UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

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

MEMORANDUM IN SUPPORT OF DEFENDANTS' CROSS-MOTION FOR SUMMARY JUDGMENT AND OPPOSITION TO PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT

This case concerns FDA's regulation under the Federal Food, Drug, and Cosmetic Act ("FDCA") of fixed-dose combination drug products ("fixed-combinations"), which are drug products that generally include two or more active ingredients in a fixed ratio, synthetically combined in a single dosage form. Ferring Pharmaceuticals, Inc. ("Ferring") is challenging FDA's conclusion that its product, Prepopik, is not entitled to 5-year new chemical entity ("NCE") exclusivity. *See* Memo. of Points and Authorities in Supp. of Pl.'s Mot. for Summ. J. ("Pl. Memo.") at 1. Under FDA's interpretation of the relevant statutory and regulatory provisions that were in effect throughout the time Ferring developed and obtained marketing approval for Prepopik, a fixed-combination that contains a previously-approved active moiety[1] as well as a new active moiety is not eligible for 5-year NCE exclusivity. Ferring and two other drug manufacturers petitioned FDA to change this interpretation and, citing policy concerns and

[1] As explained further herein, an active moiety is "the molecule or ion . . . responsible for the physiological or pharmacological action of the drug substance." 21 C.F.R. § 314.108(a).

scientific advancements, FDA agreed with the petitioners. FDA, however, concluded that the most appropriate course would be to apply the new interpretation prospectively, meaning that the products at issue, including Prepopik, were not eligible for 5-year NCE exclusivity. Unhappy with this result, Ferring filed suit, claiming that FDA's old interpretation was wrong and that FDA erred in not applying the new interpretation to Prepopik. Notably, despite the fact that FDA had consistently applied its previous interpretation for the past 30 years, Ferring did not challenge that interpretation at the time FDA applied it to deny NCE exclusivity to Prepopik in July 2012. Rather, it was not until six months later, after another petitioner (Gilead) named Prepopik as an example of a fixed-combination that was not eligible for 5-year NCE exclusivity under FDA's then-current interpretation, that Ferring belatedly took issue with the agency's long-standing interpretation. *See* AR at 104 n.2. Nor did Ferring argue in its petition to FDA, as it does here, that the "plain language" of the statute somehow compels the result it now seeks in this lawsuit. *See* AR 70-76.

That Ferring has never previously argued that FDA's prior interpretation runs afoul of the plain language of the FDCA is not surprising. Because, while the agency no longer holds to that interpretation (due primarily to reasons of policy and science), it most assuredly passes muster under *Chevron* step two. In describing the article that is eligible for 5-year NCE exclusivity, the relevant statutory provision uses the term "drug," which both parties agree has multiple meanings. FDA's prior interpretation of this ambiguous term was reasonable and furthered the congressional intent of the provision. By interpreting "drug" to mean "drug product" in the first clause of the relevant statutory provision, FDA helped ensure that only completely novel drug products received 5-year NCE exclusivity. And while the first appearance of the word "drug" can also reasonably interpreted to mean "drug substance," as FDA now construes it, Ferring's

newfound contention that this is the only possible construction of the clause does not hold up to scrutiny. However preferable FDA's new construction of the provision may be (as both parties agree), it is simply not the case that the agency's prior interpretation was unambiguously foreclosed by the plain language of the statute.

Moreover, FDA acted reasonably in proposing its new interpretation in a draft guidance, seeking comment on the proposal, and finalizing it only after the comment period had closed. Because FDA had consistently applied its prior interpretation for many years, the agency properly heeded the likelihood that regulated industry relied on that interpretation in planning drug development. Therefore, FDA determined that it would apply its new interpretation prospectively, to applications approved on or after the date the draft guidance was finalized, but wisely sought to avoid upsetting settled expectations by applying the new interpretation retroactively to previously approved applications. Ferring cannot show that this decision was arbitrary, capricious, or otherwise contrary to law. Judgment should therefore be entered in favor of FDA.

I. STATUTORY AND REGULATORY BACKGROUND

A. New Drug Applications and Abbreviated New Drug Applications

A new drug application ("NDA") must be supported by full reports of clinical investigations showing the drug product to be safe and effective. 21 U.S.C. § 355(b). The 1984 Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman Amendments") provided an alternate pathway under 21 U.S.C. § 355(b)(2) for approval of an NDA for which some or all of the safety and efficacy investigations relied on for approval were not conducted by or for the applicant and for which the applicant has not obtained a right or reference of use (a "505(b)(2) application").

The Hatch-Waxman Amendments also provided for the submission of abbreviated new drug applications ("ANDAs") for generic versions of listed drugs. 21 U.S.C. § 355(j).[2] The ANDA process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to repeat the clinical studies conducted to support approval of the listed drug. To rely on such a finding, the ANDA applicant must show, among other things, that its proposed drug product is the same as the listed drug with respect to active ingredient, dosage form, strength, route of administration, and, with certain narrow exceptions, labeling, and that its product is bioequivalent to the listed drug. 21 U.S.C. § 355(j)(2).

B. Five-Year NCE Exclusivity

The Hatch-Waxman Amendments provide incentives for pharmaceutical innovation by conferring various periods of exclusivity to protect qualified drugs approved under 21 U.S.C. § 355(b) from competition. The statute provides for a 5-year NCE exclusivity period by prohibiting the submission of certain other drug applications:

> If an application submitted under subsection (b) 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), 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 the approval of the application under subsection (b) . . .

21 U.S.C. §§ 355(c)(3)(E)(ii), (j)(5)(F)(ii).[3]

[2] A "listed" drug is a drug product listed in the Orange Book with an effective approval under 21 U.S.C. § 355(c). *See* 21 C.F.R § 314.3(b).

[3] Parallel 5-year NCE exclusivity provisions apply to ANDAs and 505(b)(2) applications.

This provision includes clauses describing eligibility for 5-year NCE exclusivity ("eligibility clause") and the parameters of such exclusivity once it attaches ("bar clause"). Under the eligibility clause, a drug is eligible for 5-year 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. Once a drug has met the requirements of the eligibility clause, the bar clause prevents the submission of any ANDA or 505(b)(2) application that "refers to the drug for which the [505(b)] application was submitted." This bar on submission lasts for "five years from the date of the approval of the [505(b)] application," but does not block the submission, review, or approval of an NDA submitted under 21 U.S.C. § 355(b)(1). The statute does provide an exception allowing an applicant to submit an ANDA four years following the date of approval if it contains a patent challenge described in 21 U.S.C. § 355(j)(2)(A)(vii)(IV).[4]

After the Hatch-Waxman Amendments were enacted and before implementing regulations were promulgated, FDA issued a series of letters to industry describing its then-current interpretation of certain statutory provisions related to ANDA and 505(b)(2) application approvals. In a letter dated April 28, 1988, from Dr. Carl Peck, the Director of FDA's Center for Drug Evaluation and Research ("CDER") ("the Peck Letter"), FDA interpreted the term "active ingredient (including any ester or salt of the active ingredient)" in the eligibility clause of the 5-year NCE exclusivity provision to mean "active moiety" and articulated an interpretation of the eligibility clause based on whether any active moiety in the drug product had previously been approved. *See* AR 322-27. Specifically, the letter stated, "[a] *drug product* will . . . not be considered a 'new chemical entity' entitled to five years of exclusivity if it contains a previously

[4] A parallel exception under 21 U.S.C. § 355(c)(3)(E)(ii) allows the submission of a 505(b)(2) application after four years under similar conditions.

approved active moiety, even if the particular ester or salt . . . has not been previously approved." AR 324 (emphasis added).

21 C.F.R. § 314.108, which was finalized in 1994, *see* 59 Fed. Reg. 50338 (Oct. 3, 1994), implements the FDCA's NCE exclusivity provisions. FDA interprets the statutory language in 21 U.S.C. § 355(j)(5)(F)(ii) & (c)(3)(E)(ii) to preclude the agency from accepting ANDAs (and 505(b)(2) applications) for drugs that contain the same active moiety as in a previously approved new chemical entity. The regulation provides:

> If a drug product that contains a new chemical entity was approved. . . in an application submitted under section [21 U.S.C. § 355(b)], no person may submit a 505(b)(2) applications or abbreviated new drug application under [21 U.S.C. § 355(j)] for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application.

21 C.F.R. § 314.108(b)(2).

FDA has 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 [21 U.S.C. § 355(b)]." 21 C.F.R. § 314.108(a). "Active moiety" in turn is defined as:

> [T]he molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

Id. "Drug product" is defined, in part, as "a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance." 21 C.F.R. § 314.3(b). "Drug substance" is defined as "an active ingredient that is intended to furnish pharmacological activity or other direct effect

in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body." *Id.*

In the preamble to what would become 21 C.F.R. § 314.108, FDA explained that after a drug product becomes eligible for 5-year NCE exclusivity, certain drug products subsequently developed that contain the same active moiety would also benefit from the original product's 5-year NCE exclusivity until the exclusivity period for the original product expired. *See* 54 Fed. Reg. 28872, 28898-28899 (July 10, 1989). Under this interpretation (known as the "umbrella policy"), 5-year NCE exclusivity does not attach only to the first approved drug product that was eligible for 5-year NCE exclusivity, but also to the line of products containing the same active moiety:

> [T]he agency interprets [5-year NCE exclusivity] to cover any subsequent approval of an application or supplemental application for a different ester, salt, or other noncovalent derivative, or a different dosage form, strength, route of administration, or new use of a drug product with the same active moiety. Any modification to the product will be protected for the period of exclusivity remaining on the original application, unless the change occurs after or toward the end of the initial 5 years of exclusivity and independently qualifies for exclusivity under another exclusivity provision.

Id.

Accordingly, under the umbrella policy, 5-year NCE exclusivity applies not just to the first approved drug product containing no previously approved active moiety, but, with some exceptions, also to any other drug product that is approved during the 5-year period that contains the same new active moiety as in the first drug product. Such a subsequent drug product will be protected for the balance of the 5-year period, which runs from the date of approval of the first approved drug product.

C. Three-Year Exclusivity

For a drug that is not eligible for 5-year NCE exclusivity, the Hatch-Waxman Amendments also provided for a 3-year period of exclusivity under certain circumstances. This type of exclusivity is available as follows:

> If an application ... for a drug which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) ... is approved ... and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) ... for such drug.

21 U.S.C. § 355(j)(5)(F)(iii); *see also* 21 U.S.C. § 355(c)(3)(E)(iii).

The first sub-clause of the eligibility clause of this provision is the mirror image of the eligibility clause of the 5-year NCE exclusivity provision. Whereas the latter applies to an application for "a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application," the 3-year exclusivity provision's eligibility clause applies to an application for "a drug which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application." Moreover, for a drug to be eligible for 3-year exclusivity, its application must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." If a drug meets these conditions and is determined to be eligible for 3-year exclusivity, the bar clause of this provision states that the Secretary "may not make approval of [a 505(b)(2) application or ANDA] for the

conditions of approval" of that drug "effective before the expiration of three years from the date of approval" of that drug.

21 C.F.R. § 314.108(b)(4) describes 3-year exclusivity as follows:

> If an application (i) [w]as submitted under section 505(b) of the act; (ii) [w]as approved after September 24, 1984; (iii) [w]as for a drug product that contains an active moiety that has been previously approved in another application under section 505(b) of the act; and (iv) contained reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application, the agency will not make effective for a period of 3 years after the date of approval of the application the approval of a 505(b)(2) application or an [ANDA] for the conditions of approval of the original application.

Like the provision implementing 5-year NCE, this provision also defines the eligibility criteria for 3-year exclusivity in terms of "a *drug product* that contains an active moiety that has been previously approved." *Id.* (emphasis added).

II. FACTUAL BACKGROUND

A. Approval of Prepopik

FDA approved Prepopik, a fixed-combination product used for cleansing the colon as a preparation for colonoscopy in adults, on July 16, 2012. FDA determined that although Prepopik contained a new active moiety, picosulfate, that had not been previously approved in any NDA prior to the approval of Prepopik, it also contained a previously-approved active moiety and thus was not eligible for 5-year NCE exclusivity. Instead, Prepopik received a 3-year exclusivity period that expired on July 16, 2015.

B. FDA's Citizen Petition Response

By letter dated February 21, 2014, FDA issued a combined response to three citizen petitions that asked FDA to change its interpretation of the 5-year NCE statutory and regulatory

provisions as they relate to fixed-dose combination drug products. *See* AR 199-216 ("FDA Resp."), attached hereto as Ex. A. FDA denied the petitions to the extent that each requested 5-year NCE for their respective products, but also issued a draft guidance for public comment that proposed the interpretation requested in the petitions. Specifically, the draft guidance set out an interpretation

> that would recognize the eligibility for 5-year NCE exclusivity of a drug substance, provided it meets the definition of a *new chemical entity* (i.e., does not contain any previously approved active moieties), regardless of whether the drug substance is first approved in a single-entity drug product or in a fixed-combination with another drug substance that does not meet the definition of *new chemical entity*.

FDA Resp. at 2. FDA explained that it was issuing the draft guidance because the governing statute and regulations were ambiguous, the petitions put forth a permissible alternative interpretation, and the policy concerns based on the evolving importance of fixed-combinations in certain critical therapeutic areas supported this alternative interpretation. *Id.*

Because the term "drug" in the relevant statutory and regulatory provisions is ambiguous (i.e., "drug" can refer to a finished drug product or an active ingredient that is a component of a finished drug product), it was left to FDA to interpret that term. FDA Resp. at 9. In the context of 5-year NCE exclusivity, FDA has interpreted "drug" in the eligibility clause narrowly to mean drug product but broadly in the bar clause to mean drug substance. *Id.* at 9-11. FDA found it appropriate to interpret the same word in two different clauses of the same statutory provision to mean different things in order to effectuate the purpose of the statute as a whole: "the Agency adopted a narrow reading of the eligibility clause to limit 5-year NCE exclusivity to only truly novel drug products (e.g., drug products that contained no previously approved active moieties), but a broad reading of the bar clause was also warranted . . . to protect those products to the

maximum extent possible so that 5-year NCE exclusivity would remain a meaningful and valuable incentive to innovate." *Id.* at 11.

FDA noted that because the word "drug" is ambiguous, it could reasonably be interpreted broadly or narrowly in either the eligibility or bar clause. FDA Resp. at 14. FDA continued that recent changes in the field of fixed-combination development and the importance of those products to key therapeutic areas warranted the agency revisiting its current interpretation, as requested by petitioners. *Id*. FDA explained, "[i]n light of these recent changes, we understand that our current interpretation of the 5-year NCE exclusivity statutory provisions may result in drug development strategies that are suboptimal from a public health perspective" in that FDA's then-current approach "may place undue importance on the order in which [] NDAs are approved." *Id.* at 15-16.

FDA issued a draft guidance because "Congress has provided the guidance process as a specific process through which FDA may adopt changes in interpretation or policy, and we believe that it is appropriate in this case to utilize the process in section 701(h) [21 U.S.C. § 371(h)] and our implementing Good Guidance Practice regulation [21 C.F.R. § 10.115] to provide for public participation." FDA Resp. at 16.[5] FDA explained that it would issue a final guidance adopting the new interpretation if the agency is convinced, after the close of the public comment period, that the new interpretation is appropriate. *Id.*

FDA declined to apply the new interpretation retroactively and recognize 5-year NCE exclusivity for petitioners' products for several reasons: 1) FDA's existing interpretation was

[5] At the time, FDA was concerned with whether it needed to undertake notice-and-comment rulemaking to change its interpretation under the then-applicable doctrine established by *Paralyzed Veterans of Am. v. D.C. Arena*, 117 F. 3d 579 (D.C. Cir. 1997). *See* AR 127-139. The Supreme Court overturned *Paralyzed Veterans* in *Perez v. Mortgage Bankers Ass'n*, 135 S. Ct. 1199, 1203 (2015).

long-standing and had been consistently applied in many prior situations involving similar facts; 2) the new interpretation represented a departure from the established interpretation and FDA wanted to avoid unnecessary disruption to regulated industry; 3) if the new interpretation were applied to products for which ANDAs had already been filed, it could impose a burden on ANDA sponsors who had relied on the existing interpretation when their ANDAs were filed; and 4) the goal of the Hatch-Waxman Amendments to foster the development of novel drugs is not furthered by granting additional exclusivity to products that have already been developed. FDA Resp. at 17. FDA thus concluded that if the new interpretation were adopted, it would be applied prospectively. *Id*. at 18.

ARGUMENT

I. Standard of Review

The usual summary judgment standard does not apply in cases involving review of final agency action under the APA "because of the limited role of a court in reviewing the administrative record." *ViroPharma, Inc. v. Hamburg*, 916 F. Supp. 2d 76, 79 (D.D.C. 2013). In such cases, "the agency resolves factual issues to arrive at a decision that is supported by the administrative record," and summary judgment is "the mechanism for deciding whether as a matter of law the agency action is supported by the administrative record and is otherwise consistent with the [Administrative Procedure Act] standard of review." *Coal. for Common Sense in Gov't Procurement v. United States*, 821 F. Supp. 2d 275, 280 (D.D.C. 2011), *aff'd*, 707 F.3d 311 (D.C. Cir. 2013); *see also Hi-Tech Pharmacal Co. v. FDA*, 587 F. Supp. 2d 13, 18 (D.D.C. 2008) (same); *Fund for Animals v. Babbitt*, 903 F. Supp. 96, 105 (D.D.C. 1995) (summary judgment is "an appropriate procedure for resolving a challenge to a federal agency's administrative decision" when, as here, "review is based upon the administrative record.") (citing

Richards v. INS, 554 F.2d 1173, 1177 (D.C. Cir. 1977)).

Under the highly deferential APA standard of review, FDA's administrative decisions may be disturbed only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A); *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971). Indeed, the agency's administrative decision is entitled to a presumption of validity. *American Wildlands v. Kempthorne*, 530 F.3d 991, 997 (D.C. Cir. 2008); *AT&T Corp. v. FCC*, 349 F.3d 692, 698 (D.C. Cir. 2003). Ferring, as "the party challenging an agency's action as arbitrary and capricious[,] bears the burden of proof." *San Luis Obispo Mothers for Peace v. NRC*, 789 F.2d 26, 37 (D.C. Cir. 1986); *see also City of Olmsted Falls v. FAA*, 292 F.3d 261, 271 (D.C. Cir. 2002). The reviewing court considers whether the agency's decision was based upon consideration of the relevant factors and whether there has been a clear error of judgment. *Overton Park*, 401 U.S. at 416. However, a reviewing court is "not empowered to substitute its judgment for that of the agency," *id.*, and must uphold the agency's action so long as it is "rational, based on consideration of the relevant factors and within the scope of the authority delegated to the agency by the statute." *Motor Vehicle Mfrs. Ass'n, Inc., v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42 (1983).

Moreover, in reviewing the FDA's interpretation of the FDCA, the Court is governed by the familiar two-step analysis of *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984). The first question under *Chevron* is "whether Congress has directly spoken to the precise question at issue." *Id.* at 842. If, after this Court "exhaust[s] the 'traditional tools of statutory construction,'" *Natural Res. Def. Council, Inc. v. Browner*, 57 F.3d 1122, 1125 (D.C. Cir. 1995) (quoting *Chevron*, 467 U.S. 837, 843 n. 9), the intent of Congress is clear, "that is the end of the matter." *Chevron*, 467 U.S. at 842. Put another way, the Court must initially decide

"whether the statute unambiguously forbids the Agency's interpretation." *Barnhart v. Walton*, 535 U.S. 212, 218 (2002).

If, however, as here, the statute "is silent or ambiguous with respect to the specific issue," the Court proceeds to the second prong of *Chevron*, under which "the question for the court is whether the agency's answer is based on a permissible construction of the statute." *Chevron*, 467 U.S. at 843. The court need not find that the agency construction was the only one it permissibly could have adopted or even the reading the court would have reached; so long as the agency's reading is permissible, it must be sustained. *See Chevron*, 467 U.S. at 843-44 & n.11; *Mylan Pharms., Inc. v. Sebelius*, 856 F. Supp. 2d 196, 208 (D.D.C. 2012). The Supreme Court has "long recognized that considerable weight should be accorded to an executive department's construction of a statutory scheme it is entrusted to administer." *United States v. Mead Corp.*, 533 U.S. 218, 227-28 (2001) (quoting *Chevron*, 467 U.S. at 844); *see also Udall v. Tallman*, 380 U.S. 1, 16 (1965); *Sara Lee Corp. v. Am. Bakers Ass'n Retirement Plan*, 512 F. Supp. 2d 32, 37 (D.D.C. 2007).

When a court is evaluating an agency's interpretation of its own regulations, the agency is entitled to "substantial deference." *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994); *United States Air Tour Ass'n v. FAA*, 298 F.3d 997, 1005 (D.C. Cir. 2002); *see also Novartis Pharms. Corp. v. Leavitt*, 435 F.3d 344, 349 (D.C. Cir. 2006) ("We have held on a number of occasions that FDA interpretations of the FDCA receive deference, as do its interpretations of its own regulations unless plainly erroneous or inconsistent with the regulations."). A court's task "is not to decide which among several competing interpretations best serves the regulatory purpose. Rather, the agency's interpretation must be given controlling weight unless it is plainly erroneous or inconsistent with the regulation." *Thomas Jefferson*

Univ., 512 U.S. at 512 (internal quotation and citation omitted). Deference is especially appropriate when the statutory and regulatory regimes implemented by the agency are complex. *See Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 766 (D.C. Cir. 2010).

II. FDA's Decision was Proper and Should be Upheld

1. FDA's Prior Approach Was Reasonable Under *Chevron*

This case turns on whether the word "drug" in the eligibility clause of 21 U.S.C. § 355(j)(5)(F)(ii) & (c)(3)(E)(ii) means "drug product" or "drug substance" – or, more precisely, whether Congress so clearly intended "drug" to mean "drug substance" in this clause that the statute unambiguously forecloses the agency's prior "drug product " interpretation. Despite Ferring's valiant attempts to convince this Court otherwise, the provision can easily be read either way. And, even though FDA now regards "drug substance" as the better interpretation, Ferring cannot plausibly argue that FDA's prior construction of the clause is not at least permissible under *Chevron* step two, much less that it is unambiguously forbidden by the plain language of the statute at *Chevron*, step one.[6]

There is no dispute that the term "drug" can and does have different meanings, depending on context. *See* Pl. Memo. at 13; *see also United States v. Generix Drug Corp.*, 460 U.S. 453, 459 (1983) (holding that 21 U.S.C. § 32l(g)(1) is "plainly broad enough to include" both "active ingredient" and "drug product"); *Pfizer, Inc. v. FDA*, 753 F. Supp. 171, 176 (D. Md. 1990) (stating that the definition of drug "covers both a finished 'drug product' and its active and inactive ingredient or ingredients."). Indeed, the FDCA explicitly defines "drug" both narrowly, to mean drug product, and broadly, to mean drug substance. 21 U.S.C. § 321(g)(1).

[6] As noted above, *see infra* note 2, Ferring did not even attempt to advance a "plain language" argument in the citizen petition it submitted to FDA. *See* AR 70-76.

In the context of 5-year NCE exclusivity, FDA previously interpreted "drug" in the eligibility clause narrowly to mean drug product but broadly in the bar clause to mean drug substance. As FDA explained in its citizen petition response:

> This approach to the definition of the term "drug" in the eligibility clause of the 5-year NCE exclusivity statutory provisions is reasonable and flows, in part, from a natural reading of the statutory language. Because the eligibility clause refers to "an application submitted under subsection (b) for a drug" and applications are generally submitted for drug products, not drug substances, a reading of "drug" as "drug product" follows logically. In addition, this reading was adopted, in part, to effectuate Congress's purpose in reserving 5-year NCE exclusivity for only the most innovative drugs.[7] In some cases, combining a new active moiety with a previously approved active moiety or moieties would not necessarily represent an innovative change. Therefore, at the time, FDA reasonably interpreted the relevant authorities such that 5-year NCE exclusivity would be available only to drug products that contained no previously approved active moiety.
>
> Moreover, when read together with the 3-year exclusivity provision, this reading of "drug" to mean "drug product" appears to cover the entire universe of drug products without any overlap. The regulation regarding 3-year exclusivity makes explicit that "drug" in the eligibility clause of the 3-year exclusivity statutory provisions refers to "drug product" not "drug substance."[8]

FDA Resp. at 10. In addition, if "drug" were interpreted to mean "drug substance" in the eligibility clause, the same drug product might be eligible for both 5-year and 3-year exclusivity, and FDA reasonably concluded that Congress intended only one exclusivity would apply to any particular drug product. *Id.* at 11.

FDA acknowledged that interpreting "drug" in the bar clause to also refer to "drug

[7] Remarks of Rep. Henry Waxman, House Floor Debate, Cong. Rec. H9113-H9114 (Sept. 6, 1984).

[8] *See* 21 C.F.R. § 314.108(b)(4) ("If an application (i) [w]as submitted under section 505(b) of the act; ... (iii) [w]as for a *drug product* that contains an active moiety that has been previously approved in another application under section 505(b) of the act ....") (emphasis added).

product" would have been the more natural reading, *see* 54 Fed. Reg. 28872 at 28897, but because such a reading would not have preserved the incentive to innovate and improve upon the initially-approved product during the exclusivity period, the agency decided not to adopt such an interpretation in the context of the umbrella policy. FDA Resp. at 11.[9] FDA explained that it "adopted a narrow reading of the eligibility clause to limit 5-year NCE exclusivity to only truly novel drug products (e.g., drug products that contained no previously approved active moieties), but a broad reading of the bar clause was also warranted, . . . to protect those products to the maximum extent possible so that 5-year NCE exclusivity would remain a meaningful and valuable incentive to innovate." *Id.*

As Ferring acknowledges, both sides agree that FDA has appropriately interpreted "drug" to mean drug substance in the bar clause. Pl. Memo. at 14. But Ferring's argument as to why "drug" cannot mean drug product in the eligibility clause is circular. Ferring contends that because FDA interprets "drug" in the bar clause to mean drug substance, the term must also have the same meaning in the eligibility clause. *Id*. at 14-15. But the very cases that Ferring cites for the notion that the same word used in the same statutory provision must have the same meaning could apply with equal force to the opposite argument: that because "drug" means drug product in the eligibility clause (i.e., the first time it appears in the provision), it must also mean drug

[9] As FDA stated in the preamble to the proposed rule that would become 21 C.F.R. § 314.108:

> [A] manufacturer of a new chemical entity ... could not make improvements in the drug, e.g., by making a new dosage form of the drug, without destroying the value of its exclusivity. Approval of a new dosage form, and certain other changes in approved drugs, require the submission of a new drug application; once approved, the new dosage form would become a new drug product that an ANDA application could copy, without being subject to the exclusivity covering the original drug product.

54 Fed. Reg. 28872 at 28897.

product in the bar clause. Indeed, as explained above, FDA noted that the most natural reading of "drug" in the bar clause is drug product, and that congressional intent rather than plain meaning urged a different interpretation. *See* FDA Resp. at 11. Ferring's brief is silent on this question that flows naturally from the argument it raises, and Ferring's circular logic based on FDA's interpretation of the second occurrence of "drug" in the provision does nothing to advance Ferring's claim that the first occurrence of "drug" unambiguously means drug substance.

Ferring misunderstands one of FDA's explanations for interpreting "drug" in the eligibility clause to mean drug product. *See* Pl. Memo. at 16-17. FDA explained, in the initial citizen petition response, *see* FDA Resp. at 10, as well as the agency's response to Ferring's request for reconsideration, *see* AR 840, that because the eligibility clause refers to "an application submitted under subsection (b) for a drug, no active ingredient . . .," and because drug applications are generally submitted for drug products rather than drug substances, interpreting "drug" to mean drug product flows logically from the text. Ferring, however, claims that FDA stated that the agency "approves only finished drug products, not active ingredients." Pl. Memo. at 16. Because Ferring misunderstands FDA's explanation on this point, the cases on which it relies are inapposite. *Id.* at 16-17.

In addition, notably absent from the various FDCA provisions that Ferring says demonstrate that FDA nearly always interprets "a drug, no active ingredient . . . of which has been approved in any other application" to mean drug substance (rather than drug product), *see* Pl. Memo at 17-19, is the introductory phrase from the provision at issue in this case, "an application submitted under subsection (b) for." But that introductory phrase indicates that the first instance of "drug" can mean drug product, as applications are (generally) submitted for drug

products, not drug substances. *See* FDA Resp. at 10. Thus the essence of Ferring's argument is that FDA sometimes interprets "drug" to mean drug product and other times to mean drug substance, a point on which FDA and Ferring agree. But this general statement lends no clarity to the question of whether "drug" in the eligibility clause means drug product or drug substance.

Ferring relies on a single case to support its argument that "[t]he fact that the term 'drug' can have multiple meanings in the statute does not convert this into a *Chevron* Step Two case." *See* Pl. Memo. at 13, n.7 (citing *Amarin Pharms. v. FDA*, (2015) (quoting *Cal. Indep. System Operator v. FERC*, 372 F.3d 395 (D.C. Cir. 2004))). But the *Cal. Indep. System Operator* decision quoted in *Amarin* does not stand for the proposition Ferring advances. Rather, the D.C. Circuit simply noted that a discussion of the reasonableness of the fit between an agency's interpretation and the statutory language is not necessarily determinative of whether a given case is appropriately decided under *Chevron* step one or two. *See Cal. Indep. System Operator*, 372 F.3d at 401. Here, the undisputed fact that the word "drug" has different meanings in different provisions of the FDCA, and that the context neither requires nor precludes either meaning, supports the conclusion that the term "drug" is ambiguous and that this case is appropriately reviewed under *Chevron* step two.

Contrary to Ferring's (unsupported) assertions, *see* Pl. Memo. at 14, it is permissible to interpret the same word to have different meanings in two different clauses of the same provision. *See, e.g.*, *Envtl. Def. v. Duke Energy Corp.*, 549 U.S. 561, 575-76 (2007) ("There is, then, no 'effectively irrebuttable' presumption that the same defined term in different provisions of the same statute must 'be interpreted identically.' Context counts.") (internal citation omitted); *Allina Health Sys. v. Sebelius*, 982 F. Supp. 2d 1, 11 (D.D.C. 2013) (same). In other words, the principle on which Ferring relies is simply that, a principle, which is rebuttable in

situations like this where congressional intent is effectuated by giving the same word different meanings. This is especially true when that word is specifically defined in the same statute to mean different things. *See* 21 U.S.C. § 321(g).

Ferring's claim that FDA's prior interpretation fails at *Chevron* step two fares no better. FDA's regulation, 21 C.F.R. § 314.108(a), is consistent with the agency's prior interpretation. FDA interpreted "drug" to mean drug product under the regulation such that a new chemical entity that is eligible for 5-year NCE exclusivity is a drug product that "contains no active moiety that has been [previously] approved." *See* FDA Resp. at 10. While acknowledging that its interpretation was not the most natural reading of the regulation, FDA adopted this interpretation, in part, to effectuate Congress' purpose in reserving 5-year NCE exclusivity for only completely innovative drugs. FDA's regulatory interpretation also found support in the 3-year exclusivity provision whereby a drug product that contained no previously approved active moiety was eligible for 5-year NCE exclusivity but a drug product that contained any previously approved active moiety was only eligible for 3-year exclusivity. As the citizen petition response explained, "FDA reasonably concluded that Congress intended for one or the other exclusivity, but not both, to apply to any given drug product approval." FDA Resp. at 11. While Ferring suggests a different interpretation of the regulation, *see* Pl. Memo. at 20-21, 23-24, Ferring wholly fails to demonstrate that FDA's interpretation is unreasonable.

Ferring's additional assertion, that FDA has offered multiple inconsistent interpretations of the 5-year NCE exclusivity provision, is flatly wrong. *See* Pl. Memo. at 22. FDA had applied its prior interpretation, that "drug" meant drug product in the eligibility clause and drug substance in the bar clause, consistently until the agency adopted the new interpretation proposed in Ferring's citizen petition. That prior interpretation was also consistent with the agency's

interpretation of 21 C.F.R. § 314.108 as it applied to fixed-combinations. Crucially, Ferring has not cited a single instance where FDA applied a different interpretation of the regulation to fixed-combinations in the more than 30 years since the enactment of the Hatch-Waxman Amendments. FDA has now, at the urging of Ferring and other parties, adopted a new interpretation but, contrary to Ferring's suggestion, that fact alone does not render FDA's prior interpretation unreasonable. Indeed, FDA issued the draft guidance before finalizing the new interpretation to provide the opportunity for public participation and advance notice of the change.

Finally, Ferring offers nothing to support its contention that FDA's prior interpretation was unreasonable beyond a general complaint that such interpretation contravened the intent behind the Hatch-Waxman Amendments and put undue importance on order of approval. *See* Pl. Memo. at 22-23, 27.[10] FDA acknowledged that its prior interpretation as applied to fixed-combinations, while reasonable at the time of the Hatch-Waxman Amendments and when articulated by FDA, was becoming outdated in light of recent scientific developments. *See* FDA Resp. at 14-16. The fact that fixed-combination therapy has recently become more important in certain disease areas (e.g., HIV) as compared with the time of the enactment of the Hatch-Waxman Amendments is one of the reasons FDA articulated for changing its interpretation. *See* FDA Resp. at 14-16. The importance of whether a single-entity product or fixed-combination product is approved first has only become clear recently as the therapeutic superiority of some

[10] Ferring relies in part on the decision in *Abbott Labs. v. Young*, 920 F.2d 984, 989 (D.C. Cir. 1990), which found that a plain language reading of the statutory language at issue placed undue significance on whether a salt or ester of an active ingredient was approved first, and served no other conceivable statutory purpose. Unlike in *Abbott*, FDA's prior interpretation of the NCE statute, as applied to fixed combinations, did serve a statutory purpose, in that it limited grants of 5-year NCE exclusivity only to products that were wholly novel, thereby rewarding the most innovative products.

fixed-combination products has come to light. Ferring has not shown, however, that this one unforeseen consequence of FDA's prior interpretation rendered that interpretation unreasonable. While Ferring may be frustrated that fixed-combination products other than Prepopik were able to make use of the agency's umbrella policy to obtain some period of exclusivity for fixed-combination products, that does not establish that the agency's previous interpretation of the statute and its own regulations was erroneous, particularly in light of the agency's well-reasoned explanations for why it consistently interpreted "drug" to mean drug product for so many years.

2. FDA's New Interpretation Need Not Apply Retroactively To Prepopik

At the time Prepopik was approved, FDA's prior interpretation was in effect. Because Prepopik contained both a previously approved active moiety and a new active moiety in the same drug product, FDA concluded that Prepopik was not eligible for 5-year NCE exclusivity. *See* FDA Resp. at 3. FDA decided to apply its new interpretation, once adopted, prospectively only, for several reasons. First, FDA's then-current interpretation was longstanding and had been applied consistently in many prior situations involving similar facts. *Id.* at 17. Second, FDA wanted to avoid any unnecessary disruption to regulated industry based on the proposed departure from an established interpretation. *Id.* Third, the new interpretation could impose an unanticipated burden on ANDA sponsors if it was applied to products for which ANDAs had already been filed at the time the new interpretation was announced. *Id.* Finally, applying the new interpretation retroactively would not advance the Hatch-Waxman Amendments' goal of encouraging the development of novel new drugs, because approved drug products have already been developed (and thus it would be impossible for additional exclusivity to incentivize their development).

Ferring's argument that FDA's new interpretation should apply retroactively to award Prepopik five instead of three years of exclusivity essentially boils down to fairness, in that Ferring did not receive the benefit of an interpretative change it helped to bring about, while companies whose products had not yet been approved at the time FDA's change in interpretation was finalized will subsequently benefit. *See* Pl. Memo at 25-29. But what would have been "fair" to Ferring would not necessarily have been fair to other affected parties and FDA appropriately took a broader view in weighing the regulatory impact of its changed interpretation on the industry as a whole. In any event, Ferring's claim that it developed Prepopik anticipating that it would receive 5-year NCE exclusivity, *see* Pl. Memo. at 5, is illogical. The interpretation in effect when Ferring was developing Prepopik meant that a new active moiety could not receive 5-year NCE exclusivity if it was approved as part of a fixed-combination with other previously-approved active moieties. Given FDA's consistent application of this interpretation, Ferring, as a member of the regulated industry, can be presumed to have been aware of this interpretation. Thus FDA's denial of 5-year NCE exclusivity for Prepopik should have come as no surprise to Ferring.

In addition, Ferring's contention that FDA's prior interpretation unreasonably treated Prepopik differently than similarly-situated products fails from the outset because the purported "similarly situated" products Ferring cites were not in fact similarly-situated to Prepopik. *See* Pl. Memo. at 25-26. Edarbyclor and Complera, fixed-combinations, benefitted from 5-year NCE exclusivity under FDA's umbrella policy, where a single-ingredient product was approved first, received 5-year NCE exclusivity, and the fixed-combinations containing that same single-ingredient also received the same 5-year NCE exclusivity upon approval. Pursuant to FDA's umbrella policy, later-approved fixed-combinations receive *the same* 5-year NCE exclusivity as

the first-approved single-ingredient product, expiring on the same date, not a separate 5-year period. So the actual length of the exclusivity period enjoyed by the fixed-combination depends on the length of time between its approval and that of the single-ingredient product. *See* FDA Resp. at 8-9. Nesina was also approved first as a single-ingredient product and then approved as a fixed-combination. Prepopik, on the other hand, was not, and could not be, approved as a single-ingredient first. Factually then, Prepopik is not "similarly situated" to the products Ferring cites as examples.

More importantly, FDA did not arbitrarily treat Prepopik differently than other fixed-combinations that received 5-year NCE exclusivity. Instead, the agency consistently applied its established interpretation of the relevant statutory provision and regulations, which resulted in Prepopik's ineligibility for 5-year NCE exclusivity. In other words, the difference in outcomes between Prepopik and the examples Ferring cites are due to factual differences between the products themselves, not FDA's disparate treatment of the products or a disparate application of the statutory and regulatory scheme. The mere fact that other fixed-combinations received 5-year NCE exclusivity while Prepopik did not does not render FDA's interpretation arbitrary, and Ferring has failed to show otherwise.

Nor has Ferring articulated any infirmity in FDA's decision to provide notice to the regulated industry before implementing a change in its long-standing interpretation. Indeed, there can be little doubt that had FDA changed a long-standing, consistently-applied agency interpretation in a way that adversely affected Ferring without providing notice and an opportunity to comment, Ferring would have challenged such change as arbitrary and capricious. Ferring's related arguments about the absence of any proven burden on industry, *see* Pl. Memo. at 28-29, does not undermine FDA's rationale at the time it issued the proposed draft guidance

and citizen petition response which appropriately took heed of the potential for such a burden. At the time FDA answered the three petitions regarding 5-year NCE exclusivity for fixed-combinations and decided to adopt a new interpretation of the relevant provisions, the fact of Prepopik's eligibility for 3-year rather than 5-year NCE exclusivity had been public knowledge for over a year. As explained previously, while 3-year exclusivity does not block the *submission* of an ANDA or 505(b)(2) application relying on the exclusivity-protected drug, 5-year NCE exclusivity does. Had FDA accepted the petitioners' invitations to apply the new interpretation retroactively to their products, any ANDA or 505(b)(2) application sponsor who may have commenced a development program relying on the fact that Prepopik was not eligible for 5-year NCE exclusivity would likely have been burdened by the change in the expected timeframe. In other words, the absence of a documented burden in the administrative record does not establish that had FDA applied its new interpretation retroactively, a burden would not have been felt. As such, FDA properly accounted for the potential burden.

Ferring's assertion that prospective application of the new interpretation should hinge on the date an ANDA was submitted rather than the date of NDA approval fares no better. As Ferring acknowledges, Pl. Memo. at 29, the exclusivity period begins on the date the NDA is approved, and thus the interpretation in effect on that date applies. Here, FDA's previous interpretation applies to Prepopik because that was the interpretation which was in effect at the time of approval, the result of which is that Prepopik is not eligible for 5-year NCE exclusivity.

FDA's decision to apply the new interpretation prospectively strikes the appropriate balance between the congressional intent of the Hatch-Waxman Amendments to encourage innovation and the interests of the parties who may be affected by the interpretive change.

Ferring has failed to demonstrate that FDA's decision is anything less than a reasoned agency decision, much less arbitrary, capricious, or otherwise contrary to law.

CONCLUSION

For the foregoing reasons, judgment should be entered in favor of the government.

Respectfully submitted,

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