." (emphasis added)). Here, the FDA relied on several rationales as support for its decision, only one of which involved inconclusive data. See A.R. at 000460–61. The other case cited by Cumberland in support of its argument on this point, Brower v. Evans, 257 F.3d 1058 (9th Cir. 2001), Pl.'s Mem. at 19, is also inapplicable. In Brower, the court rejected the agency's claim that there was insufficient data for it to make a determination that it was statutorily mandated to make. See Brower, 257 F.3d at 1071 ("[T]he Secretary cannot use insufficient evidence as an excuse for failing to comply with the statutory requirement."). There is no dispute here that the adverse event reports data is inconclusive, and the FDA has not relied on its inconclusiveness to avoid making a determination.

unavailable." (citation and quotation marks omitted)). The Court thus sees no flaw in the decision on its face.[5]

Cumberland's chief argument in support of its claim that the FDA's decision is arbitrary and capricious is that the decision is not adequately supported by the evidence before the agency. See Pl.'s Mem. at 12–17, 19–20. Cumberland contends that the FDA reversed its position regarding the safety of edetate-containing Acetadote, pointing to the postmarketing commitment the FDA elicited during the approval process for Acetadote and the July 1, 2011 Gastroenterology Division opinion as evidence that the agency "had, and continues to have, safety concerns about the [edetate]-containing formulation of Acetadote." See id. at 12–14, 19–20.

The APA requires that a court reviewing agency action "shall review the whole record or those parts of it cited by a party." 5 U.S.C. § 706. Indeed, "[i]t is a widely accepted principle of administrative law that the courts base their review of an agency's actions on the materials that were before the agency at the time its decision was made." IMS, P.C. v. Alvarez, 129 F.3d 618,

[5] Cumberland also asserts, for the first time in its reply brief, that the FDA's decision is deficient because under FDA regulations, the agency "presumes that a 'pharmaceutical manufacturer would not cease distribution of a profitable drug if safety or effectiveness concerns had not arisen,'" but does not address this presumption in its decision, Pl.'s Reply at 2 n.1, and that the agency's consideration of Cumberland's stated reasons for withdrawing the original formulation of Acetadote was inappropriate, Pl.'s Reply at 5. Because these arguments were raised for the first time in Cumberland's reply brief, thus depriving the FDA of the opportunity of responding to them, the Court need not consider them. See, e.g., Natural Res. Def. Council v. U.S. EPA, 25 F.3d 1063, 1071 n.4 (D.C. Cir. 1994) (citations omitted). However, the Court notes that, with respect to both arguments, Cumberland's quotations from the FDA's regulations are taken out of context. When each regulation is considered in its entirety, it is apparent that neither of Cumberland's belated arguments is persuasive. The rebuttable presumption that Cumberland references applies if the withdrawn drug "accounted for significant sales to [the] manufacturer" and "there is no evidence to the contrary" indicating that the drug was withdrawn for reasons other than safety or effectiveness. See 54 Fed. Reg. 28,872-01 at 28,907. When the FDA's presumption is considered in proper context, it is evident that it is inapplicable in the circumstances here because there is evidence to the contrary which indicates that the original formulation of Acetadote was withdrawn for reasons other than safety or effectiveness. Similarly, while it is true that the FDA does not consider a drug manufacturer's stated reasons for withdrawing a product to be determinative, the regulation expressly states in the preceding sentence that the FDA will consider the manufacturer's stated reasons for withdrawing a product as one consideration among many when determining whether a drug was withdrawn for safety or effectiveness reasons. The FDA's consideration of Cumberland's stated reasons for withdrawing the original formulation of Acetadote, as one of a number of factors included in its decision, was therefore in accordance with its regulations. See 57 Fed. Reg. 17,950-01 at 17,971.

623 (D.C. Cir. 1997). This review must consider the record as a whole, rather than just isolated portions of it. See Ethyl Corp. v. EPA, 541 F.2d 1, 37–38 (D.C. Cir. 1976) ("[A]fter considering the inferences that can be drawn from the studies supporting the [agency decisionmaker], and those opposing him, we must decide whether the cumulative effect of all this evidence, and not the effect of any single bit of it, presents a rational basis for the low-lead regulations." (emphasis added)); see also Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402, 420 (1971) ("[A court's] review is to be based on the full administrative record that was before the Secretary at the time he made his decision." (emphasis added)). While the record must be considered in its entirety, the agency's decision may be upheld even though some information in the record supports a different conclusion than that reached by the agency. See Am. Horse Prot. Ass'n, 917 F.2d at 598 (noting that conclusion that agency's decision must be upheld "is not to suggest that one could not locate facts in the record to support a contrary decision . . . but such a de novo reweighing of the evidence presented to the Secretary is not proper when reviewing agency action under an arbitrary and capricious test"); Ethyl Corp., 541 F.2d at 37. The proper inquiry is not, then, whether there is sufficient evidence in the record to support the opposing conclusion, but rather whether the choice made by the agency "has a rational basis in the evidence." See id.

The Court's review of the administrative record shows that it supports the FDA's determination that the original formulation of Acetadote was not withdrawn for safety reasons. Cumberland argues that "there was no reason for [the] FDA to have required [it] to do a postmarketing study on the feasibility of reducing or eliminating of [edetate] from the formulation other than that [the] FDA had safety concerns about the [edetate] in the formulation," and that it then "follows a fortiori that when Cumberland conducted that study, found that it could remove the [edetate], and promptly withdrew the [edetate]-containing formulation from the market, it did so for the same safety reasons that prompted the

postmarketing requirement in the first place." Pl.'s Mem. at 13–14. The Court disagrees. The FDA requested that Cumberland "[c]ommit to evaluate the potential benefit of [edetate] on the stability of the drug product," including specifically "a comparison of the current concentration of [e]detate to a formulation with a lower concentration and no concentration of [e]detate." A.R. at 001541. The agency rejected Cumberland's argument that this request was made for safety reasons based on the plain language of the request, see A.R. at 000460, and evidence in the record supports this conclusion. Internal memoranda regarding the postmarketing commitment contemporaneous with the request focus on the necessity for including edetate, rather than particular safety concerns, see A.R. at 000535–37.

Moreover, even if the FDA's request for the postmarketing commitment was based on safety concerns, such a motivation is not necessarily inconsistent with the challenged determination here. Having concerns about the safety of an ingredient and even expressing a preference for a formulation that does not contain it is not the same as definitively believing the ingredient to be unsafe or requiring a manufacturer to remove an ingredient. See ISTA Pharms., Inc. v. FDA, 898 F. Supp. 2d 227, 233 (D.D.C. 2012) (upholding the FDA's decision that withdrawal of drug was not for reasons of safety even though the agency "has admittedly asked some sponsors to voluntarily change their labeling to address these concerns, but has not required any changes thus far"). And, as the FDA points out, it would not have approved Cumberland's NDA for edetate-containing Acetadote if it had significant concerns regarding the product's safety. Defs.' Mem. at 23–24.

Cumberland's singular emphasis on the Gastroenterology Division's July 1, 2011 memorandum and the Division's "about-face" is similarly misplaced. See Pl.'s Mem. at 14–17, 19–20. Because the Court's inquiry here must consider the record in its entirety, the fact that a single memo in the record recommended finding that Cumberland withdrew the original

formulation of Acetadote for safety reasons is not dispositive. See Am. Horse Prot. Ass'n, 917 F.2d at 598. Admittedly, the Gastroenterology Division's July 1, 2011 report is at odds with the FDA's final conclusion. Compare A.R. at 000563–66 (July 1, 2011 Gastroenterology Division Memorandum), with A.R. at 000460–61 (FDA Response to Leydig and Cumberland Citizen Petitions). However, disagreement among agency staff during the decisionmaking process does not fatally undermine the agency's final determination, nor does it alone justify according the agency's final decision less deference than usual. See Serono Labs., 158 F.3d at 1320–21; San Luis Obispo Mothers For Peace v. U.S. Nuclear Regulatory Comm'n, 789 F.2d 26, 33 (D.C. Cir. 1986) (en banc) ("The position of an agency's staff, taken before the agency itself decided the point, does not invalidate the agency's subsequent application and interpretation of its own regulation."); Graceway Pharms., Inc. v. Sebelius, 783 F. Supp. 2d 104, 113 (D.D.C. 2011) (Walton, J.) ("The internal disagreement between the different divisions of the FDA is certainly not irrelevant, but neither is it the dispositive proof of arbitrary and capricious action that the plaintiff seems to believe it is.").

This reasoning is particularly appropriate under the circumstances here. The Gastroenterology Division's initial opinion is a four-page report which gives somewhat cursory treatment to the issues raised in the Leydig citizen petition, basing its conclusion on two studies showing adverse allergic reactions to edetate-containing products and the voluntary withdrawal of Leukine, another edetate-containing drug. See A.R. at 000563–64. Importantly, the report rests its finding that the postmarketing commitment involving edetate was based on the FDA's safety concerns solely on what was related in "subsequent discussions with [Cumberland]." A.R. at 000565 (emphasis added). In contrast, the Gastroenterology Division's second opinion on the subject is set forth in a detailed twenty-eight page memorandum that extensively reviews the FDA's internal documentation regarding the postmarketing commitment, numerous studies of

other edetate-containing drugs, adverse event reports for Acetadote, other edetate-containing products and available safety information on them, the reasons for the withdrawal of Leukine, and the FDA's own analysis regarding safety concerns relating to chelation. See A.R. at 000513–40. And, contrary to Cumberland's assertions, this is not a situation in which "the FDA entirely ignored the opinion offered by" the Gastroenterology Division initially. See Pl.'s Mem. at 19 (quoting Graceway Pharms., 783 F. Supp. 2d at 113). The later opinion by the Gastroenterology Division reviews each reason given for the initial conclusion and refutes it. See A.R. at 000534 (withdrawal of Leukine); A.R. at 000534–37 (rationale for postmarketing commitment); A.R. at 000534 (studies cited in initial opinion). Consequently, the Court has no difficulty finding that the FDA's decision is supported by the record despite the July 1, 2011 Gastroenterology Division report.

Finally, Cumberland takes issue with two considerations included in the Gastroenterology Division's later opinion—the possibility of drug shortages if there is only one drug manufacturer and the FDA's failure to recall the original formulation of Acetadote. See Pl.'s Mem. at 15–17. While this document is part of the administrative record used to assess whether the FDA's decision was arbitrary and capricious, when "there [is] a contemporaneous explanation of the agency decision[,] . . . [t]he validity of the [agency's] action must . . . stand or fall on the propriety of that finding, judged, of course, by the appropriate standard of review," Camp v. Pitts, 411 U.S. 138, 143 (1973), and therefore the focus of this Court's review of the FDA's decision must be on the reasons stated for the decision in Dr. Woodcock's response to the Leydig and Cumberland citizen petitions, not other reasons given by agency staff elsewhere in the record, see Serono Labs., 158 F.3d at 1321 ("[D]eference is owed to the decisionmaker authorized to speak on behalf of the agency, not to each individual agency employee." (citation omitted)); cf. Actavis Elizabeth LLC v. U.S. FDA, 689 F. Supp. 2d 174, 180 (D.D.C. 2010),

aff'd, 625 F.3d 760 (D.C. Cir. 2010) (rejecting the argument that the FDA's decision was arbitrary and capricious because a draft manual contradicted the approach taken in the agency's subsequent formal regulation). "[T]o hold otherwise . . . would effectively empower any individual employee not just to veto the views of the agency head, but to preclude any deference to the agency at all, since [the court] would have no basis for deciding to whose view we should defer." Serono Labs., 158 F.3d at 1321.

The Court is unconvinced by Cumberland's attempts to discredit the FDA's determination that the original formulation of Acetadote was withdrawn for safety reasons. Although the record contains some contrary evidence, the Court nonetheless finds that the FDA has met its obligations under the APA with respect to this determination.

B. Waiver of Inactive Ingredient Regulatory Requirement

Having concluded that the Court must affirm the FDA's determination that the edetate-containing version of Acetadote was not withdrawn for reasons of safety, Cumberland's objection to the FDA's grant of a waiver of the regulatory requirement that a proposed ANDA drug contain identical inactive ingredients as the reference listed drug to InnoPharma must also fail. In its response to the Leydig and Cumberland citizen petitions, the FDA noted that it may waive the regulatory requirements for inactive ingredients in proposed ANDA drugs pursuant to 21 C.F.R. § 314.99(b), so long as it satisfied the FDCA's directive not to approve any application if "information submitted in the application or any other information available to the Secretary shows that" the inactive ingredients are "unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug" or that the "type or quantity of inactive ingredients" in the drug render the "composition of the drug . . . unsafe under such conditions." A.R. at 000462; 21 U.S.C. § 355(j)(4)(H). Citing solely to a single reference in the Gastroenterology Division's July 1, 2011 memorandum, Cumberland contends that the standard

applicable to InnoPharma's ANDA is "whether the difference in inactive ingredients between the proposed ANDA product and the reference-listed drug make the proposed ANDA product less safe for use." Pl.'s Mem. at 21. This proposition is incorrect.

The FDA noted in its final decision that edetate is not a preservative, buffer, or antioxidant, and Cumberland has not challenged this determination. See A.R. at 000462. FDA regulations require that if an inactive ingredient is a preservative, buffer, or antioxidant, an ANDA applicant must "provide[] information demonstrating that the differences [in inactive ingredients] do not affect the safety or efficacy of the proposed drug product." 21 C.F.R. § 314.94(a)(9)(iii). Otherwise, neither the FDCA nor FDA regulations require a comparison of whether a proposed product is more or less safe, but only a determination of whether it is unsafe. See 21 U.S.C. § 355(j)(4)(H); 21 C.F.R. § 314.94(a)(9)(iii). The FDA concluded that edetate is not a preservative, buffer, or antioxidant, and that the original formulation of Acetadote is not unsafe, a determination which the Court has already upheld as consistent with the requirements of the APA. Accordingly, the FDA's decision to grant a waiver to InnoPharma in order to permit its proposed ANDA drug to deviate from the inactive ingredients in the current formulation of Acetadote was in accordance with the FDCA and the applicable FDA regulations.

Cumberland also argues that it was arbitrary and capricious "for [the] FDA to have granted a waiver to InnoPharma to market an [edetate]-containing formulation when [the] FDA has consistently preferred that Cumberland, if possible, reduce or remove [edetate] from its product." Pl.'s Mem. at 21. The Court does not find the agency's actions inconsistent. On the contrary, the FDA is allowing InnoPharma to market an edetate-containing generic version of Acetadote, just as it permitted Cumberland to market an edetate-containing formulation of the drug. Cumberland's argument essentially rests on the premise that the FDA believes that an edetate-containing version is unsafe and requested a postmarketing commitment from

Cumberland because of this belief, an argument that the Court has already considered and rejected. Seeing no inconsistency in the agency's treatment of Cumberland and InnoPharma, the Court therefore finds that the FDA's grant of a waiver to InnoPharma, allowing it to market an edetate-containing formulation of Acetadote, was not arbitrary and capricious.

V. CONCLUSION

For the foregoing reasons, the Court concludes that the FDA's determination in its response to the Leydig and Cumberland citizen petitions that (1) Cumberland did not withdraw the original formulation of Acetadote for safety reasons, and (2) the requirement that an ANDA proposed drug contain the same inactive ingredients as the reference listed drug could be waived to permit approval of InnoPharma's ANDA based on Acetadote was not arbitrary and capricious, an abuse of discretion, or otherwise not in accordance with law in violation of the APA. Accordingly, the Court will grant the FDA's motion for summary judgment and deny Cumberland's motion for summary judgment.

SO ORDERED this 30th day of September, 2013.[6]

REGGIE B. WALTON
United States District Judge

[6] An order consistent with this memorandum opinion shall be issued contemporaneously.