DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Ave
Building 51
Silver Spring, MD 20993

FEB 2 1 2014

David M. Fox
Hogan Lovells US LLP
Columbia Square
555 13th Street, NW
Washington, DC 20004

Theodore M. Sullivan
Edward J. Allera
Buchanan Ingersoll & Rooney PC
1700 K Street, NW, Suite 300
Washington, DC 20006-3807

Joy J. Liu
Ropes & Gray LLP
One Metro Center
700 12th Street, NW, Suite 900
Washington, DC 20005-3948

Re: FDA-2013-P-0058, FDA-2013-P-0119, FDA-2013-P-0471

Dear Mr. Fox, Mr. Sullivan, Mr. Allera, and Ms. Liu,

This is a combined response to three citizen petitions (collectively, the Petitions) that ask the Food and Drug Administration (FDA or Agency) to change its interpretation of the 5-year new chemical entity (NCE) exclusivity provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the Agency's implementing regulations as they relate to fixed-dose combination drug products (fixed-combinations). In effect, the Petitions request the following:

(1) FDA should adopt a new interpretation of section 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the FD&C Act (21 U.S.C. 355(c)(3)(E)(ii) and (j)(5)(F)(ii)) and FDA's regulations implementing those provisions, such that 5-year NCE exclusivity would be available for an active moiety that was not previously approved by FDA (a new active moiety) in the following instance:

> The new active moiety is part of a drug substance that does not contain a previously approved active moiety, even when that drug substance is approved in a fixed-combination that includes another drug substance with one or more previously approved active moieties.

(2) FDA should make conforming changes to its "Exclusivity Summary" and other affected Agency documents to reflect this new interpretation.

(3) FDA should apply this new interpretation retroactively to recognize 5-year NCE exclusivity for certain of the Petitioners' previously approved products.

The Petitions were submitted on behalf of three pharmaceutical companies (Petitioners), with respect to certain previously approved new drug applications (NDAs) for fixed-combinations. Hogan Lovells, on behalf of Gilead Sciences, Inc. (Gilead), submitted a citizen petition dated January 8, 2013, requesting 5-year NCE exclusivity for cobicistat and elvitegravir, the new active moieties in the fixed-combination Stribild (cobicistat; elvitegravir; emtricitabine; tenofovir disoproxil fumarate) (NDA 203100) (FDA-2013-P-0058) (Stribild Petition). Buchanan Ingersoll & Rooney PC, on behalf of Ferring Pharmaceuticals, Inc. (Ferring), submitted a citizen petition dated January 29, 2013, requesting 5-year NCE exclusivity for picosulfate, the new active moiety in the fixed-combination Prepopik (citric acid; magnesium oxide; sodium picosulfate) (NDA 202535) (FDA-2013-P-0119) (Prepopik Petition). Finally, Ropes & Gray LLP, on behalf of Bayer HealthCare Pharmaceuticals Inc. (Bayer), submitted a citizen petition dated April 19, 2013, requesting 5-year NCE exclusivity for dienogest, the new active moiety in the fixed-combination Natazia (estradiol valerate; dienogest) (NDA 022252) (FDA-2013-P-0471) (Natazia Petition).

We have carefully considered the information submitted in the Petitions. For the reasons described below, we are denying the Petitions to the extent that they request 5-year NCE exclusivity for Stribild, Prepopik, or Natazia (or for drug substances in those products that do not contain any previously approved active moiety). At the same time, however, we conclude that the governing statute and regulations are ambiguous, and we acknowledge that Petitioners have set forth a permissible alternative interpretation of those provisions. Furthermore, we conclude that Petitioners' policy statements based on recent changes in the nature and importance of fixed-combinations in certain critical therapeutic areas lend support to their proposed interpretation. For these reasons, and as further discussed below, FDA is issuing a draft guidance[1] for public comment in which we set out an interpretation of the relevant statutory and regulatory authorities 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.*

I. BACKGROUND

A. Fixed-Combinations

Fixed-combinations are drug products that generally include two or more drug substances (active ingredients) in a fixed ratio, synthetically combined in a single dosage form. Fixed-

[1] FDA draft guidance for industry, *New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products,* available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. When final, this guidance will represent FDA's current thinking on this topic.

combinations are used in the treatment of a wide range of conditions and have the potential to offer therapeutic benefits to patients when compared to drug products that contain a single drug substance, including improved patient adherence and reduced development of drug resistance.[2] Summary descriptions of each of the fixed-combinations that are the subjects of the Petitions are provided below.

1. Stribild

Stribild is a fixed-combination consisting of four active ingredients — cobicistat, elvitegravir, emtricitabine, and tenofovir disoproxil fumarate. FDA approved Stribild on August 27, 2012, as a complete regimen for the treatment of human immunodeficiency virus (HIV)-1 infection in adults who are antiretroviral treatment-naïve. Emtricitabine and tenofovir disoproxil fumarate are both nucleoside analog HIV-1 reverse transcriptase inhibitors, and each has been previously approved in other NDAs. Elvitegravir is an HIV-1 integrase strand transfer inhibitor, which interferes with one of the enzymes that HIV needs to replicate itself.[3] Cobicistat improves the pharmacokinetic properties of elvitegravir and enables its administration to be once-daily.[4] Neither cobicistat nor elvitegravir had been approved in an application submitted under section 505(b) of the FD&C Act prior to the approval of Stribild. Gilead submitted with its NDA for Stribild an exclusivity request seeking 5-year NCE exclusivity based on the presence of at least one drug substance containing no previously approved active moiety.[5] Although Stribild would not qualify for 5-year NCE exclusivity under FDA's existing interpretation, in light of the issues raised by Gilead (and echoed in the other petitions), an exclusivity determination for Stribild was not made at the time of approval and is currently pending.

2. Prepopik

Prepopik was approved by FDA on July 16, 2012, for cleansing of the colon as a preparation for colonoscopy in adults. Prepopik contains magnesium oxide, citric acid, and sodium picosulfate. The new active moiety in Prepopik, picosulfate, a stimulant laxative, had not been previously approved in any NDA prior to the approval of Prepopik. At the time of Prepopik's approval, FDA determined, consistent with its current interpretation, that because Prepopik contained a previously approved active moiety, it was not eligible for 5-year NCE exclusivity. FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) currently indicates that Prepopik has a 3-year exclusivity period, which will expire on July 16, 2015.

3. Natazia

Natazia is an oral contraceptive approved by FDA on May 6, 2010. It contains estradiol valerate, an estrogen, and dienogest, a progestin. Estradiol was first approved in 1954 in Delestrogen (NDA 009402). Natazia is the first FDA-approved product that contains dienogest. At the time of Natazia's approval, FDA determined, consistent with its current interpretation, that because

---

[2] See Section III of this response for a more complete discussion of the policy considerations regarding fixed-combinations.

[3] Stribild Petition at 11.

[4] Id.

[5] Id. at 12.

Natazia contained a previously approved active moiety, it was not eligible for 5-year NCE exclusivity. Natazia obtained a 3-year exclusivity period, which expired on May 6, 2013. At least one abbreviated new drug application (ANDA) that references Natazia has been filed by FDA.[6]

B. Statutory, Regulatory, and Historical Background

1. New Drug Applications and Abbreviated New Drug Applications

Section 505(b) of the FD&C Act establishes the approval requirements for NDAs. To be approved, an NDA submitted under section 505(b) must, among other things, be supported by investigations showing the drug product to be safe and effective.[7] One pathway under section 505(b) of the FD&C Act provides for approval of NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference (a 505(b)(1) application or stand-alone NDA). The 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) provided an alternate pathway under subsection 505(b)(2) of the FD&C Act for approval of an NDA for which some or all of the safety and efficacy investigations relied upon for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (a 505(b)(2) application). Like a stand-alone NDA, a 505(b)(2) application is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c) of the FD&C Act.

The Hatch-Waxman Amendments also provided for submission of ANDAs for approval of generic versions of listed drugs.[8] A *listed drug* is a drug product listed in the Orange Book with an effective approval under section 505(c) of the FD&C Act.[9] A *reference listed drug* (RLD) is the listed drug identified by FDA as the drug product on which an ANDA applicant relies in seeking approval of its application.[10] 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 an RLD rather than requiring the ANDA applicant to repeat the studies conducted to support approval of the RLD. To rely on such a finding, the ANDA applicant must show that, among other things, 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 exceptions, labeling, and that its product is bioequivalent to the RLD.[11]

2. Five-Year and Three-Year Exclusivity

In addition to establishing the abbreviated drug approval pathways in section 505(b)(2) and (j) of the FD&C Act, the Hatch-Waxman Amendments provided certain incentives for NDA sponsors, including exclusivity to delay competition from ANDAs and 505(b)(2) applications if certain conditions are met. Congress recognized that periods of exclusivity would help provide

---

[6] See FDA, Paragraph IV Patent Certifications, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM293268.pdf (last visited Dec. 2, 2013).

[7] Section 505(b)(1) of the FD&C Act.

[8] Section 505(j) of the FD&C Act.

[9] 21 CFR 314.3(b).

[10] Id.

[11] Section 505(j)(2) of the FD&C Act.

incentives for drug manufacturers to engage in the generally costly and resource-intensive process of researching and developing new drugs to bring to market in the United States.[12] Thus, for the drugs it deemed most innovative, Congress provided an exclusivity period that bars submission of certain ANDAs and 505(b)(2) applications for a period of 5 years.[13] The relevant provision states:

> 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 . . . 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) of this section . . . .[14]

Thus, the statute includes clauses describing both 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" 505(b) 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."[15] This bar (i.e., 5-year NCE exclusivity) does not block the submission, review, or approval of a stand-alone NDA.

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.[16]

---

[12] See H.R. Rep. No. 98-857, Pt. I, at 15, reprinted in 1984 U.S.C.C.A.N. 2647, 2648.

[13] See, e.g., Remarks of Rep. Henry Waxman, House Floor Debate, Cong. Rec. H9113-H9114 (Sept. 6, 1984) (stating that the 5-year NCE exclusivity period is intended to encourage the drug industry to develop "new chemical entities").

[14] Section 505(j)(5)(F)(ii) of the FD&C Act; see also section 505(c)(3)(E)(ii) of the FD&C Act.

[15] Id. A 505(b)(2) application or an ANDA may be submitted after the expiration of 4 years from the date of approval if the 505(b)(2) application or ANDA contains a certification of patent invalidity or noninfringement to a patent listed for the referenced drug. This certification is also referred to as a paragraph IV certification. Section 505(j)(2)(A)(vii)(IV) of the FD&C Act; see 21 CFR 314.108(b)(2)-(3); see also section 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the FD&C Act.

[16] Section 505(j)(5)(F)(iii); see also section 505(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, under the remainder of the eligibility clause, 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."[17] 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.[18] In contrast to the bar clause of the 5-year NCE exclusivity provision, which prevents *submission* of an ANDA or 505(b)(2) application during the exclusivity period, 3-year exclusivity is a bar on ANDA or 505(b)(2) application *approval* during the relevant period. As a result, FDA can accept for filing an ANDA or 505(b)(2) application that refers to a NDA subject to 3-year exclusivity, but cannot approve such an application during the 3-year exclusivity period. Like 5-year NCE exclusivity, 3-year exclusivity does not prevent FDA from accepting, reviewing, or approving a 505(b)(1) NDA.

3. *FDA's Existing Interpretation of the Statutory Exclusivity Provisions*

After the Hatch-Waxman Amendments were enacted and before the promulgation of implementing regulations, FDA issued a series of letters to industry describing its then-current interpretations of certain statutory provisions related to ANDA and 505(b)(2) application approvals.[19] In a letter dated April 28, 1988, from the Director of FDA's Center for Drug Evaluation and Research (CDER), Dr. Carl C. Peck, M.D. (the "Peck Letter"), the Agency provided notice to industry of its interpretation of the statutory exclusivity provisions.[20] The Peck Letter summarized the statutory criteria for exclusivity, described the types of data and information the Agency intended to rely upon to make exclusivity determinations, and offered advice on how to provide such information to the reviewing Agency staff. In interpreting the eligibility clause of the 5-year NCE exclusivity provision, the Peck Letter stated that "[t]he five-year exclusivity period is available only to new chemical entities. The Agency considers a drug product eligible for the five-year period [of exclusivity] if it contains no active moiety that was previously approved by the Agency."[21] It specified that a new chemical entity is a drug product that does not contain a previously approved active moiety.[22] It further stated 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

---

[17] See id.
[18] Id.
[19] These letters, which provided informal regulatory advice to all interested sponsors, predated FDA's implementation of Good Guidance Practices (21 CFR 10.115).
[20] Letter from Carl C. Peck, M.D., Director, Center for Drug Evaluation and Research, to all NDA or ANDA Holders and Applicants (April 28, 1988) (Peck Letter), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075014.pdf.
[21] Id. at 2.
[22] Id. at 2 n.*.

been previously approved."[23] The Peck Letter thus interpreted the term "active ingredient (including any ester or salt of the active ingredient)" in the eligibility clause of the 5-year statutory 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. To assist the Agency in determining if an application meets the criteria for 5-year NCE exclusivity, the Peck Letter recommended that sponsors provide information on "[w]hether any active moiety in the drug product for which approval is sought has ever been approved in another drug product in the United States either as a single entity or as part of a combination product."[24]

Also at that time, FDA developed a checklist and decision tree entitled "Exclusivity Summary," intended to assist the review divisions within the Agency in collecting information to be used in making exclusivity determinations. Under the current version of the checklist (which remains materially unchanged in its approach to fixed combinations from when it was initially issued), if the product is a fixed-combination and if "any one of the active moieties in the drug product" has been previously approved, the questions regarding 3-year exclusivity should be answered (presumably because 5-year exclusivity is not available under these circumstances). The checklist clarifies that eligibility for 3-year exclusivity should be considered "[i]f, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety."[25]

4. Regulations Governing 5-Year and 3-Year Exclusivity

In 1989, FDA published a proposed rule interpreting and implementing the 5-year and 3-year exclusivity statutory provisions, along with other provisions of the Hatch-Waxman Amendments (Proposed Rule).[26] FDA finalized its regulations in 1994 (Final Rule) without substantive changes to the exclusivity-related provisions proposed in the Proposed Rule.[27] The regulations, as finalized, describe 5-year NCE exclusivity as follows:

> If a *drug product* that contains a *new chemical entity* was approved . . . 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 5 years from the date of approval of the first approved new drug application . . . .[28]

This provision uses several terms that are defined either in 21 CFR 314.108 or in other sections of the regulations. "Drug product" is defined, in part, as "a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance."[29] "Drug substance" is further 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

---

[23] Id. at 2.
[24] Id.
[25] See Exclusivity Checklist at 3.
[26] FDA, "Abbreviated New Drug Application Regulations," Proposed Rule, 54 FR 28872 (July 10, 1989).
[27] FDA, "Abbreviated New Drug Applications; Patent and Exclusivity Provisions," Final Rule, 59 FR 50338 (Oct. 3, 1994).
[28] 21 CFR 314.108(b)(2) (emphasis added).
[29] 21 CFR 314.3(b).

structure or any function of the human body . . . . "[30] "Active moiety" is defined as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt . . . , or other noncovalent derivative . . . of the molecule, responsible for the physiological or pharmacological action of the drug substance."[31] "New chemical entity" is defined as "a *drug* that contains no active moiety that has been [previously] approved . . ." [32] (emphasis added). Thus, the regulation describes eligibility for 5-year NCE exclusivity with reference to a drug product that contains a "drug" that "contains no active moiety that has been previously approved." In defining these terms, the regulations interpret the statutory phrase "an active ingredient (including any ester or salt of the active ingredient)" in the eligibility clause of the statute to refer to an "active moiety."[33] The preamble to the Proposed Rule further states that "[t]he Agency notes that the term "drug" is used throughout section 505 of the act. FDA interprets the term 'drug' to mean 'drug product' unless otherwise specified."[34]

In describing the 5-year bar, the regulation provides that a 505(b)(2) application or an ANDA for a "drug product that contains the same active moiety as in the new chemical entity" is blocked from approval.[35] Thus, it interprets the phrase "application . . . which refers to the drug for which the subsection (b) application was submitted" in the statutory bar clause to mean an application for a drug product that contains the same active moiety as a drug that contains no active moiety that has been previously approved.

The preamble to the Proposed Rule further elaborated on 5-year NCE exclusivity. In the preamble, the Agency 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. [36] 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. The preamble stated:

> [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.[37]

Accordingly, under the umbrella policy, 5-year NCE exclusivity will apply not just to the first approved drug product containing no previously approved active moiety, but, with some

---

[30] 21 CFR 314.3(b).
[31] 21 CFR 314.108(a).
[32] Id. (emphasis added).
[33] 59 FR 50338 at 50358 ("The agency has concluded that the term 'active ingredient,' as used in the phrase 'active ingredient (including any salt or ester of the active ingredient),' means active moiety.").
[34] 54 FR 28872 at 28877.
[35] 21 CFR 314.108(b)(2).
[36] 54 FR 28872 at 28898-28899.
[37] Id.

exceptions, also to any other drug product that contains the same new active moiety as in the first drug product, and that is approved during the 5-year period. 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.

A second provision of 21 CFR 314.108 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 . . . ."[38]

This provision also interprets the statutory phrase, "active ingredient (including any ester or salt of the active ingredient)," in the relevant eligibility clause to mean "active moiety" and defines the eligibility criteria for 3-year exclusivity in terms of "a drug product that contains an active moiety that has been previously approved." In interpreting this provision in the context of an original application, the regulation essentially repeats the statutory language that prohibits the approval of an ANDA or 505(b)(2) application "for the conditions of approval of such drug" during the exclusivity period.

II. FDA'S CURRENT INTERPRETATION OF GOVERNING STATUTE AND REGULATIONS

The term "drug" in the statute and regulations is ambiguous, and the task of interpreting it in context has been delegated to FDA.[39] Section 201(g)(1)(B)-(C) of the FD&C Act (21 U.S.C. 321(g)(1)(B)-(C)) defines the term "drug" as a finished drug product "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man" or "intended to affect the structure or any function of the body of man," but section 201(g)(1)(D) of the FD&C Act defines the term "drug" as "articles intended for use as a component" of a finished drug product. Therefore, FDA has recognized, and courts have accepted, that "drug" can be interpreted narrowly to mean "drug product" or more broadly to mean "drug substance."[40] In this context, FDA has interpreted the term "drug" in the eligibility clause of the 5-year NCE exclusivity statutory provisions narrowly to mean "drug product," not "drug substance." FDA stated that it "considers a *drug product* to be eligible for the five-year period [of exclusivity] if it contains no active moiety that was previously approved by the Agency," and "a *drug product* will . . . not be

---

[38] 21 CFR 314.108(b)(4).

[39] See, e.g., *Pharmanex v. Shalala*, 221 F.3d 1151, 1156 (10th Cir. 2000) ("[T]he term 'drug' is defined in [section 201(g) of the FD&C Act] to include both finished drug products as well as individual constituents. Thus, the definition of 'new drug' is largely colored by the ambiguity that attends the broad term 'drug.'"). See also *United States v. Sullivan*, 332 U.S. 689, 694 (1948) ("[FDA] is given rather broad discretion [in administering the FD&C Act].").

[40] See, e.g., *United States v. Generix Drug Corp.*, 460 U.S. 453, 459 (1983) (holding that section 201(g)(1) of the FD&C Act 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.").

considered a 'new chemical entity' entitled to five years of exclusivity if it contains a previously approved active moiety."[41]

After issuing the Final Rule in 1994, FDA continued to interpret the term "drug" to mean "drug product" in the definition of "new chemical entity" in 21 CFR 314.108. Thus, under FDA's current interpretation, 5-year NCE exclusivity is available for "an application submitted under section (b) for a [drug product] no [active moiety] of which has been approved in any other application under subsection (b)." Similarly, under the regulation, "drug" has been interpreted to mean "drug product" 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."[42] As the preamble to the Proposed Rule states, "[a] drug product will thus not be considered a 'new chemical entity' entitled to 5 years of exclusivity if it contains a previously approved active moiety."[43] Under this interpretation of the statute and regulations, if an active moiety that has never been previously approved is approved for the first time in an application for a fixed-combination that also includes one or more active moieties that have been previously approved, that fixed-combination is a drug product that contains a previously approved active moiety. As such, it is not eligible for 5-year NCE exclusivity, because it is not an application for a "drug [product] no [active moiety] of which has been approved in any other application under [section 505(b)]."[44, 45]

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.[46] 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."[47]

---

[41] Peck Letter, supra note 20, at 2 (emphasis added).
[42] 21 CFR 314.108(a).
[43] 54 FR 28872 at 28898.
[44] Section 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the FD&C Act.
[45] The preamble to the Proposed Rule also makes this point explicitly, albeit in the related 10-year exclusivity context (54 FR 28872 at 28898) ("A drug product is entitled to 10 years of exclusivity only if it does not contain an active moiety that has been part of a drug product previously approved under section 505(b) of the act either as a single ingredient or as one ingredient of a combination drug product.").
[46] Remarks of Rep. Henry Waxman, House Floor Debate, Cong. Rec. H9113-H9114 (Sept. 6, 1984).
[47] See 21 CFR 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).

Under FDA's current interpretation, a drug product that contains no previously approved active moiety is eligible for 5-year exclusivity, but a drug product that contains any previously approved active moiety can only be eligible for 3-year exclusivity. Given the structure of the statute, FDA reasonably concluded that Congress intended for one or the other exclusivity, but not both, to apply to any given drug product approval.

We acknowledge, however, that under the umbrella policy embodied in FDA's regulations and explained in the Proposed Rule, FDA has interpreted 5-year NCE exclusivity, once it attaches, such that it protects not only the drug product that is the subject of the application but also subsequently approved drug products that contain the same active moiety. Although FDA explicitly recognized that reading the term "drug" in the bar clause to also refer to "drug product" would have been the more natural reading, it declined to adopt this reading in the context of the umbrella policy, because such a reading would not preserve the incentive to innovate and improve upon the initially approved product during the exclusivity period.[48] Under the broad interpretation adopted by FDA, subsequently approved drug products with the same active moiety are not open to immediate generic competition until after the exclusivity for the first approved product expires.[49] Thus, if exclusivity attaches, it prevents submission of ANDAs and 505(b)(2) applications that contain the same active moiety as in the drug product for which exclusivity was received. As stated in the preamble to the Proposed Rule, if FDA had adopted the narrower interpretation, then:

> [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.[50]

It is permissible to interpret the same word in two different clauses to mean different things, and FDA found it appropriate to do so in this context to effectuate the purpose of the statute as a whole.[51] In this case, 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, as described above, to protect those products to the maximum extent possible so that 5-year NCE exclusivity would remain a meaningful and valuable incentive to innovate.

---

[48] 54 FR 28872 at 28897.

[49] See id. at 28896-28897 ("The language of the five exclusivity provisions (similarly worded in both sections 505(c)(3)(D) and 505(j)(4)(D) of the act) is inconsistent . . . , tending to support the narrower interpretation of the coverage of exclusivity for new chemical entities").

[50] Id. at 28897.

[51] See *Abbott Laboratories v. Young*, 920 F.2d 984, 987 (D.C. Cir 1990); see also *Atlantic Cleaners & Dyers, Inc. v. United States*, 286 U.S. 427, 433 (1932) ("Most words have different shades of meaning and consequently may be variously construed, not only when they occur in different statutes, but when used more than once in the same statute or even in the same section.").

III. PETITIONERS' ARGUMENTS

Petitioners present statutory, regulatory, and policy reasons that, in their view, not only justify but require a departure from FDA's current interpretation of the eligibility clause. They, too, focus on the ambiguous word "drug" in the statute and regulations, but they contend that "drug" in the 5-year NCE exclusivity context must always refer to a "drug substance" not "drug product."

Petitioners note that the relevant statutory provisions state that a "drug" qualifies 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 [previously] approved."[52] They agree that the term "drug" in the 5-year NCE exclusivity statutory provisions is ambiguous and can mean either finished "drug product" or "drug substance."[53] They further note that the statute does not plainly state whether exclusivity should be recognized as to each "drug substance" that is the subject of the 505(b) application or, in the alternative, whether it should be recognized for the "drug product" as a whole.[54]

Petitioners maintain that the ambiguous term "drug" must be interpreted to refer to a "drug substance" for several reasons.[55] Petitioners focus on the definitions of the terms "drug product," "new chemical entity," and "active moiety" in FDA's regulations. First, Petitioners note that FDA has interpreted the statutory phrase "active ingredient (including any ester or salt of the active ingredient)" to mean "active moiety," which is defined in the regulations in relation to a "drug substance" rather than a "drug product."[56] They note that under the applicable definitions, a "drug product" contains a "new chemical entity" and a "drug substance," and both "new chemical entity" and "drug substance" are defined to contain an "active moiety." Petitioners conclude that if "drug" in the new chemical entity definition meant "drug product," then the exclusivity provision, which provides for 5 years of exclusivity to "a drug product that contains a new chemical entity," would award exclusivity to a drug product that contains a "drug product that contains no active moiety that has been previously approved." Because drug products ordinarily do not contain other drug products, Petitioners conclude that 21 CFR 314.108(b)(2) must be read to mean that any drug product that contains a drug substance that contains no active moiety that has been previously approved should be eligible for 5-year NCE exclusivity.[57]

Next, they note that, in describing the extent of exclusivity, FDA's regulations and preamble attribute 5-year NCE exclusivity to the drug substance, and not the drug product. Specifically, they assert that the umbrella policy is predicated on this reading of the word "drug" in the bar clause of the statutory 5-year NCE exclusivity provision.[58] In the Petitioners' view, the word "drug" in the eligibility clause of the same provision must also mean "drug substance" because, in their view, both instances of the term "drug" in the same statutory provision must be given the same meaning.[59]

---

[52] Section 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the FD&C Act.
[53] Stribild Petition at 14, Prepopik Petition at 5, Natazia Petition at 6.
[54] Stribild Petition at 14, Natazia Petition at 6.
[55] Stribild Petition at 14-16, Natazia Petition at 6.
[56] Stribild Petition at 15.
[57] Stribild Petition at 17, Natazia Petition at 8.
[58] Stribild Petition at 15-16.
[59] Id., Natazia Petition at 6.

Petitioners also claim that the legislative history of the Hatch-Waxman Amendments supports their position that 5-year NCE exclusivity should be awarded to all drug substances containing no previously approved active moiety, whether such a drug substance was first approved in a single-entity drug product or in a fixed-combination.[60] According to Petitioners, Congress intended to reward the development and approval of new active ingredients (drug substances) with 5-year NCE exclusivity, because they require more time and resources to bring to market compared to those drug products that consist of a previously approved active ingredient.[61] Therefore, Petitioners maintain that the interpretation of "drug" in the definition of "new chemical entity" as "drug substance," not "drug product," is more consistent with Congressional intent.

Petitioners further assert that FDA's current interpretation of the provisions governing 5-year NCE exclusivity leads to illogical and arbitrary results for certain fixed-combinations, in particular, by putting undue weight on the order in which a sponsor's applications are approved in determining their eligibility for 5-year NCE exclusivity.[62] Under FDA's existing interpretation of the relevant authorities, including the Agency's umbrella policy, if a single-entity drug product containing a new active moiety was approved before a fixed-combination drug product containing the same moiety together with a previously approved moiety, both the single-entity product and the fixed-combination product would benefit from the first product's 5-year NCE exclusivity.[63] If the order of approval of these applications were to be reversed, however, neither the fixed-combination nor the single-entity drug product would be eligible for 5-year NCE exclusivity. Petitioners assert that in no other situation does the operation of 5-year NCE exclusivity hinge on such an "arbitrary" issue of sequence.[64]

In addition, Petitioners stress that timing the order of approval to preserve exclusivity may not be available in some situations, such as for a new active moiety that may not be effective or safe unless it is marketed in a fixed-combination.[65] Ferring asserts that sodium picosulfate could never have been eligible for 5-year NCE exclusivity as the sole drug substance in a single-entity drug product because Ferring could not have received approval of an application for a drug product that contained only sodium picosulfate.[66] Therefore, Ferring concludes that FDA's approach leads to inequitable exclusivity determinations for drug substances that do not contain a previously approved active moiety, and that cannot be approved in a single-entity drug product.[67]

Moreover, Petitioners claim that FDA's policy favors the development of new active moieties in single-entity drug products that are cross-labeled for use together with another drug product that contains a previously approved active moiety, as opposed to developing the new active moiety in a fixed-combination.[68] According to Petitioners, FDA's policy results in an arbitrary distinction between an active moiety specifically required in a drug's labeling to be used in combination

---

[60] Stribild Petition at 20, Prepopik Petition at 9-14, Natazia Petition at 7.
[61] Stribild Petition at 20, Prepopik Petition at 9-14, Natazia Petition at 7.
[62] Stribild Petition at 23; Prepopik Petition at 21-22; Natazia Petition at 8-9
[63] Stribild Petition at 23; Prepopik Petition at 21-22; Natazia Petition at 8-9.
[64] Stribild Petition at 23; Prepopik Petition at 21-22; Natazia Petition at 8-9.
[65] Prepopik Petition at 21.
[66] Id. at 8, 17.
[67] But Ferring does not identify any such drug substance other than sodium picosulfate.
[68] Stribild Petition at 23-24, Natazia Petition at 9.

with another drug product containing a previously approved active moiety, and those same moieties formulated together in a fixed-combination.

Petitioners conclude that FDA's current interpretation of the relevant exclusivity provisions discourages the development of new active moieties in fixed-combinations. They state that combination therapy has become the standard of care in certain therapeutic areas, such as HIV, hepatitis C virus, tuberculosis, and cancer.[69] Petitioners claim that fixed-combinations are vital for these and many other conditions, because they may improve dosing compliance and patient adherence, which are essential to improving patient outcomes.[70]

IV. AGENCY'S RESPONSE

We have carefully considered Petitioners' contentions.[71] We continue to conclude that the word "drug" is ambiguous in both the eligibility and bar clauses of the 5-year NCE exclusivity statutory provisions. We further conclude that, although FDA's current interpretation of relevant statutes and regulations is permissible, Petitioners have articulated an alternative interpretation of the relevant statute and regulations that would also be permissible. In other words, in either the eligibility or the bar clause, FDA may reasonably interpret "drug" narrowly to mean "drug product" or broadly to mean "drug substance." We further conclude that recent changes in drug development, particularly in the field of fixed-combination development in the last 20 years, and the importance of fixed-combinations to key therapeutic areas — such as HIV, cardiovascular disease, tuberculosis, and cancer — warrant revisiting our current policy. In the nearly 20 years since FDA finalized the regulations on exclusivity, the Agency has approved 19 NDAs for fixed-combinations containing at least one new active moiety. More than half of these NDAs have gained approval within the last 7 years. These numbers suggest that fixed-combinations containing new active moieties are becoming more prevalent in drug development.

Through various policies and initiatives, we have been encouraging the development of fixed-combinations. The Agency recently finalized a guidance document entitled, *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (Codevelopment Guidance).[72] The Codevelopment Guidance was developed to "assist sponsors in the codevelopment of two or more new investigational drugs," "[b]ecause existing developmental and regulatory pathways focus primarily on assessment of the safety and effectiveness of a single new investigational drug acting alone, or in combination with a previously approved drug."[73] We recognize that combination therapies are "an important treatment modality in many disease settings, including

---

[69] Stribild Petition at 8-11, Natazia Petition at 10-11.

[70] Id.

[71] Two comments were submitted to the Stribild, Prepopik, and/or Natazia dockets in support of the Petitioners' positions (which largely repeated the Petitioners' arguments). Additionally, Mylan, Inc. submitted a comment in opposition to the Petitions on December 17, 2013, more than 11 months after the Stribild Petition had been filed. Under 21 CFR 10.30, we are not required to address comments in our response to a petition. In this case, Mylan's argument appears to be based on its position that the term "drug" in the eligibility clause is not ambiguous, and can only mean "drug product." Mylan also asserts that Stribild, Prepopik, and Natazia should not be eligible for 5-year NCE exclusivity. The Agency's position on these issues is generally set forth in this section and elsewhere in this response.

[72] See FDA guidance for industry, *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf.

[73] Id. at 2.

cancer, cardiovascular disease, and infectious diseases."[74] In the Codevelopment Guidance, the Agency explains the potential therapeutic benefits of combination therapies, such as improvement in treatment response, lower risks of developing resistance, and lower rates of adverse events:

> Recent scientific advances have increased our understanding of the pathophysiological processes that underlie these and other complex diseases. This increased understanding has provided further impetus to develop new therapeutic approaches using combinations of drugs directed at multiple therapeutic targets to improve treatment response, minimize development of resistance, or minimize adverse events. In settings in which combination therapy provides significant therapeutic advantages, there is growing interest in the development of combinations of new investigational drugs.[75]

Similarly, in a guidance document on HIV treatment, the Agency has acknowledged that fixed-combinations "can simplify regimens to allow easier distribution and improved patient adherence, particularly in resource poor settings."[76] Likewise, international organizations and the U.S. medical community have similarly identified the benefits of fixed-combinations over several single-entity drug products. The World Health Organization (WHO) has associated fixed-combinations with real clinical benefits, including potential increases in efficacy and patient adherence, as well as reductions in adverse events and the development of resistance to antimicrobial treatments.[77] WHO had also listed potential cost savings and simpler distribution logistics as monetary benefits of fixed-combinations. In addition, many healthcare professionals have espoused the benefits of fixed-combinations in a wide range of therapeutic areas.[78] Most notably, for HIV treatment, fixed-combinations have become a mainstay, and have resulted in reducing pill burden and dosing frequency, which in turn increases the likelihood of adherence and improved patient outcomes.[79]

In 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. For example, we agree with Petitioners that sponsors may prefer to submit two NDAs (one for a single-entity drug product containing only the new active moiety, and another one for a fixed-combination containing the same active moiety, along with others that were previously approved) and our current approach may place undue importance on

---

[74] Id.

[75] Id.

[76] FDA guidance for industry, *Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV* at 6 (October 2006), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079742.pdf.

[77] See, e.g., World Health Organization, *Adherence to Long-Term Therapies. Evidence for Action* (2003), available at http://www.who.int/chp/knowledge/publications/adherence_report/en/; J. Connor, *Effect of Fixed-Dose Combination (FDC) Medications on Adherence and Treatment Outcomes* (2003), available at http://whqlibdoc.who.int/publications/2003/a86263_part7.pdf.

[78] See, e.g., S. Bangalore, G. Kamalakkannan, S. Parkar, and F. Messerli, *Fixed-Dose Combinations Improve Medication Compliance: A Meta-Analysis,* 120 Am. J. of Medicine 713 (2007); A. M. L. Anderson and J. L. Lennox, *Abacavir/Lamivudine Fixed Dose Combination in the Treatment of Patients With HIV Infection*, 3 Future Medicine 19 (2009); C. Cheong, J. C. Barner, K. A. Lawson, and M. T. Johnsrud, *Patient Adherence and Reimbursement Amount for Antidiabetic Fixed-Dose Combination Products Compared with Dual Therapy Among Texas Medicaid Recipients*, 30 Clin. Therapeutics 1893 (2008).

[79] See T. L. Kauf, K. L. Davis, S. R. Earnshaw, and E. A. Davis, *Spillover Adherence Effects of Fixed-Dose Combination HIV Therapy,* 6 Patient Preference and Adherence 155 (2012).

the order in which these two NDAs are approved.[80] We also acknowledge that, in some situations, such a strategy may not be available if a new active moiety does not clinically lend itself to approval in a single-entity drug product. Finally, we recognize that, in certain instances, it may be preferable to develop a fixed-combination instead of developing a drug product with a single new active moiety, cross-labeled for use together with one or more other drug product(s).

We therefore agree that the increasing importance of fixed-combinations for certain therapeutic areas means that it would be in the interest of public health to encourage the development of fixed-combinations as a policy matter. One way to accomplish this goal would be to adopt a new interpretation of the relevant statutory and regulatory authorities that would encourage the development of fixed-combinations that contain novel drug substances (i.e., those that contain no previously approved active moieties), irrespective of whether the fixed-combination also includes a drug substance that contains a previously approved active moiety or moieties.

The FD&C Act provides FDA with explicit authority to "develop guidance documents . . . [that] present the views of [FDA] on matters under the jurisdiction of [FDA],"[81] and specifies further that for "guidance documents that set forth initial interpretations of a statute or regulation, changes in interpretation or policy that are of more than a minor nature," among others, FDA "shall ensure public participation."[82] Thus, 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) and our implementing Good Guidance Practice regulation[83] to provide for public participation.[84]

Accordingly, we are issuing draft guidance[85] proposing and seeking public comment on an interpretation that would recognize 5-year NCE exclusivity for a drug substance that does not contain a previously approved active moiety, even where such a drug substance is approved in a fixed-combination with another drug substance that contains at least one previously approved active moiety. If at the conclusion of the comment period we are convinced that our proposed new interpretation is appropriate, we will issue a final guidance adopting the new interpretation.

---

[80] For example, the anti-HIV-1 drug product Complera (NDA 202123), a fixed-combination containing rilpivirine hydrochloride in combination with two previously approved active moieties benefited from FDA's umbrella policy for Edurant, the single-ingredient drug product containing the new active moiety rilpivirine hydrochloride. See Prepopik Petition at 22. Edurant was approved on May 20, 2011, several months before FDA approved Complera on August 10, 2011. Edurant was eligible for 5-year NCE exclusivity because it did not contain a previously approved active moiety. Complera was able to benefit from Edurant's exclusivity under FDA's umbrella policy. If the approvals had occurred in the reverse order, however, neither Complera nor Edurant would have been eligible for 5-year NCE exclusivity.

[81] Section 701(h)(1)(A) of the FD&C Act (21 U.S.C. 371(h)(1)(A)).

[82] Section 701(h)(1)(C) of the FD&C Act (21 U.S.C. 371(h)(1)(C)) (emphasis added).

[83] See 21 CFR 10.115.

[84] Because we conclude that the Administrative Procedure Act does not require FDA to engage in notice and comment rulemaking before we can adopt a new interpretation of the relevant authorities, we need not address Petitioners' comments on this point.

[85] FDA draft guidance for industry, *New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products,* available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. When final, this guidance will represent FDA's current thinking on this topic.

Petitioners also have requested that we recognize 5-year NCE exclusivity for cobicistat, elvitegravir, picosulfate, and dienogest. After careful consideration, we decline to recognize 5-year NCE exclusivity for these active moieties in this situation.

Exclusivity runs from the date of approval of a drug product. At the time of approval of the drug products at issue here (i.e., Stribild, Natazia, and Prepopik), our existing interpretation of the relevant statutory and regulatory provisions was in effect. We have decided not to recognize 5-year NCE exclusivity based on our new interpretation of these provisions, which we had not announced prior to the approval of these products. We based this conclusion on numerous factors, including those discussed below.

First, although the relevant statutory and regulatory provisions are ambiguous, our existing interpretation of these provisions is longstanding and has been consistently applied in many prior cases presenting similar facts. Second, the new interpretation we are proposing represents a departure from our past interpretation, and we wish to avoid any unnecessary disruption to regulated industry. Third, 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.

In addition, we do not believe that applying our new interpretation to the Petitioners' products would advance the goals of the Hatch-Waxman Amendments. Although we recognize that the Hatch-Waxman Amendments contain incentives to reward the development and approval of novel drugs, these particular products already have been developed and approved. Recognizing additional exclusivity in this case is not necessary to encourage the *development* of novel drugs. We believe that changing our interpretation going forward will foster Congress's goal of encouraging the development and approval of novel drugs.

We believe that this outcome strikes the appropriate balance among the congressional intent of the Hatch-Waxman Amendments and the interests of the parties who may be affected by our decision.[86]

V. CONCLUSION

The relevant statutory and regulatory provisions are ambiguous, and our existing interpretation of these terms with respect to the eligibility of fixed-combinations for 5-year NCE exclusivity is permissible.

At the same time, we recognize that Petitioners have suggested an alternative interpretation of the relevant authorities that is also permissible. Moreover, we agree that the interpretation suggested by Petitioners is desirable as a matter of policy. Therefore, we are issuing a draft guidance document in which we announce a change in our interpretation of the 5-year NCE exclusivity provisions of the FD&C Act and implementing regulations. Under the new interpretation, 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.

---

[86] See, e.g., *Retail, Wholesale & Department Store Union v. NLRB*, 466 F.2d 380, 390 (1972).

If the new interpretation is adopted, the Agency intends to apply the new interpretation prospectively. Accordingly, we conclude that Stribild, Prepopik, and Natazia are not eligible for 5-year NCE exclusivity. In addition, we will not make any changes to the Exclusivity Summary or any other relevant Agency documents or policies at this time. If, after considering any comments, the draft guidance is finalized such that FDA adopts the proposed new interpretation of the statute and regulations, the Agency intends to make any necessary conforming changes to any relevant documents at that time.

For these reasons, your Petitions are denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research