IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

FERRING PHARMACEUTICALS INC., Plaintiff, v. SYLVIA MATHEWS BURWELL, in her official capacity as SECRETARY, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, and STEPHEN OSTROFF, M.D., in his official capacity as ACTING COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, Defendants.	Civil Action No. 1:15-cv-802 (RC)

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT

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Dated: July 23, 2015

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INTRODUCTION

Ferring's PREPOPIK® contains three drugs. One of them, sodium picosulfate, has never before been approved by the Food and Drug Administration (FDA). As a novel active ingredient, sodium picosulfate is entitled to five years of new chemical entity (NCE) exclusivity under the federal Food, Drug, and Cosmetic Act (FDCA).

FDA acknowledged that picosulfate, the active component in sodium picosulfate, was novel. A.R. 201.[1] But it nevertheless denied NCE exclusivity on the ground that PREPOPIK also contains *other*, previously-approved active ingredients. That interpretation is wrong; it violates the plain meaning of the FDCA and it violates FDA's own regulations.

Ferring and several other companies recently petitioned FDA to correct its erroneous reading of the statute. The agency agreed. But there is a catch: FDA decided to apply its new—correct—construction of the statute *only to newly approved drug products*. Because PREPOPIK was approved *before* FDA brought its interpretation into line with the governing statute and regulations, the agency is still treating Ferring's drug under FDA's old—unlawful—policy.

FDA's conduct runs afoul of the APA.

STATEMENT OF FACTS

I. STATUTORY BACKGROUND

A. The Drug Approval Process

The FDCA requires all new prescription drugs to obtain approval from FDA before they can be marketed. 21 U.S.C. § 355(a). Manufacturers of brand name (also known as "pioneer" or "innovator") drug products must demonstrate the safety and effectiveness of their products in order to gain FDA approval. Typically, manufacturers make that demonstration by conducting

[1] All pages of the administrative record cited herein are attached as Exhibit 1.

pre-clinical and clinical studies and submitting the resulting data to FDA in a new drug application (NDA). *Id.* § 355(b)(1).

Generic drugs, in contrast to innovator drugs, are approved by means of an abbreviated new drug application (ANDA). 21 U.S.C. § 355(j)(1). ANDAs generally do not contain new clinical data. Instead, an ANDA relies on FDA's finding of safety and efficacy for a previously approved pioneer drug (which is termed at that point the "reference listed drug" or "RLD"). *Id.* § 355(j)(2). In order to obtain approval of a generic drug, an ANDA applicant must show that its proposed drug product is the "same as" the RLD in all key respects (including active ingredient(s), dosage form, strength, route of administration, and, with certain exceptions, labeling), and that its product is bioequivalent to the RLD. *Id.* §§ 355(j)(2)(A)(ii)-(v).

Between the extremes of a full NDA and an ANDA lies a third option: an application submitted under Section 505(b)(2) of the FDCA. *Id.* § 355(b)(2). A 505(b)(2) application is a type of NDA; it must directly demonstrate that the proposed drug is safe and effective. *Id.* But a 505(b)(2) applicant does not have to conduct all of the burdensome scientific studies required of a full NDA. Instead, the 505(b)(2) applicant can show safety and effectiveness by relying on studies that were not conducted by the applicant and for which the applicant does not have a right of reference. *Id.*

B. Five- and Three-Year Exclusivity

The 1984 Hatch-Waxman Act amended the FDCA to put in place an incentive structure designed both to promote the development of innovative drugs and to expedite the approval of generic drugs. *See generally Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 765 (D.C. Cir. 2010) (recognizing that the exclusivity provisions "struck a balance between expediting generic drug applications and protecting the interests of original drug manufacturers"). As part of that balance,

the Hatch-Waxman Act granted five years of NCE exclusivity to successful developers of new drugs, meaning that a manufacturer of a pioneer drug was protected from generic competition for five years:

> If an application submitted under subsection (b) of this section for a drug**,** no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of approval of the application under subsection (b) * * * .

21 U.S.C. § 355(j)(5)(F)(ii); *see also* 130 Cong. Rec. H9114 (daily ed. Sept. 6, 1984) (Rep. Waxman explaining that the five-year exclusivity period provided "the drug industry the incentives needed to develop new chemical entities"). If a drug approved in an NDA is awarded NCE exclusivity, no application for a generic version of that drug may even be *submitted* to the FDA until five years after the NDA's approval (unless the generic application contains a challenge to the innovator's patent or patents, in which case it may be submitted after four years). 21 U.S.C. § 355(j)(5)(F)(ii).

The Hatch-Waxman Act created a shorter exclusivity period for changes to a previously approved drug: It confers three years of exclusivity on a sponsor who submits one or more new clinical studies supporting a change in the conditions of use of an approved product, so long as FDA considers the studies to have been essential to its approval of the change. 21 U.S.C. §§ 355(c)(3)(E)(iii), (j)(5)(F)(iii). This lesser exclusivity precludes only the *approval* of a generic application, meaning that an ANDA may be submitted and reviewed by the agency at

any time during the three-year period. *Compare* 21 U.S.C. §§ 355(c)(3)(E)(ii), (j)(5)(F)(ii) *with* 21 U.S.C. §§ 355(c)(3)(E)(iii), (j)(5)(F)(iii). [2]

II. FACTUAL BACKGROUND

A. Approval of Ferring's NDA for PREPOPIK

Ferring's PREPOPIK is a low-volume, pleasant-tasting formulation designed for cleansing the colon as a preparation for colonoscopy in adults. A.R. 201. PREPOPIK is a fixed-dose combination drug product, meaning that it contains two or more active ingredients combined in a single dosage form. PREPOPIK contains three active ingredients: sodium picosulfate, magnesium oxide, and anhydrous citric acid.[3] Sodium picosulfate is a salt form of the active component picosulfate, a stimulant laxative, which had never before been approved in an NDA before Ferring submitted PREPOPIK for approval. *Id*. The other two active ingredients in PREPOPIK had previously been approved in other NDAs. *Id*.

FDA approved PREPOPIK in July 2012. *Id.* Normally, when presented with a combination drug product, the agency would have required "factorial studies" from the applicant manufacturer. Factorial studies are used to evaluate the individual contribution of each substance to the drug product's overall efficacy. A.R. 69-70. But FDA did not require factorial studies to evaluate PREPOPIK's individual components separately. That is because sodium

[2] The difference between five-year exclusivity and three-year exclusivity is even greater when taking into account the operation of the associated 30-month regulatory stay. If the RLD sponsor timely files patent litigation against the generic applicant, a regulatory stay arises during which time FDA may not approve the generic application. 21 U.S.C. §§ 355(c)(3)(C); (j)(5)(B)(iii). Under three-year exclusivity, a 30-month stay begins on the date that the RLD sponsor receives notice from the generic sponsor that FDA has accepted for review the generic application. *Id.* As a result, the regulatory stay may begin to run during the three-year exclusivity period and expire shortly after it expires. By contrast, under five-year exclusivity, the regulatory stay runs until seven-and-one-half years following approval of the RLD, effectively adding 30-months at the end of the complete five-year exclusivity period. 21 C.F.R. § 314.107(b)(3)(B).

[3] Magnesium oxide and anhydrous citric acid react in water to form magnesium citrate, an osmotic laxative.

picosulfate—PREPOPIK's novel active ingredient—was not suitable as a single-ingredient drug for use as a colon cleanser; its therapeutic benefit is realized in combination with the other components. A.R. 70. As a result, FDA determined that single-ingredient clinical trials of sodium picosulfate would raise "serious ethical concerns." A.R. 69-70. In other words, FDA could neither review nor approve that active ingredient as a single-entity product.[4] *Id.*

B. FDA's Determination of the Exclusivity Period for PREPOPIK

Ferring developed PREPOPIK with the expectation that sodium picosulfate, as a novel active ingredient, would be awarded five years of NCE exclusivity. Ferring thus requested five years' exclusivity at the time it submitted its NDA for PREPOPIK.[5] But FDA did not award Ferring NCE exclusivity: instead, the agency took the position that PREPOPIK was ineligible for five-year exclusivity because it *also* contained two other active ingredients that had previously been approved by FDA. A.R. 201.[6] FDA's decision was based on its then-policy that a fixed-dose combination drug product is not entitled to NCE exclusivity unless *all* of its active ingredients are novel. A.R. 210-11.

FDA grounded its decision in an "informal" letter to the industry in 1988 suggesting that "[a] drug product will . . . not be considered a 'new chemical entity' entitled to five years of exclusivity if it contains a previously approved active moiety, even if the particular ester or salt . . . has not been previously approved." A.R. 324; A.R. 204-05. The "informal" letter did not specifically address application of the NCE exclusivity rules to fixed-dose combination drug products. A.R. 322-27.

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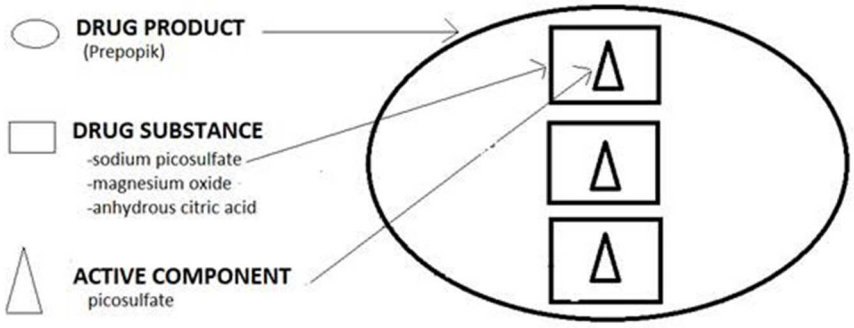
[4] *See* Exhibit 2, NDA 202535, Summary Review at 40, *available at* www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202535Orig1s000SumR.pdf.
[5] *See also* Exhibit 3, NDA 202535, Administrative and Correspondence Documents, Exclusivity Summary at 2, *available at* www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202535Orig1s000Admincorres.pdf.
[6] *Ibid.*

The agency thus granted PREPOPIK only three-year exclusivity. A.R. 64. FDA's decision not only reduced exclusivity for sodium picosulfate by two years; it also meant that generic manufacturers could submit ANDAs containing the same active ingredient during that shortened exclusivity period.

C. Ferring's Challenge to FDA's Exclusivity Determination

In January 2013, Ferring submitted a Citizen Petition requesting that FDA amend the exclusivity award for PREPOPIK from three to five years. A.R. 62-96. Two other companies also submitted similar Citizen Petitions asking FDA to award five-year exclusivity for drug products that similarly combined novel and previously-approved ingredients: Gilead Sciences, Inc. submitted a Citizen Petition in January 2013 for STRIBILD®, A.R. 97-142, and Bayer HealthCare Pharmaceuticals, Inc. submitted a Citizen Petition in April 2013 for NATAZIA®. A.R. 143-59. Collectively, the petitioners argued that Congress unmistakably intended to award NCE exclusivity to drug *substances*, not to *finished drug products*. A.R. 62-159. There is a meaningful difference between the two terms. A drug *product* is a finished dosage form that contains one or more drug substances, often along with other ingredients. A drug *substance* usually is comprised of an active ingredient intended to furnish pharmacological activity. An active ingredient, in turn, is comprised of a therapeutically active component, either as a base molecule or as some other closely related form, such as a salt or ester.



The word "drug" in the FDCA expressly can mean either drug *product* or drug *substance*. *See* 21 U.S.C. § 321(g)(1) (offering multiple definitions of "drug," including both finished drug products and "articles intended for use as a component of" such drug products); *U.S. v. Generix Drug Corp.*, 460 U.S. 453, 459-460 (1983) ("drug," as used in FDCA, includes both active ingredients and drug products).

In their Citizen Petitions, the petitioners explained that in the context of the FDCA's exclusivity provision, exclusivity attaches to a "drug," which in context plainly means a "drug *substance*" like sodium picosulfate. *Id.* The petitioners pointed out that the statutory sentence at issue, found in 21 U.S.C. § 355(j)(5)(F)(ii) (*see supra* at 3), uses the word "drug" twice—the second time using "the" drug, to explicitly refer back to the original "a" drug—and that FDA has long interpreted the second reference to "drug" to mean "drug substance." *Id.* And the petitioners likewise pointed out that FDA has elsewhere long recognized that NCE exclusivity attaches to the drug *substance*, not the drug product, such that exclusivity travels with the drug substance to other drug products containing the same drug substance developed by the same sponsor. *Id.* And because exclusivity travels with the drug substance, petitioners further explained, that in turn meant that *some* fixed-dose combination drugs can obtain exclusivity for their novel active ingredients—so long as those novel ingredients are approved as part of a *single*-ingredient product first. *Id.* The petitioners pointed out that the agency's informal policy on fixed-dose combination drug products therefore was arbitrary; it placed undue importance on the order in which such drug products are approved relative to single-ingredient drug products. *Id.*

FDA issued a consolidated response to the three companies' Citizen Petitions in February 2014. A.R. 829. Defending its interpretation of the statute, FDA candidly acknowledged that it

construed the operative word "drug" later in the very same sentence to refer to a drug substance, not a drug product—but the agency nevertheless argued that it was "permissible to interpret the same word in two different clauses to mean different things." A.R. 209.

However, FDA agreed with the petitioners that the agency's previous position on exclusivity "may place undue importance on the order in which . . . NDAs are approved." A.R. 214. And the agency acknowledged that the strategy of seeking approval of a single-ingredient product before a fixed-dose combination product "may not be available if a new active moiety does not clinically lend itself to approval in a single-entity drug." *Id.* Moreover, FDA conceded that its previous position—that a drug product did not qualify for five-year NCE exclusivity unless *all* the ingredients were new—"may result in drug development strategies that are suboptimal from a public health perspective." A.R. 213. *Id.*

FDA thus concluded that changing its position was "desirable as a matter of policy." A.R. 215. Accordingly, FDA issued a draft guidance document abandoning its previous position on exclusivity. FDA explained that under the agency's new policy, "a drug substance containing no previously approved active moiety would be eligible for 5-year NCE exclusivity even when such a drug substance is approved in a fixed-combination with another drug substance containing one or more previously approved active moieties." *Id.*

There is no dispute that PREPOPIK satisfies this standard: neither picosulfate nor sodium picosulfate has previously been approved by FDA, notwithstanding that the two other active ingredients in PREPOPIK (magnesium oxide and anhydrous citric acid) have previously been approved. FDA refused, however, to apply its new interpretation to PREPOPIK (or to Bayer's or Gilead's drugs). A.R. 215. Instead the agency declared that it would apply its new

interpretation—that is to say, the *correct* interpretation—only to NDAs that were not yet approved. A.R. 215.

D. FDA's Refusal to Reconsider its Exclusivity Determination for PREPOPIK

Ferring requested that FDA reconsider its denial of the Citizen Petition and decision not to grant PREPOPIK five years of exclusivity. A.R. 001-42. As Ferring explained, FDA's position treats similarly situated applicants differently, artificially distinguishes between applicants whose NDAs were approved before FDA made its decision and those whose applications were pending or not yet submitted, and otherwise constitutes arbitrary and capricious conduct. A.R. 001-42. FDA denied Ferring's request for reconsideration. A.R. 832-42. That same day, FDA finalized a guidance document outlining the agency's new, "prospective"-only application of the five-year exclusivity provision. A.R. 217-27.

PREPOPIK thus still remains protected only by the weaker, three-year exclusivity period. And the generic market has noticed: In January 2015, Ferring received notice from Par Pharmaceutical, Inc. that it had filed an ANDA seeking permission to market a purported generic version of PREPOPIK.

ARGUMENT

A court "shall . . . 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). "[W]hen a party seeks review of agency action under the APA, the district judge sits as an appellate tribunal. The entire case on review is a question of law." *Am. Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1083 (D.C. Cir. 2001) (internal quotation marks and citation omitted). Summary judgment in a suit under the APA thus "serves as a mechanism for deciding, as a matter of law, whether the administrative record supports the agency action

and whether the agency action is consistent with the APA standard of review." *Int'l Swaps & Derivatives Ass'n v. CFTC*, 887 F. Supp. 2d 259, 266 (D.D.C. 2012) (citation omitted).

Agency action is routinely set aside as unlawful where it violates a statute. *See, e.g.*, *Bennett v. Donovan*, 4 F. Supp. 3d 5, 13 (D.D.C. 2013). An agency also acts arbitrarily and capriciously in violation of the APA when it violates its own regulations. *Brock v. Cathedral Bluffs Shale Oil Co.*, 796 F.2d 533, 536 (D.C. Cir. 1986) ("It is axiomatic that an agency must adhere to its own regulations." (citations omitted)). And agency action is arbitrary and capricious when it treats similarly situated parties differently without adequate explanation. *See Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27 (D.D.C. 1997).

FDA fails all of these tests. First, FDA violated the FDCA's plain language by failing to recognize the five years of NCE exclusivity the statute confers on the sodium picosulfate. Second, FDA failed to follow its own NCE regulation, which makes clear that NCE exclusivity attaches to the drug *substance*, not the drug *product*. And third, the agency acted arbitrarily and capriciously when it treated similarly situated entities differently: Under FDA's view, a novel active ingredient is eligible for NCE exclusivity if it is first approved as part of a single-entity NDA, but not if it is first approved as part of a fixed-dose combination drug product containing other, previously-approved active ingredients. And under FDA's view, *pending* NDAs receive the benefit of the correct interpretation of the statute; *approved* NDAs suffer the consequences of FDA's erroneous old reading.

I. FDA'S DECISION VIOLATED THE FDCA.

FDA's refusal to grant PREPOPIK five-year exclusivity was based on the agency's position that if any of the active ingredients in a drug *product* have previously been approved, the product as a whole is ineligible for five-year exclusivity. A.R. 199-215. The agency has

now rescinded that position, applying what Ferring and others have maintained all along is the correct interpretation of the governing statute. But FDA refused to apply that new—correct—interpretation to PREPOPIK. That was error; FDA's old interpretation ran afoul of the statute.

The FDCA makes clear that if any drug *substance* contains a novel active component, that drug substance is eligible for NCE exclusivity even if the drug *product* also contains other, previously approved active components. Because FDA's old interpretation does not comport with that statutory command, the agency cannot lawfully persist in applying that impermissible (and now rescinded) interpretation to PREPOPIK.

The two steps of *Chevron* are old hat. "First, always, is the question whether Congress has directly spoken to the precise question at issue." *Chevron, U.S.A., Inc. v. Natural Resources Def. Council, Inc.*, 467 U.S. 837, 842 (1984). To determine Congress's intent, a court is charged with "employing traditional tools of statutory construction," including evaluation of a statute's "text, structure, purpose and history." *Hearth, Patio & Barbecue Ass'n v. U.S. Dep't of Energy*, 706 F.3d 499, 503 (D.C. Cir. 2013) (citations omitted). "If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Chevron*, 467 U.S. at 842-43.

It is only when the statute is ambiguous or leaves gaps for the agency to fill that a court moves on to *Chevron* Step Two, where the question becomes whether the agency's interpretation is "based on a permissible construction of the statute." *Chevron*, 467 U.S. at 843. A court only defers to an agency's permissible interpretation under Step Two "if the agency has offered a reasoned explanation for why it chose that interpretation." *Amarin Pharms. Ireland Ltd. v. F.D.A.*, No. 14-cv-00324 (RDM), --- F. Supp. 3d ---, 2015 WL 3407061, at *17 (D.D.C. May 28, 2015) (citation omitted). "This analysis overlaps substantially with the APA's 'arbitrary and

capricious' inquiry," because "[w]hether a statute is unreasonably interpreted is close analytically to the issue whether an agency's actions under a statute are unreasonable." *Id.* (alteration in original) (citations omitted).

Even under Step Two, the reasonableness of an agency's construction "depends on the construction's 'fit' within the statutory language as well as its conformity to statutory purposes." *Abbott Labs. v. Young*, 920 F.2d 984, 988 (D.C. Cir. 1990). *See also Council for Urological Interests v. Burwell*, No. 13-5235, --- F.3d ---, 2015 WL 3634632, at *9 (D.C. Cir. June 2, 2015) ("our deferential analysis under *Chevron* step two is limited to determining whether the regulation is rationally related to the goals of the Stark Law" (citation omitted)); *Van Hollen v. F.E.C.*, No. 11-0766 (ABJ), --- F. Supp. 3d ---, 2014 WL 6657240, at *5 (D.D.C. Nov. 25, 2014) (under *Chevron* Step Two, challenged interpretation "must also be tested against the policy that [the statute] was intended to advance").

A. FDA's Interpretation Fails Under *Chevron* Step One.

Like many federal statutes, the FDCA's provisions are complex and detailed. But that does not render them ambiguous; for once the relevant details are unpacked, it is clear that Congress plainly intended that a drug *substance* would be entitled to five-year exclusivity if it is based on a novel active ingredient, *e.g.*, sodium picosulfate, whose active component, *e.g.*, picosulfate, had never previously been approved. Because the text, structure, and purpose of the statute itself leave no room for ambiguity, this case is governed by *Chevron* Step One.

First, a refresher on the text of the statute: The FDCA sets forth eligibility for the five-year exclusivity period and specifies which subsequent applications will be blocked pursuant to that grant of exclusivity:

> If an application submitted under subsection (b) of this section for *a drug*, no active ingredient (including any ester or salt of the active ingredient) of which has

> been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application may be submitted under this subsection which refers to *the drug* for which the subsection (b) application was submitted before the expiration of five years from the date of approval of the application under subsection (b)….

21 U.S.C. § 355(j)(5)(F)(ii) (emphases added); *see also* 21 U.S.C. § 355(c)(3)(E)(ii) (analogous provision for 505(b)(2) NDAs). The word "drug" appears twice in this provision: first in the so-called "eligibility" clause (because it defines what is eligible for exclusivity), and again in the so-called "bar" clause (because it defines what is barred by that exclusivity). The key question is what the statute's first reference to "drug"—the "*a drug*" in the eligibility clause—means in the context of the statute. Did Congress intend to refer here to a drug *substance*, like sodium picosulfate? Or to the entire completed drug *product*, like PREPOPIK?

The answer depends on context. Congress expressly specified in the relevant definitional section of the FDCA that the word "drug" can mean different things, all depending on the statutory context in which the word is deployed.[7] *See* 21 U.S.C. § 321(g)(1) (offering multiple definitions of "drug," including both finished drug products and "articles intended for use as a component of" such drug products); *U.S. v. Generix Drug Corp.*, 460 U.S. 453, 459-460 (1983) ("drug," as used in FDCA, includes both active ingredients and drug products). And so for present purposes, the word "drug" can mean either "drug substance" or "drug product," again

[7] The fact that the word "drug" can have multiple meanings in the statute does not convert this case into a *Chevron* Step Two case. *See, e.g., Amarin Pharms.*, --- F. Supp. 3d ----, 2015 WL 3407061, at *10 ("This analysis may sound like *Chevron* step two because the term 'active ingredient' is ambiguous in some applications, but, under *Chevron* step one, where the text and reasonable inferences from it give a clear answer against the government . . . that. . . is the end of the matter.") (quotations omitted); *see also A.T. Massey Coal Co v. Holland*, 472 F.3d 148, 160 (4th Cir. 2006) ("[W]e do not deny that in the abstract, the word 'reimbursements' can have several meanings, [but] '[r]eimbursements' as used in 26 U.S.C. § 9704(b)(2) has a statutory context and historical context, and both reveal a uniform and precise meaning of the term" (citation omitted)).

depending on where and how the word is deployed in the statute. *See also* A.R. 831 (conceding that the word "drug" in the FDCA can mean either "drug substance" or "drug product").

FDA's denial of five-year exclusivity to PREPOPIK was based on the agency's assertion that the *first* reference to drug in the statute— the "**a drug**" to which the second "**the drug**" refers—means "drug *product*," not "drug substance." But FDA's interpretation is inconsistent with basic principles of statutory construction.

To begin with, the two appearances of "drug" in the provision have to mean the same thing. The first reference is to "**a** drug"; the second is to the definite article "**the** drug." When a definite article ("the") precedes a noun, it signals that the noun has been introduced before. *See Work v. United States ex rel. McAlester-Edwards Coal Co.*, 262 U.S. 200, 208 (1923) (use of definite article "the" shows Congress' intent to refer back to the appraisement referenced earlier in the same sentence).

And it is undisputed between the parties that the *second* time the word "**drug**" is used in that very same provision, the word means drug *substance*, not drug *product*. In its Citizen Petition Response, FDA effectively admitted that under its so-called "umbrella policy," the agency has long interpreted the word "drug" in the statutory bar clause as a drug substance, not a finished drug product. A.R. 209. FDA's umbrella policy, which interprets the *second* "drug" in the same statutory sentence at issue here, recognizes that NCE exclusivity attaches to the drug substance, not the drug product. *See, e.g.*, 54 Fed. Reg. 28872, 28897 (July 10, 1989). And FDA has acknowledged that this interpretation of "drug" as meaning "drug substance" under the umbrella policy is based on clear Congressional intent. *Id.*

That means the first "drug" – the "a" drug – must mean drug substance, too. When Congress uses the same word in close proximity in a statute—here, in the exact same *sentence*—

it should be afforded the same meaning. *Brown v. Gardner*, 513 U.S. 115, 118 (1994) (recognizing that the "presumption that a given term is used to mean the same thing throughout a statute" is "surely at its most vigorous when a term is repeated within a given sentence" (internal citation omitted)). *See also Lewis v. Philip Morris Inc.*, 355 F.3d 515, 536 (6th Cir. 2004) ("[I]t would take an extremely strong showing of Congressional intent to defeat the conclusion that the first use of the word 'customer' in the same sentence carries the same meaning."). This is particularly true where, as here, the word is introduced as "a" thing and later referred back to as "the" thing. *United States. v. Wilcox*, 487 F.3d 1163, 1176 (8th Cir. 2007) ("use of the definite article indicates that 'the victim' who may be reimbursed is the victim described at the beginning of the subsection"); *Nat'l Foods, Inc. v. Rubin*, 936 F.2d 656, 660 (2d Cir. 1991) (" 'the court' referred to the second time in sub-paragraph (b) should be the same one referred to the first time"); *Work*, 262 U.S. at 208 (use of definite article "the" shows Congress' intent to refer back to the appraisement referenced earlier in the same sentence). And lest there be any doubt, the statute specifically identifies the second drug as "the drug *for which the subsection (b) application was submitted*" – which is the exact same description given to "a drug." The only permissible interpretation of both uses of "drug," then, is that Congress intended in both instances for the word "drug" to refer to "drug substance."

Moving beyond the word "drug," the rest of the sentence at issue also supports Ferring's interpretation. That sentence says the following about the drug at issue: it is "a drug, **no active ingredient (including any ester or salt of the active ingredient) of which** has been approved in any other application . . . ." 21 U.S.C. § 355(j)(5)(F)(ii) (emphasis added). "Esters and salts are molecules that form in chemical reactions when the hydrogen atom of an acid molecule is replaced by another substance. Esters and salts are typically closely related to their parent acid

molecules." *Amarin Pharms.*, --- F. Supp.3d ---, 2015 WL 3407061, at *1. The bolded language above can be thought of to refer to an "active component" of a drug—and the statute plainly asks whether that active component has previously been approved by FDA. In other words, exclusivity is intended to cover not just the active ingredient that comprises the specific drug substance at issue (the "drug"), but also closely-related variations of the active ingredient (such as esters and salts). FDA recognized this intent by coining a new term, "active moiety," in its regulations to replace the bolded statutory phrase above. FDA's definition of "active moiety" makes clear that minor variations on an active ingredient, such as salts and esters, should not be entitled to NCE exclusivity. *See* 21 C.F.R. §§ 314.108(b) and (a).

In its reconsideration denial, FDA seized on the phrase "an application submitted . . . for a drug" to argue that "applications are typically submitted for drug products, not drug substances." A.R. 840. This argument—that FDA approves only finished drug products, not active ingredients—is inconsistent with the statute itself, which makes express reference to an active ingredient being approved in the very same sentence. 21 U.S.C. § 355(j)(5)(F)(ii) ("no active ingredient . . . of which has been approved in [a prior] application"). It also has been rejected by both this Court and the Tenth Circuit. In his recent *Amarin* decision, addressing the "no active ingredient of which has been approved" language, Judge Moss noted that "[i]t is not correct . . . to say that the FDA does not approve 'active ingredients' when it approves drugs or drug products." *See Amarin Pharms.*, --- F. Supp. 2d ---, 2015 WL 3407061, at *14. Rather:

> At times, the FDCA refers to the approval of "drugs," *see, e.g.*, 21 U.S.C. § 355(j)(6); at times, it refers to the approval of "active ingredients," *see, e.g., id.* at § 355(j)(3)(E)(v) (referring to drugs which "include an active ingredient . . . that has been approved."). Most frequently, including in the provisions at issue in this case, the statute suggests that it is the new drug application, or NDA, that is subject to "approval." *See* 21 U.S.C. §§ 355(c)(3)(E)(ii), 355(j)(5)(F)(ii) . . . . It does not require a substantial leap to conclude that . . . the FDCA contemplates

> that "active ingredients," as well as drugs, may be the subject of the FDA's approval.

Id. (citation omitted). The Tenth Circuit has agreed, explaining that "it is evident from § 355 that approval of active ingredients is integral to the overall new drug approval process." *Pharmanex v. Shalala*, 221 F.3d 1151, 1156 (10th Cir. 2000) (citation omitted).

Congress also used similar or identical language ("a drug, no active ingredient . . . of which") numerous other times in the FDCA. In all but one case,[8] FDA has interpreted this language to mean "a drug substance no active moiety of which has been approved," even if that drug substance is first approved in a fixed-dose combination product. Accordingly, FDA has applied these provisions to cover fixed-dose combination drug products, such as PREPOPIK, that contain a novel active ingredient in combination with a previously-approved one. These include:

- **Referral to an advisory committee (21 U.S.C. § 355(s)):** In this provision, Congress said: "Prior to the approval of a drug *no active ingredient (including any ester or salt of the active ingredient) of which has been approved*" in an NDA or biologics license application, FDA must either refer the drug to an FDA advisory committee for review prior to approval or must state in the approval letter its reasons for not doing so. 21 U.S.C. § 355(s) (emphasis added). This safety provision springs from the risks associated with new active ingredients. The extra risks of a new active ingredient are no less when a sponsor combines them in a fixed-dose combination with a previously-approved moiety. For that reason, FDA typically has applied this

[8] The only exception is the statutory provision governing tropical disease priority review vouchers (21 U.S.C. § 360(n)). FDA took the position that this provision did not apply to fixed drug combination products in a 2008 Draft Guidance document that never was finalized. *See* Exhibit 4, *Draft Guidance for Industry, Tropical Disease Priority Review Voucher* (October 2008) at 6-7. FDA does not appear to have ever applied this interpretation to deny a priority review voucher to a fixed dose combination drug product.

provision to fixed dose combination products that contain both new and previously-approved active ingredients – including PREPOPIK.[9]

• **Posting of review documents (21 U.S.C. § 355(l)):** This provision requires that FDA publish on its website the review documents for an NDA not later than 30 days after approval of "*a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved* in any other [NDA] . . . ." 21 U.S.C. § 355(l)(2)(A)(i) (emphasis added). FDA has interpreted this language to require timely public posting of approval documents for all drug products that contain new active ingredients, even fixed dose combination products that also contain previously approved active ingredients.[10]

• **Rare pediatric disease priority review vouchers 21 U.S.C. § 360(ff):** To be eligible for a priority review voucher, a rare pediatric disease product application must be for a "*drug . . . that contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved* in [an NDA]." 21 U.S.C. § 360(ff)(4)(A)(ii) (emphasis added). FDA does not require that all active ingredients be new in order to fall within the statutory language. *See* Exhibit 6, *Draft Guidance for Industry, Rare Pediatric Disease Priority Review Vouchers* (Nov. 2014).

Congress clearly intended all of these provisions to apply to fixed-dose combination drug products, because to exempt them would create a huge gap in the drug approval process. *All* new ingredients, for example, must be held up to heightened safety standards, regardless of whether the FDA is examining them for the first time in conjunction with another previously approved

[9] For that reason, FDA specifically noted in the Summary Review for each drug the reasons why the agency did not convene an advisory committee meeting. *See, e.g.*, Exhibit 5, NDA 202535, Approval Letter at 2, *available at* www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202535Orig1s000Approv.pdf .

[10] Consistent with this provision, the review documents for PREPOPIK were posted by FDA on August 3, 2012.

ingredient. Thus, when Congress used the "drug, no active ingredient (including any ester or salt of the active ingredient) of which" language in these other places, it plainly intended to include fixed-dose combination drug products. There is no reason to believe that Congress intended a different meaning in the particular NCE exclusivity provision at issue here. *See F.D.A. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000) (recognizing the "fundamental canon of statutory construction that the words of a statute must be read in their context and with a view to their place in the overall statutory scheme"). Rewarding the development of a novel active ingredient with NCE exclusivity goes hand in hand with the heightened safety measures Congress has required of FDA: it is costlier to demonstrate the safety and effectiveness of a novel active ingredient.

When read in light of the text, structure, and purpose of the FDCA, the statute compels the conclusion that exclusivity attaches to drug substances and the active ingredients thereof, not to finished drug products. PREPOPIK is entitled to five-year NCE exclusivity.

B. FDA's Interpretation Fails Even Under *Chevron* Step Two.

Although this case should be resolved under *Chevron* Step One, FDA's statutory interpretation also fails even under the more lenient Step Two. For if any interpretation of the agency is entitled to deference under Step Two, it is the interpretation reflected in FDA's formal regulations. *See Fox v. Clinton*, 684 F.3d 67, 76 (D.C. Cir. 2012) (regulations promulgated through formal notice and comment rulemaking entitled to more deference than other agency interpretations); *Barrick Goldstrike Mines, Inc. v. Whitman*, 260 F. Supp. 2d 28, 36-37 (D.D.C. 2003) (agency's interpretation that is inconsistent with its own regulations is invalid). And FDA's formal regulations interpret the statute the exact same way Ferring does.

In 1994, FDA finalized a comprehensive set of regulations implementing the Hatch-Waxman Act. These regulations—promulgated by formal notice-and-comment rulemaking—supersede any prior informal pronouncements by the agency on NCE exclusivity. Among those regulations was one intended to help the agency and the public decide which applications are eligible for 5-year exclusivity and which applications will be "blocked" by that exclusivity:

> If a **drug product** that contains a **new chemical entity** was approved after September 24, 1984, in an application submitted under section 505(b) of the act, no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for **a drug product that contains the same active moiety as in the new chemical entity** for a period of five years from the date of approval of the first approved new drug application[.]

See 21 C.F.R. § 314.108(b)(2) (emphases added). The regulation coined two new terms not present (and thus not defined) in the statute itself: "new chemical entity" and "active moiety." The agency defined "new chemical entity" to mean "**a drug** that contains no active moiety that has been approved by FDA in any other application submitted under 505(b) of the [A]ct." *Id.* § 314.108(a) (emphasis added).[11] And FDA defined "active moiety" to mean a "molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt . . . or other noncovalent derivative . . ., responsible for the physiological or pharmacological action of the drug substance." *Id.*

Putting these definitions together, the regulation makes clear that a drug **product** *contains* the new chemical entity (NCE) that is the subject of statutory exclusivity, and that the

[11] FDA's definition of new chemical entity clearly mirrors the critical statutory phrase "a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section . . . ." 21 U.S.C. § 355(j)(5)(F)(ii). In other words, the "a drug" in the statute and the "a drug" in FDA's definition of "new chemical entity" must refer to the same thing.

NCE is comprised of the active moiety that must not previously have been approved.[12] Accordingly, under FDA's own regulations, an NCE eligible for exclusivity must contain no previously approved active moiety. To the extent this Court even gets to *Chevron* Step Two, it is this interpretation—promulgated through formal rulemaking—that is entitled to deference, not the agency's ad hoc interpretation set forth in its Citizen Petition Response. *Barrick Goldstrike Mines*, 260 F. Supp. 2d at 36-37 (agency's interpretation that is inconsistent with its regulations is invalid).

FDA may argue that it used to read its regulation differently—that the phrase "new chemical entity" meant "drug *product* that contains no active moiety"—and that its (now superseded) interpretation is entitled to judicial deference. *See* A.R. 221. But FDA's position results in a tortured reading of the regulation. If "new chemical entity" means "drug *product* that contains no active moiety," then the regulation as a whole would read: "If a drug product contains a drug product that contains no active moiety . . . ."[13] *See* 21 C.F.R. §§ 314.108(b)(2) and (a). Judicial deference to an agency's interpretation of its own regulation is not warranted where the interpretation is nonsensical. *Auer v. Robbins*, 519 U.S. 452, 461 (1997). Nor is it warranted where the regulation is clear on its face. *Gardebring v. Jenkins*, 485 U.S. 415, 430 (1988) (agency's interpretation receives no deference where an "alternative reading is compelled by the regulation's plain language"); *see also Pfizer, Inc. v. Heckler*, 735 F.2d 1502, 1509 (D.C. Cir. 1984).

[12] This interpretation is analogous to the concepts of drug product, drug substance, and active component explained in Argument I.A, *supra*.

[13] In contrast, if "new chemical entity" means "drug *substance* that contains no active moiety," then the regulation as a whole would much more logically read: "If a drug product contains a drug substance that contains no active moiety . . . ."

But there is another reason that FDA's informal interpretation cannot stand. Because the agency has offered several different inconsistent interpretations of the statute, its (now superseded) interpretation is entitled to considerably less deference. *See I.N.S. v. Cardoza-Fonseca*, 480 U.S. 421, 446 n.30 (1987) ("An agency interpretation of a relevant provision which conflicts with the agency's earlier interpretation is 'entitled to considerably less deference' than a consistently held agency view.") (*quoting Watt v. Alaska*, 451 U.S. 259, 273 (1981); *see also Prevor v. F.D.A.*, 895 F. Supp. 2d 90, 97 (D.D.C. 2012) (same). The agency has now offered three interpretations of the statute: one in its regulations, one in defending its prior policy, and another in announcing the new policy. Two of those interpretations—in the formal regulations, and now—support Ferring's construction. There is no particular reason to defer to the third, other than it helps the agency win this particular lawsuit. FDA's prior interpretation of the statute reflects a "bewildering statutory exegesis—one [that] cannot be affirm[ed] even under Chevron's deferential standard of review." *Council for Urological Interests*, --- F.3d ---, 2015 WL 3634632, at *9.

FDA also has argued that its erroneous interpretation should be given deference because it was the long-standing practice of the agency, A.R. 215, but "age is no antidote to clear inconsistency with a statute, and the fact, again, that [the interpretation] flies against the plain language of the statutory text exempts courts from any obligation to defer to it." *Brown*, 513 U.S. at 122 (citations omitted). And of course, even under *Chevron* Step Two, an agency's interpretation must "be tested against the policy that [the statute] was intended to advance." *Van Hollen*, --- F. Supp. 3d ---, 2014 WL 6657240, at *5 (agency's interpretation failed under *Chevron* Step Two); *Prevor v. F.D.A.*, 9 F. Supp. 3d 125, 137-39 (D.D.C. 2014) (finding that FDA's interpretation of an FDCA provision failed under *Chevron* Step Two). Congress

unmistakably intended to provide NCE exclusivity in order to encourage drug companies to research and develop new drug substances. A.R. 321; 130 Cong. Rec. H9114 (daily ed. Sept. 6, 1984) (Rep. Waxman explaining that the five-year exclusivity period provided "the drug industry the incentives needed to develop new chemical entities"); *Abbott Labs.*, 920 F.2d at 985 (observing that Congress created NCE exclusivity "to encourage innovation in the drug industry . . . while protecting consumers from unduly high prices by refusing to give a long period of market exclusivity to drugs which required *no new research effort.*" (emphasis added)). That purpose is contravened if NCE exclusivity is denied to fixed-dose combination products containing a new active ingredient. Such products undeniably require a significant investment in research, and they provide real benefits to patients. It does not and should not matter under the statute whether the active ingredient is approved alone or in combination with other, older active ingredients. FDA's analysis fails even under *Chevron* Step Two.

II. FDA'S REFUSAL TO AWARD FERRING FIVE-YEAR EXCLUSIVITY VIOLATED ITS OWN REGULATIONS.

"It is axiomatic that an agency must adhere to its own regulations." *Brock*, 796 F.2d at 536. Administrative agencies "may not violate their own rules and regulations to the prejudice of others." *Battle v. F.A.A.*, 393 F.3d 1330, 1336 (D.C. Cir. 2005) (citation omitted). And yet that is exactly what FDA has done here.

As we have explained, *supra* at I.B, FDA's own regulations make clear that Ferring is entitled to five-year NCE exclusivity. *See* 21 C.F.R. § 314.108(b)(2). FDA's regulations apply to a "drug product that contains a new chemical entity" and define "new chemical entity" to mean "a drug that contains no active moiety that has been approved by FDA in any other application submitted under 505(b) of the [A]ct." *Id.* § 314.108(b)(2) and (a). In other words, the finished drug product contains the protected "new chemical entity," which in turn is

comprised of the active moiety that must be novel. FDA's regulation, by its plain terms, thus attaches NCE exclusivity to the drug substance, not the drug product. *Id.* § 314.108(b)(2).

FDA's tortured (alternative) interpretation of its own regulation—that the phrase "new chemical entity" means "drug product that contains no active moiety"—merits no deference. *See supra* at I.B. Under FDA's own regulations, fixed-dose combination products that contain more than one drug substance are entitled to NCE exclusivity so long as one of those drug substances is comprised of a novel active moiety. PREPOPIK fits this statutory and regulatory bill. It should have received five-year exclusivity.

* * *

Because FDA's now-cast-off interpretation of the NCE exclusivity provision ran afoul of the agency's governing statute, it was *never* reasonable—and because it was never reasonable, and always in error, it cannot continue to apply to Ferring and the handful of other sponsors in Ferring's position.

III. FDA ACTED ARBITRARILY AND CAPRICIOUSLY BY TREATING SIMILARLY-SITUATED PARTIES DIFFERENTLY.

It is a fundamental rule of administrative law that "an agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so." *Bracco Diagnostics*, 963 F. Supp. at 27-28 (citations omitted). "Government is at its most arbitrary when it treats similarly situated people differently." *Id.* (quoting *Etelson v. Office of Personnel Mgmt.*, 684 F.2d 918, 926 (D.C. Cir. 1982)). "The disparate treatment of functionally indistinguishable products is the essence of the meaning of arbitrary and capricious." *Prevor*, 895 F. Supp. 2d at 99. *See also Cnty. Of Los Angeles v. Shalala*, 192 F.3d 1005, 1022 (D.C. Cir. 1999) ("A long line of precedent has established that an agency action is arbitrary when the agency offer[s]

insufficient reasons for treating similar situations differently." (internal quotation marks and citations omitted)); *Freeman Eng'g Assocs. Inc v. F.C.C.*, 103 F.3d 169, 180 (D.C. Cir. 1997) (remanding to agency to remedy inconsistent treatment). In order to justify treating similarly-situated entities differently, an agency must "do more than enumerate factual differences, if any, between [one case] and the other cases; it must explain the relevance of those differences to the purposes of the [underlying law]." *Melody Music, Inc. v. F.C.C.*, 345 F.2d 730, 733 (D.C. Cir. 1965).

FDA has violated this basic maxim in two different ways. First, FDA's *old* interpretation of the NCE statute arbitrarily treats PREPOPIK differently than other fixed-dose combination drug products, rendering it arbitrary and capricious. And second, FDA just as arbitrarily limited its *new*, and correct, interpretation of the statute to NDAs submitted after the agency finalized its new guidance.

A. FDA's Policy Results in Disparate Treatment of Similarly Situated Fixed-Dose Combination Drug Products.

Under FDA's "umbrella policy," if a *single*-entity drug product containing a new active ingredient is approved before a fixed-dose *combination* drug product containing the same active ingredient, both products—the single-entity and the combination—receive the benefit of the five-year NCE exclusivity. 54 Fed. Reg. 28872, 28897 (July 10, 1989). This is true even when the gap between approvals is measured not in years or months, but in hours. *Id.*

For example, EDARBYCLOR—a fixed-dose combination product containing two previously approved ingredients, azilsartan kamedoxomil and chlorthalidone—received the benefit of the five-year exclusivity FDA had awarded to the same sponsor's single-ingredient azilsartan kamedoxomil less than a year earlier. A.R. 908-09. FDA similarly extended five-year exclusivity to the fixed-dose combination drug product COMPLERA (NDA 202123), which

contained rilpivirine hydrochloride in combination with two previously approved active ingredients, because the agency had approved a single-ingredient drug containing rilpivirine hydrochloride several months earlier. A.R. 214 n.80. Even more dramatically, FDA "first" approved an NDA for the single-ingredient product NESINA (alogliptin) in January 2013, and then *later that same day* approved two NDAs containing alogliptin in combination with other, previously approved ingredients. *See* A.R. 907; *see also* Exhibit 7, Letter from Curtis Rosebraugh, FDA, to Takeda Pharmaceuticals U.S.A., Inc. (Jan. 25, 2013) (stating that FDA was "approving the single entity [product] first, before approving the combination products"). Because the single-entity product was approved "first," all three products received the benefit of NCE exclusivity. In all of the foregoing cases, if the order of the approvals had been reversed and the fixed-dose combination drug product had been approved just hours before the single-ingredient product, *none* of the products would have been awarded NCE exclusivity, because each would have contained a previously approved active ingredient.

Unlike the sponsors in these examples, however, Ferring could not game the timing of agency approval for PREPOPIK. The new active ingredient in PREPOPIK—sodium picosulfate—is not suitable as a single-ingredient drug product. Indeed, FDA determined that single-ingredient clinical trials for sodium picosulfate would raise "serious ethical concerns." A.R. 70; *see also* A.R. 214 (acknowledging that the strategy of seeking approval of a single-ingredient product before a fixed-dose combination product in order to ensure five-year exclusivity for both products "may not be available if a new active moiety does not clinically lend itself to approval in a single-entity drug").

Thus, under FDA's old construction of the NCE statute, a fixed-dose combination drug never would benefit from five-year exclusivity if its novel ingredients were ineligible for

approval as a single-entity product. FDA's position puts undue weight on an irrelevant temporal factor: the order in which a sponsor's applications are approved. *See Abbott Labs*, 920 F.2d at 989 (finding "farfetched" and "fail[ing] to serve any conceivable statutory purpose" an interpretation that would base the degree of exclusivity protection a drug receives on the sequence in which a sponsor's applications are approved).

FDA has utterly failed to present a rational explanation for treating PREPOPIK differently than other similarly situated fixed-dose combination drug products. Indeed, the agency has all but admitted that its earlier interpretation of the statute was arbitrary on this point: "our current [now discarded] approach may place undue importance on the order in which these two NDAs are approved." A.R. 213-214. That candid acknowledgment further dooms the agency's old interpretation. *See Bracco Diagnostics*, 963 F. Supp. at 28; *Transactive Corp. v. United States*, 91 F.3d 232, 237 (D.C. Cir. 1996); *Independent Petroleum Assoc. v. Babbitt*, 92 F.3d 1248, 1259 (D.C. Cir. 1996).

B. FDA Acted Arbitrarily By Refusing to Apply The Correct Construction of the Statute to Already-Approved Drugs.

FDA also acted arbitrarily and capriciously by denying Ferring the benefit of the change the agency put in place as a result of Ferring's Citizen Petition. In announcing its change of course, FDA expressly *excluded* the three drug products that had been the subject of the Citizen Petitions, stating that they were ineligible for treatment under the new policy, and that the policy only applied to drug products approved after the new finalized guidance document issued. A.R. 215. FDA offered three explanations for this position: (i) first, its previous interpretation of the statute had been "longstanding"; (ii) second, FDA desired to avoid "any unnecessary disruption to regulated industry"; and (iii) third, FDA noted that "if the new interpretation were to be applied to products for which ANDAs already have been filed, it could impose a burden on the

ANDA sponsors, who relied on our existing interpretation in filing their applications." A.R. 215. None of these explanations survives scrutiny.

First, an erroneous interpretation of a statute cannot be justified merely because it is long-standing. *Brown*, 513 U.S. at 122 ("A regulation's age is no antidote to clear inconsistency with a statute." (citations omitted)). And here, the challenged agency interpretation was not even a regulation; it was an informal policy that actually conflicted with the agency's own (long-standing) regulation. 21 C.F.R. § 314.108(b)(2). If anyone was justified in relying on a long-standing interpretation of the statute, it was Ferring, which relied on an agency interpretation promulgated through formal notice and comment rulemaking.

FDA's second and third explanations are just as easily dispatched; the agency's volte-face caused no "disruption to regulated industry" and placed no "burden" on ANDA filers. There is nothing in the administrative record to suggest that at the time FDA issued its initial Citizen Petition Response, FDA had received any ANDAs that sought to rely on PREPOPIK as a reference listed drug.[14] A.R. 21, 835. In other words, the record shows there *are no* third parties who relied on FDA's previous interpretation, and whose expectations would somehow be "disrupt[ed]" or otherwise "burden[ed]," by FDA arriving at the correct interpretation of its statutory charge. A.R. 21, 835.

FDA attempted to sidestep this problem by asserting that Ferring had not "conclusively establish[ed] that no sponsor has undertaken a development program with the expectation that the Agency would continue to apply its historical interpretation." A.R. 839. But it is not Ferring's burden to somehow prove that negative. The administrative record does not suggest

[14] The same is true of Gilead. A.R. 835. And although Bayer had received at least one Paragraph IV certification from an ANDA filer, it resulted in patent litigation which delayed the ANDA's entry into the market beyond the time period relevant here. *Id.* n.33.

that any such third parties actually exist. And FDA's ostensible concern about a hypothetical ANDA filer who might or might not have undertaken a development program—notwithstanding that Ferring's Citizen Petition was publicly known, and notwithstanding that FDA's own regulations afforded PREPOPIK five-year exclusivity—is simply too speculative to supply a "rational" explanation for its disparate treatment of similarly situated entities. In any event, any hypothetical third-party filers were on notice that Ferring's exclusivity was being challenged at least as early as January 2013, when Ferring filed its Citizen Petition mere months after FDA approved PREPOPIK. A.R. 62.

FDA's decision to draw a line between NDAs that had previously been approved and those that had not was arbitrary and capricious for yet another reason. FDA based its decision on its contention that "exclusivity runs from the date of approval of a drug product." A.R. 838. This is simply missing the point. While the exclusivity period itself is calculated from the approval date, the preclusive effect of the exclusivity only arises when a subsequent application is submitted. Exclusivity thus operates only at the point when an ANDA or 505(b)(2) applicant seeks to rely upon the innovator drug, not when the innovator's NDA is initially approved. After all, the NCE exclusivity provisions appear in the portions of the statute governing when an ANDA or 505(b)(2) filer can seek approval. 21 U.S.C. §§ 355(j)(5) (timing of approval of ANDA applications); 355(c)(3) (timing of approval of 505(b)(2) NDAs). As a result, even if the agency believed that it could or should apply the correct statutory interpretation only "prospectively," that "prospective" application should not hinge on the date of approval of innovator's NDA, but on the date of submission of the generic ANDA.

CONCLUSION

For all of the foregoing reasons, Plaintiff's Motion for Summary Judgment should be granted and FDA should be ordered to recognize five-year exclusivity for PREPOPIK under the FDCA.

Respectfully submitted,

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Dated: July 23, 2015