DEPARTMENT OF HEALTH & HUMAN SERVICES

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Re: Docket Nos. FDA-2013-P-0058 and FDA-2013-P-0119

Dear Mr. Fox and Mr. Allera:

This is a combined response to two petitions for reconsideration (Reconsideration Petitions) dated March 21, 2014, received by the Food and Drug Administration (FDA or the Agency), submitted by Hogan Lovells US LLP, on behalf of petitioner Gilead Sciences, Inc. (Gilead) (Gilead Reconsideration Petition, FDA-2013-P-0058),[1] and by Buchanan Ingersoll & Rooney PC, on behalf of Ferring Pharmaceuticals, Inc. (Ferring) (Ferring Reconsideration Petition, FDA-2013-P-0119).[2] In 2013, Gilead had originally petitioned FDA to recognize 5-year new chemical entity (NCE) exclusivity for Stribild (new drug application (NDA) 203100) because Stribild is a fixed-dose combination drug product (fixed-combination) that contains cobicistat and elvitegravir, both of which were previously unapproved active moieties (new active moieties) at the time of Stribild's approval.[3] After Gilead's petition was filed, Ferring put forth a similar contention for its fixed-combination Prepopik (NDA 202535), that contains picosulfate, which was a new active moiety at the time of approval.[4]

Both original petitions (2013 Petitions) asserted that the Agency's longstanding interpretation of the relevant statutory and regulatory provisions was erroneous, notwithstanding the fact that, for over 25 years, FDA had consistently applied that interpretation to determine that certain fixed-combinations such as Stribild and Prepopik would be ineligible for 5-year NCE exclusivity. Gilead also proposed a new interpretation under which Stribild would be eligible for 5-year NCE exclusivity.

[1] The Gilead Reconsideration Petition was received by the Agency on March 24, 2014, and filed on March 25, 2014.

[2] The Ferring Reconsideration Petition was received by the Agency on March 21, 2014, and filed on March 24, 2014.

[3] Stribild also contains two previously approved active moieties.

[4] Picosulfate is present in Prepopik as sodium picosulfate. Prepopik also contains two previously approved active moieties.

In its original response to Ferring and Gilead (collectively referred to as Petitioners) dated February 21, 2014[5] (Original Response), the Agency agreed that the proposed interpretation would be legally permissible. At the same time, FDA disagreed with Petitioners that FDA's longstanding interpretation was impermissible, and denied the Petitioners' requests. FDA also issued a draft guidance for industry titled *New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products* (Exclusivity Guidance). The draft Exclusivity Guidance proposed to adopt a new interpretation of the relevant statutory and regulatory provisions, under which certain fixed-combination products (such as Stribild and Prepopik) would be eligible for 5-year NCE exclusivity. The draft guidance stated that FDA would apply the new interpretation prospectively, starting on the date that the Agency finalized the Exclusivity Guidance.

Petitioners request FDA to reconsider its denial of the 2013 Petitions and to recognize 5-year NCE exclusivity for Stribild and Prepopik. Ferring also requests that FDA stay application of the Exclusivity Guidance, until the issues raised in the Reconsideration Petitions are resolved. Ferring submitted a supplement to the Ferring Reconsideration Petition on May 29, 2014 (Ferring Supplement) with additional information to support its request for reconsideration.

We have carefully considered the assertions presented in the Reconsideration Petitions and the Ferring Supplement. For the reasons discussed below, we conclude that Petitioners have not satisfied the requirements for reconsideration under § 10.33 (21 CFR 10.33), and therefore, the Reconsideration Petitions are denied. Ferring's request for stay of action is also denied. Simultaneously with this response, the Agency will issue the Exclusivity Guidance in final form[6] and apply its new interpretation of the relevant statutory and regulatory provisions to fixed-combinations approved from this day forward.

I. BACKGROUND

Gilead and Ferring submitted the Reconsideration Petitions after the Agency denied citizen petitions submitted separately by Gilead and Ferring in 2013[7] (Gilead Petition[8] and Ferring Petition,[9] respectively), each of which asked FDA to recognize 5-year NCE exclusivity for a new

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[5] See February 21, 2014, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research (CDER), to David M. Fox, Theodore M. Sullivan, Edward J. Allera, and Joy J. Liu, Docket Nos. FDA-2013-P-0058, FDA-2013-P-0119, and FDA-2013-P-0471.

[6] FDA, Guidance for Industry, New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM386685.pdf.

[7] Ropes & Gray LLP, on behalf of Bayer HealthCare Pharmaceuticals Inc. (Bayer), also 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). Bayer has not filed a petition for reconsideration.

[8] See Docket No. FDA-2013-P-0058. The Gilead Reconsideration Petition was submitted to this docket and retains the same docket number.

[9] See Docket No. FDA-2013-P-0119. The Ferring Reconsideration Petition was submitted to this docket and retains the same docket number.

active moiety in a fixed-combination with at least one previously approved active moiety.[10] Specifically, Gilead requested that FDA recognize the eligibility for 5-year NCE exclusivity of Stribild because it contains cobicistat and elvitegravir, both of which were new active moieties. Stribild is an anti-HIV fixed-combination that also contains two previously approved active moieties, emtricitabine and tenofovir disoproxil fumerate. In its petition dated January 29, 2013, Ferring requested that FDA recognize eligibility for 5-year NCE exclusivity for Prepopik, which contained the new active moiety picosulfate. Prepopik, indicated for cleansing of the colon as a preparation for colonoscopy in adults, also contains two previously approved active moieties, citric acid and magnesium oxide.

To support its request, Gilead proposed an alternative interpretation of the 5-year NCE exclusivity provisions in section 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 355(c)(3)(E)(ii) and (j)(5)(F)(ii)) and the implementing regulations (5-year NCE exclusivity provisions). Under this proposed interpretation, in contrast to the result under FDA's longstanding, historical interpretation and application of these provisions, a fixed-combination would be eligible for 5-year exclusivity upon approval if it contained any drug substance that contained no previously approved active moiety. This alternative interpretation was based on a new reading of the term *drug* in the "eligibility clause"[11] of the 5-year NCE exclusivity provisions, and in the regulatory definition of *new chemical entity*. FDA has historically and consistently[12] interpreted *drug* to mean *drug product* in this context. Petitioners asserted that the Agency should have interpreted *drug* to mean *drug substance* instead.

As we stated in both the Original Response and the draft Exclusivity Guidance, we disagreed with Petitioners that the term *drug* can only mean *drug substance* in the 5-year NCE exclusivity eligibility context. We concluded that the Agency's historical interpretation of the 5-year NCE exclusivity provisions is legally permissible, in that the term *drug* is ambiguous and can reasonably be interpreted to mean either *drug product* or *drug substance*. We agreed that the Petitioners' alternative interpretation was also legally permissible, given the ambiguity inherent

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[10] Petitioners also asked FDA to make any necessary changes to FDA's policy documents to reflect an interpretation of the applicable statute and regulations that recognize 5-year exclusivity for previously unapproved active moieties, whether first approved as single-agent drug products or fixed-combinations with at least one previously approved active moiety.

[11] As explained in the Original Response, the "eligibility clause" describes the types of applications that may be eligible for 5-year NCE exclusivity. See Original Response at 5 ("[u]nder 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"); see also section 505(j)(5)(F)(ii) and 505(c)(3)(E)(ii) of the FD&C Act.

[12] In 1988, the Agency announced its policy that FDA "consider[ed] 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 considered a 'new chemical entity' entitled to five years of exclusivity if it contains a previously approved active moiety." 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) at 2 (emphasis added), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075014.pdf. The Agency's regulation at § 314.108 (21 CFR 314.108) was interpreted to be consistent with the Peck Letter, in that if a drug product contained no previously approved active moiety, then the drug product would be eligible for 5-year NCE exclusivity.

in the term *drug*. We further acknowledged that the Petitioners' alternative permissible interpretation was consistent with FDA's public health goals and may be preferable because of the increasing importance of fixed-combinations to treat serious diseases and conditions and the Agency's recently expressed interest in encouraging their development.[13] Moreover, the proposed interpretation would not have availability of 5-year NCE exclusivity turn on the type of product in which a new active moiety was first approved.[14] Accordingly, in the Original Response, we announced our issuance of the draft Exclusivity Guidance, in which we proposed to adopt the Petitioners' permissible interpretation of the term *drug* in the eligibility clause of the statutory provisions and in the regulatory definition of *new chemical entity* to mean *drug substance*. Under this interpretation, a drug substance that contained no previously approved active moiety would meet the regulatory definition of *new chemical entity*, even if it were approved in a fixed-combination with a drug substance that contained a previously approved active moiety. Such a fixed-combination would therefore be eligible for 5-year NCE exclusivity, even though it would not have been eligible under the Agency's historical interpretation of the term *drug*. Accordingly, FDA would examine each drug substance in a fixed-combination separately to assess whether it contained a previously approved active moiety. If it did not, then that drug substance (and the fixed-combination) would be eligible for 5-year NCE exclusivity.

Because this new interpretation of the 5-year NCE exclusivity provisions and our implementing regulations constituted a change from our longstanding, consistent interpretation, we issued a draft version of the Exclusivity Guidance proposing and seeking public comment on the new interpretation.[15] At the same time, because we determined that our historical interpretation was permissible and consistently applied, in order not to upset settled expectations, we announced that the new interpretation would be applied prospectively and only after the Exclusivity Guidance was published in final form.[16] As we explained:[17]

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[13] Specifically, in the Original Response, we acknowledged the importance of fixed-combinations in simplifying treatment regimens for certain diseases, which can improve patient compliance and outcomes (Original Response at 15). We also stated that the Agency has been developing policies to encourage the development of fixed-combinations, particularly for complex diseases such as the treatment of the human immunodeficiency virus (HIV) (Original Response at 14-15) We also recognized that the Agency's interpretation of "drug" in the eligibility clause to mean drug product and in the bar clause to mean drug substance may inadvertently encourage suboptimal drug development strategies, such as submission of two separate NDAs (one for a new active moiety and one for a previously approved one) and cross-labeling the new active moiety with a previously approved drug when the fixed-combination would be preferable (Original Response at 15).

[14] See Original Response at 8. Under the FDA's "umbrella policy," if an active moiety is eligible for 5-year NCE exclusivity, then "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." (FDA, "Abbreviated New Drug Application Regulations," Proposed Rule, 54 FR 28872 28898-28899 (July 10, 1989)). Thus, under FDA's previous interpretation, if a single-entity drug product containing a new active moiety was approved before a fixed-combination containing the same moiety together with a previously approved moiety, both the single-entity product and the fixed-combination product would, under the Agency's "umbrella policy" for exclusivity, benefit from the first product's 5-year NCE exclusivity. 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.

[15] Original Response at 16.

[16] Id. at 16-17.

[17] Id. at 17.

> 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 [abbreviated new drug applications] already have been filed, it could impose a burden on the ANDA sponsors, who relied on our existing interpretation in filing their applications.
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> 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.

In light of these factors, we concluded that fixed-combinations (such as Stribild and Prepopik) approved before finalizing the Exclusivity Guidance would be subject to the Agency's historical interpretation because that was the interpretation in effect at the time of their approval. In the Reconsideration Petitions, Petitioners assert that the factors that the Agency cited for applying the new interpretation prospectively do not apply to Stribild and Prepopik. Petitioners thus take the position that the Agency did not need to finalize the Exclusivity Guidance before applying it to Stribild and Prepopik.[18] Furthermore, Ferring claims that the Agency should stay application of the Exclusivity Guidance until the issues in the Ferring Reconsideration Petition have been resolved.[19]

II. REGULATORY REQUIREMENTS

The Commissioner may grant a petition for reconsideration if the Commissioner determines the petition to be in the public interest and in the interest of justice.[20] In addition, the Commissioner will grant a petition for reconsideration if the Commissioner determines that *all* of the following apply:[21]

(1) The petition demonstrates that relevant information or views contained in the administrative record were not previously or adequately considered.
(2) The petitioner's position is not frivolous and is being pursued in good faith.
(3) The petitioner has demonstrated sound public policy grounds supporting reconsideration.
(4) Reconsideration is not outweighed by public health or other public interests.

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[18] Gilead Reconsideration Petition at 3; Ferring Reconsideration Petition at 3-4, 7-8.

[19] Ferring Reconsideration Petition at 1-3, 8.

[20] 21 CFR 10.33(d).

[21] Id.

In addition, a petition for reconsideration may not be based on information and views not contained in the administrative record on which the original decision was made (§ 10.33(e)).

Similarly, the Commissioner will grant a stay if all of the following apply:[22]

(1) The petitioner will otherwise suffer irreparable injury.
(2) The petitioner's case is not frivolous and is being pursued in good faith.
(3) The petitioner has demonstrated sound public policy grounds supporting the stay.
(4) The delay resulting from the stay is not outweighed by public health or other public interests.

III. PETITIONERS' ASSERTIONS IN THE RECONSIDERATION PETITIONS

A. Reconsideration

Petitioners claim that they satisfy the regulatory standards for reconsideration in § 10.33. If, however, FDA determines that the criteria for reconsideration are not satisfied, Petitioners urge FDA to grant the Reconsideration Petitions in the public interest or interest of justice for the same reasons.

First, both Gilead and Ferring claim that FDA did not previously or adequately consider relevant information or views in the administrative record. Specifically, Gilead asserts that the general factors that FDA cited to support its decision not to recognize 5-year NCE exclusivity for cobicistat and elvitegravir are not relevant to the facts surrounding Stribild,[23] and claims that this lack of relevance suggests that FDA did not adequately consider the relevant information or views in the administrative record.[24] Gilead further states that the date of approval is not the controlling date for determining Stribild's exclusivity.[25] Rather, Gilead maintains that because the Agency deferred the exclusivity determination for Stribild (in light of Gilead's request for 5-year NCE exclusivity in its NDA and the Gilead Petition), exclusivity remained undetermined for Stribild, and in fact could have been determined when the Original Response issued.[26] Gilead also asserts that it developed the new active moieties in Stribild with the expectation that Stribild would receive 5-year exclusivity.[27]

Although Gilead agrees with FDA that the term *drug* is ambiguous in the 5-year NCE exclusivity statutory provisions, it appears to assert that the Agency's broad interpretation of *drug* in the bar clause of the statute must control its narrower interpretation of the same term in the eligibility clause.[28] Gilead claims that the Agency recognized this contention, but offered no response in the Original Response. Gilead thus reiterates that the regulatory provision, which protects new

[22] 21 CFR 10.35(e).

[23] Gilead Reconsideration Petition at 6, 11.

[24] Id. at 11.

[25] Id. at 6.

[26] Id. at 6-7.

[27] Id. at 8.

[28] Id. at 8-10.

chemical entities, bars an applicant with a 505(b)(2) NDA or an ANDA from submitting an application for 5 years from the date of approval of "a drug product that contains a new chemical entity . . ."[29] In Gilead's view, the Agency's historical and consistent interpretation where FDA interpreted *drug* narrowly to determine the eligibility of fixed-combinations for 5-year NCE exclusivity is incorrect because the Agency simultaneously interpreted *drug* broadly to determine the scope of that exclusivity.

Both Gilead and Ferring claim that FDA did not adequately consider the particular facts regarding their drugs and any possible reliance by ANDA and 505(b)(2) applicants or application holders on the Agency's historical interpretation. Petitioners state that to their knowledge, FDA had not filed any ANDAs or 505(b)(2) NDAs that cite Stribild or Prepopik as the listed drug at the time of the Original Response.[30] They maintain that there are no holders of approved ANDAs (or 505(b)(2) NDAs) that relied on FDA's historical interpretation to submit such applications that reference their drugs. Furthermore, Gilead claims that industry has been on notice of the exclusivity issues since mid-September 2012, when FDA listed Stribild in the *Approved Drug Products With Therapeutic Equivalence Evaluations* (Orange Book) without an exclusivity determination.[31] Similarly, Ferring states that stakeholders have been on notice of the exclusivity issues for Prepopik since the company filed the Ferring Petition.[32] Thus, Petitioners assert that industry's expectations would not be disrupted if the new interpretation is applied to Stribild and Prepopik.[33]

Both Gilead and Ferring assert that the Agency did not adequately consider Congressional intent of the Hatch-Waxman Amendments.[34] Gilead asserts that the application of the new policy would in fact further the goals of these Amendments because Stribild, as a fixed-combination, "would be more beneficial to patients and scientifically feasible" than single active ingredient drug products containing cobicistat or elvitegravir.[35] Ferring goes further by asserting that FDA's historical interpretation was inconsistent with the Hatch-Waxman Amendments,[36] and that Congress intended to reward manufacturers of all novel active moieties, including those contained in certain fixed-combinations, with 5-year exclusivity.[37]

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[29] Id. at 9-10.

[30] Id. at 2, 6; Ferring Reconsideration Petition at 10, 21.

[31] Gilead Reconsideration Petition at 7.

[32] Ferring Reconsideration Petition at 21.

[33] Ferring also submitted a supplement in which it claims that at the time the Original Response had issued, only Bayer's Natazia had been the subject of a paragraph IV notification, indicating that an ANDA had been filed that referenced Natazia (Ferring Supplement at 2). Ferring states that Bayer sued the ANDA applicant, Lupin Pharmaceuticals (Lupin), for patent infringement of U.S. Patent No. 8,071,577 ('577 Patent) after Lupin submitted a paragraph IV certification for that patent. According to Ferring, the parties settled their patent infringement case, and Lupin changed its paragraph IV certification to a paragraph III certification, suggesting that Lupin is seeking approval of its ANDA upon the expiration of the '577 Patent. Therefore, Ferring asserts that FDA's concerns that applying the new interpretation to Stribild, Prepopik, and Natazia would cause undue hardship on existing ANDA sponsors are no longer valid, and that these three drugs should benefit from the new policy.

[34] Gilead Reconsideration Petition at 8; Ferring Reconsideration Petition at 9, 15-20.

[35] Gilead Reconsideration Petition at 8.

[36] Ferring Reconsideration Petition at 9, 15-20.

[37] Id. at 9.

To further support its contention that the Agency did not adequately consider relevant information in the administrative record, Ferring asserts that the Agency failed to address the inconsistencies in applying the exclusivity period for fixed-combinations attributable in part to FDA's umbrella policy.[38] Ferring claims that FDA recognized the importance of creating incentives to innovate and seek approval for new active moieties, while at the same time defending a policy that denied 5-year exclusivity for products containing new active moieties, such as Prepopik.[39]

Petitioners also contend that the Reconsideration Petitions are not frivolous and are being submitted in good faith. They assert that the only point of disagreement between the Agency's change in policy regarding 5-year NCE exclusivity and the proposal they offered in their 2013 Petitions is the temporal application of this new policy to Stribild and Prepopik.[40] Petitioners also attempt to invoke the "good faith" clause in § 10.33(d)(2) by restating their positions that the term drug should have the same meaning in both the eligibility clause and the bar clause of the 5-year NCE statutory exclusivity provision,[41] and note that the Agency has interpreted the latter to refer to drug substance. They maintain that this reading predated the Original Response,[42] and thus, 5-year NCE exclusivity should be available for a "drug substance" no active ingredient for which has been approved by the Agency.

To further support its claim that its reconsideration petition was submitted in good faith, Ferring contends that FDA's issuance of its Exclusivity Guidance is "legally incorrect" and that the Agency should have "regulated directly from the statute."[43] The company disagrees with FDA's approach to issuing guidance because guidances are not binding, do not create or confer rights, are intended to help industry carry out its obligations, and may be deviated from in appropriate circumstances.[44] According to Ferring, FDA's change in interpretation is meant to be binding, creates rights, is meant to help FDA (not industry) carry out its obligation, and cannot be departed from by FDA reviewers.[45] Instead, Ferring asserts that FDA should regulate directly from the FD&C Act, and cites precedent for which Ferring claims FDA regulated directly from the FD&C Act for exclusivity determinations.[46] Finally, if the Exclusivity Guidance is found to be legally supportable, Ferring claims that FDA should have issued it as a Level 1[47] guidance

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[38] Id. at 11-15.

[39] Id. at 12.

[40] Gilead Reconsideration Petition at 11; Ferring Reconsideration Petition at 8.

[41] Gilead Reconsideration Petition at 9; Ferring Reconsideration Petition at 6.

[42] Gilead Reconsideration Petition at 8-9.

[43] Ferring Reconsideration Petition at 23-24, 32-34.

[44] Id. at 23, 25-29.

[45] Id.

[46] Id. at 32-34.

[47] Ferring refers to the Exclusivity Guidance as "Class 1" guidance. We understand "Class 1" guidance to mean Level 1 guidance as that term is defined in our regulations. 21 CFR 10.115(c)(1).

with immediate implementation that should apply to Prepopik because it is in the best interest of public health.[48]

Finally, Petitioners contend that not only are there are sound public policy reasons for reconsideration, but also that reconsideration is not outweighed by public health or other public interests. They assert that while FDA recognized in the Original Response that public policy supported the Petitioners' interpretation of 5-year NCE exclusivity because the Agency wants to develop policies that encourage the development of fixed-combinations, particularly those containing novel ingredients,[49] the Agency's current position may discourage participation in the public process to improve policy because petitioners may not benefit from their attempts to change policy.[50] Petitioners assert that, in fact, their interpretation more closely aligns with the Agency's public health goals, such as encouraging the development of fixed-combinations.[51]

B. Stay of the New Policy in the Exclusivity Guidance

Ferring also requests that the Agency stay application of the new policy in the Exclusivity Guidance until the issues in the Ferring Reconsideration Petition are addressed. Ferring asserts that policy grounds support the stay, because Ferring will otherwise suffer irreparable injury if the stay is not granted.[52] Ferring states that failure to grant its Reconsideration Petition and the stay would limit the exclusivity for Prepopik to 3 years, instead of 5 years, causing irreparable harm because FDA could approve generic versions of Prepopik earlier.[53]

IV. DISCUSSION

For the reasons discussed below, we conclude that Petitioners have not satisfied the criteria for reconsideration or, in Ferring's case, for a stay. Furthermore, we are not convinced that the Reconsideration Petitions must be granted to serve the public interest or the interest of justice. Therefore, we are denying the Reconsideration Petitions in their entirety.

A. Petitioners Have Not Satisfied The Criteria For Granting Their Reconsideration Petitions.

We have reviewed the information submitted in support of the 2013 Petitions, the Original Response, and the Reconsideration Petitions. We conclude that the relevant information and views in the administrative record were adequately considered when we denied the 2013 Petitions. We also conclude that Petitioners have not demonstrated sound public policy grounds supporting reconsideration. Because all four requirements in 10.33(d) must be satisfied to grant such petitions, and all four reasons must be satisfied to grant a stay under § 10.35(e) (21 CFR 10.35(e)), we deny the Reconsideration Petitions.

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[48] Ferring Reconsideration Petition at 36-39.

[49] Gilead Reconsideration Petition at 11; Ferring Reconsideration Petition at 3, 12.

[50] Gilead Reconsideration Petition at 11; Ferring Reconsideration Petition at 20.

[51] Gilead Reconsideration Petition at 11; Ferring Reconsideration Petition at 19, 38.

[52] Ferring Reconsideration Petition at 8, 22.

[53] Id. at 8, 22.

First, with respect to Gilead's assertions, the contention that "the date of approval is not the relevant date for Stribild"[54] because FDA did not immediately announce an exclusivity determination for Stribild is unavailing. We thus reject Gilead's contention that the Original Response did not adequately consider whether Gilead's proposed new interpretation could apply to Stribild. We reiterate our conclusion in the Original Response that exclusivity runs from the date of approval of a drug product.[55] At the time of Stribild's approval, our historical interpretation was in effect. We determined that because FDA's historical interpretation was not impermissible, that interpretation applied to Stribild at the time of approval regardless of whether FDA had made an exclusivity determination for Stribild at that time. Gilead alludes to "numerous" instances where the Agency applied an exclusivity decision to a product that had been approved prior to the decision. The single case Gilead cites in support of this proposition is inapplicable here.[56] In that case, no existing, longstanding, and consistently applied interpretation was in effect for that product at the time of that product's approval. In contrast, FDA had a longstanding, historical interpretation with respect to 5-year NCE exclusivity for fixed-combinations, such as Stribild. Gilead devoted a considerable portion of the Gilead Petition to assert that the Agency need not engage in notice and comment rulemaking to adopt a new interpretation of the 5-year NCE exclusivity provisions.[57]

Furthermore, Gilead's assertion that the plain language of the Agency's implementing regulation dictates the result Gilead prefers is also without merit. When considered as a whole, especially in light of the relevant statutory language, the regulation does not compel Gilead's interpretation. Gilead bases its assertion, that the Agency's longstanding interpretation of the statutory eligibility clause is erroneous, on the "plain meaning" of a single subsection of the regulations at § 314.108(b)(2) (21 CFR 314.108(b)(2)). According to Gilead, because this subsection refers to "a drug product that contains a new chemical entity," the phrase *new chemical entity* must mean *drug substance* because a drug product cannot contain another drug product. Gilead then concludes that this language represents "FDA's clear and reasonable interpretation of the statute."[58] We disagree. First, the very next subsection, § 314.108(b)(3), which describes the timing of a patent infringement action against an ANDA or 505(b)(2) applicant, states that such an action must commence "during the 1-year period beginning 48 months after the date of approval of *the new drug application for the new chemical entity* . . . ." New drug applications are submitted for drug products, not drug substances. Therefore, a compelling interpretation of neighboring § 314.108(b)(3) is that *new chemical entity* means *drug product*. Second, the statutory eligibility clause also refers to "an application submitted . . . for a drug,"[59] which, by the same reasoning, also strongly supports the interpretation of *drug* to mean *drug product* in the eligibility context.

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[54] Gilead Reconsideration Petition at 6.

[55] Original Response at 17.

[56] See Gilead Reconsideration Petition at 5, note 10 (citing the Agency's exclusivity decision for Vascepa).

[57] See Gilead Petition at 30-43 (making the case that administrative law permits a change in interpretation without notice and comment rulemaking).

[58] Gilead Reconsideration Petition at 24.

[59] Section 505(c)(3)(E)(iii) and (j)(5)(F)(iii) of the FD&C Act.

Moreover, the exclusivity regulations are meant to track - not be independent of - the Agency's interpretation of the statutory exclusivity provision. Accordingly, under FDA's historical interpretation, the Agency recognizes exclusivity for a drug product, but, once exclusivity attaches, the Agency applies it to the new active moiety in that product to "preserve the incentive to innovate and improve upon the initially approved product during the exclusivity period."[60] Given the complexity of the statutory exclusivity provision and FDA's goal of effectuating the purpose of the Hatch-Waxman Amendments as a whole, the Agency stated that it needed to adopt this hybrid approach in its regulations.[61] In other words, even though an arguably more natural reading of the statute would be that *drug* means *drug product* in both the eligibility clause and the bar clause,[62] the Agency interpreted the term *drug* in the eligibility clause narrowly and the same word in the bar clause broadly when it issued its regulations.[63] We explained this relationship between FDA's historical interpretation of the exclusivity statute and the regulation in the Original Response when we acknowledged that, 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."[64] Gilead offers no convincing explanation as to why the Original Response failed to adequately address this issue.

Both Gilead and Ferring also assert that they are unaware of any ANDA or 505(b)(2) NDA submitted to the Agency that cites Stribild or Prepopik as the listed drug. Nonetheless, as we described in the Original Response, the historical interpretation was in effect at the time of both approvals. In the Original Response, we explained the numerous factors that resulted in our decision to not recognize 5-year NCE exclusivity for Stribild and Prepopik. One factor was the reliance by potential ANDA sponsors on our longstanding interpretation.[65] Another factor was the consistent application of this interpretation to similar cases. Regardless of whether ANDAs or 505(b)(2) applications have been submitted referencing these drugs, that would not conclusively establish that no sponsor has undertaken a development program with the expectation that the Agency would continue to apply its historical interpretation. Thus, neither Gilead nor Ferring have submitted information to satisfy the Agency that the Original Response failed to adequately consider this issue.

Regarding the intent of the Hatch-Waxman Amendments, Gilead's bare assertion that it developed Stribild with the expectation that cobicistat and elvitegravir would be eligible for 5-year NCE exclusivity is not persuasive. When Gilead submitted an NDA that included these two new active moieties in combination with two previously approved active moieties, it was fully aware of FDA's longstanding, consistent interpretation regarding 5-year NCE exclusivity for

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[60] Id. at 11. See 54 FR 28872 at 28897 ("The broader interpretation of the coverage of exclusivity is that it covers the active moieties in new chemical entities . . . rather than covering only specific drug products. Thus exclusivity would protect the new active moiety of a new chemical entity . . .").

[61] Original Response at 11.

[62] See 54 FR 28872 at 28897 ("The language of the five exclusivity provisions . . . [tend] to support the narrower interpretation of the coverage of exclusivity for new chemical entities . . . .").

[63] Original Response at 11.

[64] Id. at 17.

[65] Id.

fixed-combinations; and it was aware that, under that interpretation, Stribild would not be eligible for 5-year NCE exclusivity.[66] Although Gilead proposed an alternative interpretation, to be sure, Gilead has not offered any explanation of why or how it expected that the historical interpretation, which was still in effect at the time Gilead commenced developing the new active moieties in Stribild, would not determine the period of exclusivity for Stribild at the time of its approval.

Furthermore, Ferring's assertion that the Agency did not consider Congressional intent is not consistent with the Original Response. As stated in the Original Response, the Agency believes that changing the interpretation prospectively balances Congress's goal of encouraging the development and approval of novel active moieties and the interests of the ANDA applicants, 505(b)(2) applicants and other parties who may be affected by our decision.[67] The legislative history for the Hatch-Waxman Amendments is silent on the statute's application to fixed-combination drug products. As we have explained in this response and the Original Response, given the statutory reference to "application submitted . . . for a drug" and the fact that applications are typically submitted for drug products, not drug substances, the Agency reasonably and appropriately interpreted the term *drug* in the statutory eligibility clause to mean drug product, and has applied this interpretation to fixed-combinations for over 25 years.

Finally, neither Ferring's Reconsideration Petition nor the Original Response supports the company's assertion that the Agency failed to consider in the Original Response the inconsistencies for fixed-combinations because of the umbrella policy. As stated in the Original Response, and as acknowledged by Ferring in its reconsideration petition, [68] we considered assertions about the inconsistencies and agreed with the Petitioners' claims that the Agency's previous interpretation of the statute may result in suboptimal drug development strategies from a public health perspective. At that time, we resolved to consider a new approach as proposed in the Exclusivity Guidance.[69] Therefore, we reject this claim by Ferring, because, as the company also recognizes, the Agency considered these inconsistencies in responding to the original petition and proposed a new approach.

Although Petitioners assert that FDA did not consider relevant information contained in the administrative record in responding to the 2013 Petitions, it appears that they simply disagree with the conclusions that we reached in the Original Response. Because the relevant information and views in the administrative record were previously and adequately considered when we reviewed and denied the 2013 Petitions, Petitioners have failed to satisfy § 10.33(d)(1).

Petitioners have also failed to demonstrate sound policy reasons for reconsideration. Both Petitioners repeat the Agency's acknowledgment that public policy supports a change in the

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[66] See Gilead Petition, supra note 8.

[67] Id.

[68] See Ferring Reconsideration Petition at 6.

[69] Original Response at 15 (stating "we agree with Petitioners that sponsor 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 the order in which these two NDAs are approved").

Agency's interpretation regarding 5-year NCE exclusivity so as to encourage the development of fixed-combinations that contain novel drug substances. However, neither Petitioner offers any convincing reason for why the same incentives for encouraging the development of novel drug substances should apply retrospectively to drugs that have already come on the market.[70] Therefore, Petitioners have also failed to meet the criteria for reconsideration under 21 CFR 10.33(d)(3).

FDA's regulation at § 10.33(d) requires that all four criteria be met for the Agency to grant a petition for reconsideration. Petitioners have failed to meet at least two of these criteria. Therefore, we need not evaluate the other criteria in § 10.33(d).

B. Petitioners Have Not Demonstrated That Reconsideration Is In the Public Interest or the Interest of Justice.

We have also considered whether, despite the failure to meet all criteria in § 10.33(d)(1) through (4), the Reconsideration Petitions nevertheless should be granted, because doing so would be in the public interest and in the interest of justice. Gilead and Ferring have not demonstrated, however, that reconsideration is in the public interest or the interest of justice. In fact, the factors articulated in the Original Response suggest that prospectively applying the new statutory interpretation after finalizing the Exclusivity Guidance in this case ensures public participation and input regarding a proposed change from a longstanding and consistently applied interpretation while minimizing any potential disruption to regulated industry.[71] The approach articulated in the Original Response allows FDA to give stakeholders notice and an opportunity to comment on the new interpretation, which represents a significant change from a longstanding, clearly stated, and consistently applied historical interpretation, before the Agency starts making exclusivity decisions based on the new interpretation.[72]

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[70] Ferring claims to find support in two cases where the Agency has, according to Ferring, recognized 3-year exclusivity without requiring human clinical studies because of ethical concerns. These examples are both inapt and unavailing. The Agency's policy decisions regarding the availability for 3-year exclusivity have little bearing, if any, on the policy grounds for reconsideration here. Moreover, Ferring's claim that it was "ethically barred" from obtaining approval for a single ingredient drug containing sodium picosulfate is overstated. The summary review does not state that a single ingredient NDA containing sodium picosulfate would be ethically problematic, only that "a full factorial study" (which is typically how a fixed-combination would establish its safety and effectiveness (see 21 CFR 300.50(a))) would be problematic because "the reviewers determined that available data do not support that each component of Prepopik could be expected to provide adequate bowel cleansing as a stand alone product." Division Director Review at 47. In effect, Ferring appears to have benefited from not being required to conduct a full factorial study to gain approval because FDA determined, based on a literature review, that the studies that Ferring would otherwise be required to perform would not suffice. In any event, Ferring did receive 3-year exclusivity for its clinical studies, which places it in the same position as the sponsors of the drugs to which it alludes.

[71] Original Response at 17.

[72] See generally, FDA, "Draft Guidance for Industry on New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products"; Availability; Docket No. FDA-2013-D-1675; 79 FR 10167 (February 24, 2014). The comment period for the Exclusivity Guidance ended on April 25, 2014.

C. Stay of the New Policy in the Exclusivity Guidance

For the same reasons as discussed above, Ferring has failed to meet all of the criteria for a stay under § 10.35(e). Therefore, we are also denying Ferring's request for a stay of action regarding the draft Exclusivity Guidance.

V. CONCLUSION

For the reasons stated above, your Reconsideration Petitions are denied.

Sincerely,

Leslie Kux
Assistant Commissioner for Policy