UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

FERRING PHARMS. INC.,	)	
Plaintiffs,	)	
v.	)	Civil Action No. 15-802 (RC)
THOMAS E. PRICE, Secretary of Health and Human Services, *et al*.,	)	
Defendants.	)	

DEFENDANTS' OPPOSITION TO PLAINTIFF'S MOTION TO ENFORCE JUDGMENT

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The current dispute between FDA and Ferring arises out of an unfortunate mistake that was only recently discovered. FDA's mistake was accepting the veracity of Ferring's statement that sodium picosulfate, one of the drug substances in its product Prepopik, contained no active moiety that had been previously approved in any other new drug application ("NDA"). In actuality, sodium picosulfate contains an active moiety that *was* previously approved, as FDA discovered when it analyzed the chemical structure of that drug substance on remand. *See* Letter from K. Uhl to E. Thygesen (June 9, 2017) ("FDA Remand") (attached as Ex. D to Ferring's brief). Prepopik was thus never eligible for 5-year new chemical entity ("NCE") exclusivity, under either of FDA's interpretations of the relevant statutory and regulatory provisions. FDA acknowledges that all parties would have been saved the effort of prior litigation in this matter had FDA identified this error sooner, however, as explained below, FDA complied with this Court's mandate on remand and Ferring's motion should therefore be denied.

I. FACTUAL AND PROCEDURAL HISTORY

A. FDA's 2012 Determination That Prepopik Was Not Eligible for 5-year NCE Exclusivity

The Food Drug and Cosmetic Act provides that a drug is eligible for 5-year new chemical entity ("NCE") exclusivity if it is "a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other" new drug application. 21 U.S.C. §§ 355(c)(3)(E)(ii), (j)(5)(F)(ii). FDA's regulations contain definitions that further explicate the statutory terms. "New chemical entity" is defined as "a drug that contains no active moiety that has been approved by FDA in any other NDA…." 21 C.F.R. § 314.108(a). "Active moiety" is defined as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt … or other noncovalent derivative … of the molecule, responsible for the physiological or pharmacological action of the drug substance." *Id.*

Prior to October 2014, FDA interpreted these statutory and regulatory provisions to mean that a fixed-combination drug such as Prepopik was not eligible for 5-year NCE exclusivity if the drug product contained a previously approved active moiety, even if it also contained one or more active ingredients that contained no previously approved active moiety (hereinafter, "FDA's pre-2014 interpretation"). Under FDA's pre-2014 interpretation, once FDA determined that a drug product contained at least one previously approved active moiety, the agency's evaluation of eligibility for 5-year NCE exclusivity was complete. This was the interpretation utilized by FDA at the time Prepopik was approved in July of 2012.

In its NDA, Ferring requested 5-year NCE exclusivity for Prepopik. Ferring asserted that two of the three active ingredients in Prepopik, citric acid and magnesium oxide, contained active moieties that had been previously approved by FDA. With regard to the third active ingredient in Prepopik, sodium picosulfate, Ferring asserted that the active moiety was picosulfate, which had never been previously approved by FDA. Mem. from K. Flanagan, CDER, at App. A at 3-4 (June 9, 2017) ("FDA Memo") (attached hereto as Ex. 1). From the administrative record, it appears that FDA relied upon Ferring's assertion that picosulfate was the active moiety in sodium picosulfate, and that it had never been previously approved by FDA, without conducting an independent evaluation of the chemical structure of the molecule. FDA Remand at 7; *see also* FDA Memo at App. A at 3.

The administrative record contains an "Exclusivity Summary," which summarizes the analysis FDA conducted when it determined that Prepopik was not eligible for NCE exclusivity.

Exclusivity Summary, CDER (July 9, 2012) (attached hereto as Ex. 2).[1] That form poses the question:

> If the product contains more than one active moiety…, has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes."

Id. at 3. In response to this question, FDA answered "yes" and listed the NDA numbers of previously approved NDAs that contained the same active moieties as magnesium oxide and citric acid. *Id.* The administrative record does not contain any indication that FDA conducted a structural analysis of sodium picosulfate when it made its initial determination that Prepopik was not eligible for NCE exclusivity. *See* FDA Remand at 7.

FDA did not need to address the question of whether sodium picosulfate contained a previously approved active moiety to decide Prepopik's eligibility for 5-year NCE exclusivity because the other drug substances in Prepopik both contained previously approved active moieties. Thus, at the time of its approval, under the agency's then-current interpretation, Prepopik was not eligible for 5-year NCE exclusivity, regardless of whether sodium picosulfate contained a previously approved active moiety. FDA Memo at App. A at 4 ("under [FDA's pre-2014] interpretation, the presence of two previously approved active moieties (citric acid and magnesium oxide) sufficed to make Prepopik ineligible for 5-year NCE exclusivity. Accordingly, there was no need to closely examine the structure of picosulfate to more thoroughly assess the assumption that it did not contain a previously approved active moiety.").

[1] *Also available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202535Orig1s000Admincorres.pdf (last visited August 17, 2017).

B. This Court's Memorandum Opinion

Ferring initiated this case on June 1, 2015, challenging FDA's pre-October 2014 interpretation of the relevant statutory and regulatory provisions for 5-year NCE exclusivity as applied to fixed-combinations. On September 9, 2016, upon Ferring's motion for reconsideration, this Court granted judgment in favor of Ferring, holding that FDA's pre-October 2014 interpretation was arbitrary and capricious in the context of certain fixed-combinations. *See* Mem. Op., *Ferring Pharms., Inc. v. Burwell*, Civil Action No. 15-0802 (RC) (D.D.C. Sept. 9, 2016). This Court then remanded the matter to FDA for "further proceedings not inconsistent with this opinion." *Id.* at 23.

C. FDA's Determination on Remand That Prepopik is Not Eligible for 5-year NCE Exclusivity Under FDA's October 2014 Interpretation

On remand, in accordance with this Court's memorandum opinion, FDA analyzed whether Prepopik was eligible for NCE exclusivity under FDA's October 2014 interpretation of 5-year NCE exclusivity for fixed-combinations. *See* FDA Remand at 1-2; FDA Memo at 1-2. Under this interpretation, a drug substance (i.e., an active ingredient) containing no previously approved active moiety will be eligible for 5-year NCE exclusivity *even when* such a drug substance is approved in a fixed-combination with another drug substance containing a previously approved active moiety. Thus, while it was irrelevant under FDA's pre-October 2014 interpretation whether sodium picosulfate contained a previously approved active moiety (because two other Prepopik ingredients admittedly did – making the drug per se ineligible for exclusivity regardless), under FDA's October 2014 interpretation, Prepopik would still qualify for exclusivity despite the presence of two ingredients containing previously approved active moieties so long as the third ingredient, sodium picosulfate, did not itself contain a previously

approved active moiety. On remand, then, it was incumbent on FDA to confirm Ferring's assertion that sodium picosulfate did not contain a previously approved active moiety.

In order to do so, FDA evaluated for the first time the chemical structure of sodium picosulfate. *See* FDA Remand at 7; *see also* FDA Memo at App. A at 3-4.

As FDA explained in its remand decision,

> In determining whether a drug product is eligible for 5-year NCE exclusivity, FDA's analysis begins with the chemical structure of each drug substance (or active ingredient) in the drug product. The Agency starts with the molecule that comprises that drug substance in the drug product, and excludes the ester and salt-bonded portions of the molecule (consistent with the statutory language stating that "no active ingredient (including any ester or salt of the active ingredient . . .)" is eligible for 5-year NCE exclusivity). Once the portions of the molecule comprising esters, salts, and other non-covalent derivatives of a drug substance are excluded, the molecule or ion that remains will be considered the active moiety.

FDA Remand at 6. After excluding the salt and ester[2] portions of the sodium picosulfate molecule, as required by statute, what remains is bis-(p-hydroxyphenyl)-pyridyl-2-methane ("BHPM"). *See id*. at 7; FDA Memo App. A at 4-12. This means that BHPM is the active moiety in sodium picosulfate. *Id.* In other words, FDA's structural analysis of the molecule revealed that the agency had been mistaken when it had previously accepted Ferring's assertion that picosulfate was the new active moiety in sodium picosulfate. Picosulfate is not the active moiety in sodium picosulfate because it is an ester of BHPM. And because BHPM is also the active moiety of the drug substance bisacodyl, which was approved many years before Prepopik, sodium picosulfate was not a drug substance that contained no previously approved active

[2] Esters are substances that result from combining an alcohol and an acid. Sodium picosulfate is the combined product of an alcohol and sulfuric acid, and is therefore an ester under standard scientific definitions of that term. *See* FDA Remand at 7-8; FDA Memo App. A at 4-12.

moiety. *Id.* In light of the discovery of this error, FDA had no choice but to deny 5-year NCE to Prepopik.

Ferring notes that FDA classified the Prepopik NDA as "Type 1- New Molecular Entity," and otherwise referred to sodium picosulfate as an "NME."[3] But the classification of Prepopik as an NME was the result of the same mistake that led FDA to erroneously determine that picosulfate was the active moiety of sodium picosulfate: FDA's adoption, without scientific verification, of Ferring's assertion that sodium picosulfate was "new."

FDA acknowledges and regrets that the time and resources expended by the parties and the Court on this litigation could have been spared had FDA conducted a chemical analysis of the picosulfate molecule at the time of its original NCE exclusivity determination for Prepopik in 2012. However, having now identified its error and determined that each of Prepopik's active ingredients contained a previously approved active moiety, the statutory and regulatory provisions governing 5-year NCE exclusivity required FDA to deny 5-year NCE exclusivity to Prepopik.

II. ARGUMENT

A. FDA's Action on Remand does not violate the Doctrine of Law of the Case

The doctrine of law of the case is inapplicable here because the factual issue of whether sodium picosulfate contains a new active moiety was never raised as a disputed issue to be decided during the litigation and FDA's actions on remand were fully within the scope of the Court's mandate.

The law of the case doctrine does not apply where an issue was assumed by the court in a prior proceeding, but the issue was never disputed and therefore never "decided" in the prior

[3] "NME" stands for new molecular entity, which, as relevant to the instant matter, is substantively the same as NCE: an active ingredient that contains an active moiety that has not been previously approved. *See* FDA Remand at 7, n.34.

proceeding. *See Petaluma FX Partners, LLC v. Commissioner of Internal Revenue*, 792 F.3d 72, 79 (D.C. Cir. 2015) ("[L]aw of the case doctrine does not apply where an issue was not raised before the prior panel and thus was not decided by it."). In this litigation prior to remand, FDA did not dispute Ferring's assertion that sodium picosulfate contained a never previously approved active moiety, and the Court adopted that assumption without having reason to analyze or decide the accuracy of that fact. That issue was therefore never raised for decision in this litigation prior to remand.

Stated another way, in its memorandum opinion remanding this matter to FDA, this Court did not direct FDA to make a particular finding as to the active moiety in sodium picosulfate. Ferring correctly notes that under the law of the case doctrine, an administrative agency is bound by the mandate of a reviewing court. Pl.'s Memo at 7, (citing 18B Charles Alan Wright et al., Federal Practice & Procedure Jurisprudence § 4478.3 (2d ed. 2017)). Ferring is wrong, however, as to the scope of this Court's mandate, as delineated in its memorandum opinion remanding this case to FDA. Ferring asserts that the fact that sodium picosulfate contained a new active moiety was a part of this Court's mandate by which the agency was bound on remand. Pl. Mem at 8. In actuality, this Court identified an error of law on the part of FDA, holding that FDA's pre-October 2014 interpretation of the 5-year NCE exclusivity provisions was arbitrary and capricious, and then remanded the matter back to FDA to evaluate Prepopik's eligibility for NCE exclusivity under the proper legal framework. Mem. Op. at 22-23. The Court did not mandate that Prepopik would be granted 5-year NCE exclusivity, or rule on a disputed issue regarding the active moiety in sodium picosulfate. Indeed, it is a foundational principle of review under the Administrative Procedure Act that the function of a reviewing court ends when "an error of law is laid bare"; at that point, courts remand to agencies

and do not typically perform an "administrative function." *Fed. Power Comm'n v. Idaho Power Co.*, 344 U.S. 17, 20 (1952).

On remand, FDA acted within the mandate of this Court by evaluating Prepopik's eligibility for NCE exclusivity under FDA's October 2014 interpretation of the NCE statute, which does not suffer from the legal deficiencies identified by this Court in its memorandum opinion. It was in the course of conducting that evaluation that FDA discovered for the first time that it had committed a serious error in accepting Ferring's position that picosulfate was the active moiety in sodium picosulfate and failing to exclude the ester portions of the molecule, as required by statute and regulation. FDA's remand decision, as articulated in the June 9, 2017 letter to Ferring, fully accords with this Court's remand order.

B. FDA's Action on Remand is Not Barred by Judicial Estoppel

The doctrine of judicial estoppel applies in cases where a party intentionally changes its position in order to gain a tactical advantage in litigation, but not in cases of good faith mistake. *See New Hampshire v. Maine*, 532 U.S. 742, 753 (2001) (inconsistent statements made because of inadvertence or mistake generally do not justify application of judicial estoppel); *Konstantinidis v. Chen*, 626 F.2d 933, 939 (D.C. Cir. 1980) (judicial estoppel inapplicable where the prior position was taken because of a good faith mistake rather than as part of a scheme to mislead the court); *see also Burnes v. Pemco Aeroplex, Inc.*, 291 F.3d 1282, 1286 (11th Cir. 2002) (noting that "the doctrine of judicial estoppel applies in situations involving intentional contradictions, not simple error or inadvertence"). FDA's change of position regarding the active moiety in sodium picosulfate is based on a good faith mistake, not based on any intent on the part of FDA to harm Ferring or to avoid compliance with this Court's remand order.

As explained above, in its initial 2012 5-year NCE exclusivity determination for Prepopik, FDA mistakenly relied upon Ferring's claim that sodium picosulfate contained no active moiety that had been previously approved. FDA did not evaluate the accuracy of Ferring's claim because, under FDA's pre-2014 interpretation, whether or not sodium picosulfate contained a novel active moiety did not impact the eligibility of Prepopik for 5-year NCE exclusivity. This mistake only came to FDA's attention when FDA evaluated the chemical structure of the sodium picosulfate molecule on remand. At that point it became clear that picosulfate could not be the active moiety in sodium picosulfate, because picosulfate was an ester of BHPM, and the NCE statutory provisions and implementing regulations require that FDA disregard all portions of the molecule that cause it to be an ester. This is simply not a situation in which FDA is gaming the judicial system in order to gain a litigation advantage.

Further, this is not a case in which FDA "succeeded in persuading a court to accept that party's earlier position," the second factor of judicial estoppel under the framework set out in *New Hampshire*, 532 U.S. at 750-51. As this phrase is used in the context of judicial estoppel, it implies that a party took some advantage from relying on an earlier, inconsistent position. *See Moses v. Howard University Hospital*, 567 F.Supp.2d 62, 68 (D.D.C. 2008) (holding that inconsistent statements threaten judicial integrity only when a party succeeds in the prior proceeding and that Plaintiff benefited from his inconsistent position in prior proceeding). Here, FDA did not derive any benefit from "persuading this Court to accept the agency's previous position – that sodium picosulfate was a novel active ingredient." Pl. Mem. at 9. First, FDA did not prevail in the previous litigation. Further, FDA concedes that it would have saved all parties, the agency itself included, the time and effort of this litigation had it identified its mistake earlier.

For these reasons, the doctrine of judicial estoppel does not apply to FDA's action on remand in this matter.

C. Ferring's Arguments Regarding Retroactivity, Due Process, and Arbitrariness are Not Properly Raised in a Motion to Enforce Judgment and Fail on the Merits

1. Ferring's Remaining Arguments are Not Properly Raised in a Motion to Enforce Judgment

Ferring's final three arguments – that FDA's action on remand violates principles of retroactivity, violates due process, and is arbitrary and capricious – are not appropriately raised in a motion to enforce judgment.

The D.C. Circuit clearly set out the scope of available relief on a motion to enforce judgment in *Heartland Regional Medical Center v. Leavitt*, 415 F.3d 24 (D.C. Cir. 2005). The D.C. Circuit held that "[s]uccess on a motion to enforce a judgment gets a plaintiff only the relief to which [the plaintiff] is entitled under [its] original action and the judgment entered therein." *Id.* at 29, (citing *Watkins v. Washington*, 511 F.2d 404, 406 (D.C. Cir. 1975)). The Court made clear that if the original judgment did not address a question, that question was not properly raised in a motion to enforce judgment. *Id.* at 30. The Court in *Heartland* specifically held that an arbitrary and capricious challenge to the agency's action on remand could not be raised in a motion to enforce judgment, and must be reserved for a subsequent APA action. *Id.* at 30 ("[W]hether or not the agency's [action on remand] was arbitrary is a determination that must be made in Heartland's separate APA action challenging [the agency]'s post-remand decisions. Nothing in *Heartland I* itself addresses that question, therefore a motion to enforce the *Heartland I* judgment is not the proper means to answer it."). The Court similarly held that a challenge to the agency's actions on remand as impermissible retroactive rulemaking must be raised in a separate APA action challenging that remand action, not in a motion to enforce judgment. *Id.*

All of Ferring's remaining arguments center around FDA's determination on remand that sodium picosulfate is an ester of BHPM and the question of whether FDA's remand decision here announced a new agency policy regarding whether "esters" include molecules with sulfur-based functional groups. Those issues were never raised or considered in the prior litigation before this Court and are not addressed in this Court's remand decision. Therefore, Ferring's arguments that FDA's action on remand violates principles of retroactivity, violates due process, and is arbitrary and capricious are not properly raised in a motion to enforce judgment.

2. FDA's Action on Remand Does Not Violate Principles of Retroactivity, Does Not Violate Due Process, and Is Not Arbitrary and Capricious

Not only are Ferring's three remaining arguments – that FDA's action on remand violates principles of retroactivity, violates due process, and is arbitrary and capricious – improperly raised in a motion to enforce judgments, those arguments also fail on the merits. All three arguments rest on the same premise: that FDA announced for the first time in its remand decision a new policy that "ester" includes molecules with sulfur-based functional groups. Pl.'s Mem. at 10, 13, 15. However, FDA's determination on remand that the active moiety in sodium picosulfate is BHMP, rather than picosulfate, was not based on a change in agency policy regarding whether an ester can have a central sulfur atom, but on the agency's failure to consider whether sodium picosulfate was an ester *at all* during the initial NCE exclusivity determination. As explained *supra*, it appears that the agency's failure to analyze the chemical structure of sodium picosulfate during that initial NCE determination was due to the irrelevance of that issue under FDA's pre-October 2014 interpretation in light of the fact that Prepopik contained two other ingredients with previously approved active moieties.

Contrary to Ferring's suggestion (Pl. Mem. at 10), FDA has previously found the term "ester" includes sulfur-based esters, which is also the case with sodium picosulfate. *See* FDA

Remand at 6-8. Although FDA's proffered examples of instances when the agency considered organosulfates to be sulfur-centric esters pre-date the NCE exclusivity provisions, FDA's definition of an ester is not tied to any particular statutory provision; rather "ester" is a scientific term that has independent meaning. *See* FDA Memo at App. A at 4-6. FDA does not define ester differently in the context of a 5-year NCE exclusivity determination than in any other context. Therefore, despite the fact that those examples predate the NCE exclusivity statutory provisions, they still provide evidence that FDA has defined "ester" to include sulfur-centric esters prior to its remand decision regarding Prepopik.

For the same reason, Ferring's observation that the sulfur-based esters in the cited examples only formed after ingestion of the drugs at issue is of no moment. FDA provided the examples to demonstrate that this was not the first time FDA described a sulfur-based ester as an ester. FDA's conclusion that sodium picosulfate is an ester and that the active moiety in sodium picosulfate is therefore BHPM is consistent both with general scientific principles and with the longstanding FDA position that the term ester includes molecules derived from inorganic acids, including sulfur-centric esters.[4]

Nor can Ferring point to FDA's 2012 NCE exclusivity decision for Prepopik as the sole example of a case in which FDA previously found that esters do not include a sulfur based functional group. As explained above, FDA's prior position that picosulfate was the active moiety in sodium picosulfate was based on the agency's mistaken reliance on Ferring's assertion to that effect without conducting an independent analysis of the molecular structure. That

[4] Indeed, Ferring itself repeatedly used "ester" in reference to sodium picosulfate in its NDA for Prepopik. *See* FDA Memo at App. A at 9-11.

position was not based on an analysis or determination on the part of the agency that "esters" do not include sulfur-based esters.

Because FDA did not apply a new policy for the first time in its remand decision, Ferring's arguments concerning the *Retail Wholesale* test for retroactivity are irrelevant. For the same reason, Ferring's due process argument lacks merit. FDA did not announce a new policy with no warning that deprived Ferring of a property interest to which it was entitled.[5] Finally, FDA's scientific analysis was well reasoned and was not arbitrary and capricious. FDA carefully considered both the agency's prior treatment of inorganic esters and the standard scientific definitions of esters. *See* FDA Remand at 7-8; FDA Memo App. A. at 4-8. Deference to agency decision-making is particularly strong when the agency is evaluating scientific data within its technical expertise. *American Wildlands v. Kempthorne*, 530 F.3d 991, 1000 (D.C. Cir. 2008).

CONCLUSION

As explained above, FDA's remand decision complied with the mandate of this Court in its remand order. That is the only issue properly raised on a motion to enforce judgment and this Court should therefore deny Ferring's motion to enforce judgment.

[5] Ferring has also failed to show that it has a constitutionally protected property interest in 5-year NCE exclusivity for Prepopik. The single case on which Ferring relies concerns protected property interests under *state law*, *see Mpras v. District of Columbia*, 74 F. Supp. 3d 265, 271 (D.D.C. 2014) ("Mpras has not alleged a legitimate claim of entitlement under District of Columbia law to the identification."); *see also* Pl. Mem. at 14.

Respectfully submitted,

Of Counsel:

JEFFREY F. DAVIS
Acting General Counsel

REBECCA K. WOOD
Associate General Counsel
Food and Drug Division

PERHAM GORJI
Deputy Chief Counsel, Litigation

SHOSHANA HUTCHINSON
Senior Counsel
U.S. Dept. of Health & Human Services
Office of the General Counsel
10903 New Hampshire Ave.
White Oak 31, Room 4560
Silver Spring, MD 20993-0002
301-796-8566

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CHAD A. READLER
Acting Assistant Attorney General

ETHAN P. DAVIS
Deputy Assistant Attorney General

JOSHUA I. WILKENFELD
Acting Director

s/ Ann F. Entwistle
ANN F. ENTWISTLE
Trial Attorney
Consumer Protection Branch
Civil Division
U.S. Department of Justice
P.O. Box. 386
Washington, D.C. 20044-0386
202-305-3630
Ann.F.Entwistle@usdoj.gov