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ELECTRONIC SUBMISSION

Dockets Management Branch, HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. FDA-2013-P-0058

PETITION FOR RECONSIDERATION

Gilead Sciences, Inc. (Gilead) respectfully submits this petition for reconsideration pursuant to 21 CFR 10.33, among other provisions of law, to request that the Commissioner of Food and Drugs reconsider the February 21, 2014, decision denying Gilead 5-year exclusivity for the two new chemical entities in the approved drug product, STRIBILD (cobicistat; elvitegravir; emtricitabine; tenofovir disoproxil fumarate).[1]

DECISION INVOLVED

Gilead's petition requested that FDA interpret the governing statute and regulations to recognize 5-year exclusivity for new chemical entities that are approved for the first time in combination with previously approved active moieties. In its response, the agency agreed that Gilead's request would benefit the public health; that it reflects a permissible interpretation of the statute; and that it can be applied without any change to the applicable exclusivity regulations. As the agency concluded, "Petitioners have articulated an alternative interpretation of the relevant statute and regulations that would…be permissible," and "[FDA's] current interpretation

[1] FDA Petition Response, Docket No. FDA-2013-P-0058 (Feb. 21, 2014) (Petition Response).

of the 5-year NCE exclusivity statutory provisions may result in drug development strategies that are *suboptimal from a public health perspective*."[2]

With respect to STRIBILD, the agency recognized that Gilead had properly requested New Chemical Entity (NCE) exclusivity for STRIBILD and had taken appropriate steps to have the exclusivity determination deferred to give the agency time to consider the issue. The Petition Response also recognizes that as of the date of the agency's decision, an exclusivity determination for STRIBILD remained open and "is currently pending."[3] Thus, as of the date of the Petition Response, the award of exclusivity to the two new chemical entities in STRIBILD could be made *prospectively*.

Nevertheless, FDA declined to apply its decision to STRIBILD based on several factors. None, however, fits the facts surrounding STRIBILD. *See* Section II.A., *infra.* In particular, there is *no evidence* in the petition record that immediate application of the new approach to STRIBILD would meaningfully disrupt the industry.[4] FDA allowed the STRIBILD docket to remain open for more than one year and, in that time, only a single comment from a single sponsor was submitted in opposition.

Moreover, if FDA is asked to receive or file a 505(j) or 505(b)(2) application that references STRIBILD, the agency remains bound by the plain language of its exclusivity regulation. The regulation bars a third party from submitting such an application for 5 years from the date of approval of "a drug product that contains a new chemical entity...." 21 CFR 314.108(b)(2). In its Petition Response, the agency offers no response or rebuttal to the basic point that under the regulation, FDA must refuse to accept a 505(j) or 505(b)(2) application if it references a product that contains a new chemical entity, even if the product also contains a

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2 *Id.* at 14-15 (emphasis added).

3 *Id.* at 3.

4 *See id.* at 17.

previously approved drug substance.[5] The term "new chemical entity," in the context of the rule, is an entity within a product – not the product itself. *See* Section II.B., *infra.*

Thus, Gilead believes the agency erred in not applying its legal and policy findings in the Petition Response immediately to STRIBILD. However, Gilead has no objection to the agency using its guidance process to memorialize and announce its new approach to the broader community. Gilead encourages the agency to finalize the guidance as soon as possible, given the important public health benefits of incentivizing the development of medically important fixed-combination products. Moreover, the agency need not wait to finalize a guidance document before immediately applying its thinking to a specific product. The reasoning in the Petition Response sets forth a sound basis for making an immediate and affirmative decision for STRIBILD.

ACTION REQUESTED

Gilead respectfully requests that the Commissioner reconsider the decision not to recognize 5-year NCE exclusivity for cobicistat (COBI) and elvitegravir (EVG) and, upon reconsideration, acknowledge that the agency will refuse to accept 505(b)(2) and 505(j) applications for products that contain COBI or EVG for a period of 5 years from the date of approval of STRIBILD (or 4 years if the application contains a "paragraph IV" certification).

STATEMENT OF GROUNDS

I. BACKGROUND

Gilead developed and markets the approved product STRIBILD (cobicistat; elvitegravir; emtricitabine; tenofovir disoproxil fumarate) oral tablets. Prior to the approval of STRIBILD, FDA had not previously approved any drug product containing the active moieties in COBI and

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[5] *Id.* at 12.

EVG. Pursuant to 21 CFR 314.50(j), Gilead included a request for 5-year NCE exclusivity as part of the STRIBILD NDA, which was submitted on October 26, 2011. Immediately following approval of STRIBILD, Gilead submitted a letter to FDA reiterating Gilead's request that FDA recognize 5-year NCE exclusivity for STRIBILD.

Due to the issues raised by Gilead, the agency deferred making an exclusivity determination for STRIBILD. Accordingly, no exclusivity award was listed in the *Orange Book* when STRIBILD was approved.[6] As of the date of the Petition Response, FDA stated that "an exclusivity determination for STRIBILD was not made at the time of approval and is currently pending."[7] To the best of Gilead's knowledge, the agency has not received an ANDA or filed a 505(b)(2) NDA referencing STRIBILD. On or about March 14, 2014, FDA for the first time published an exclusivity determination for STRIBILD, providing 3-year exclusivity for the product but not recognizing 5-year exclusivity for COBI and EVG.

Gilead submitted its citizen petition on January 8, 2013, asking that FDA re-evaluate its approach to NCE exclusivity for fixed dose combinations (FDCs) and recognize 5-year NCE exclusivity for the new active moieties in STRIBILD.[8] Pursuant to agency procedure, FDA established a public docket to permit public review and comment on the Gilead Petition. Shortly after Gilead filed its petition, Ferring Pharmaceuticals, Inc. (Ferring) and Bayer HealthCare Pharmaceuticals, Inc. (Bayer) submitted similar petitions regarding the drug products Prepopik and Natazia, respectively.

FDA issued a consolidated response to the citizen petitions on February 21, 2014. FDA agreed with petitioners that new active moieties in FDC products should receive NCE

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6 *Approved Drug Products with Therapeutic Equivalence Evaluations* (*Orange Book*), Prescription and OTC Drug Product Patent and Exclusivity List at ADA 37 of 215 (34th ed., 2014).

7 Petition Response at 3.

8 Petition, Docket No. FDA-2013-P-0058-0001 (Jan. 8, 2013) (Gilead Petition).

exclusivity, but declined to apply this new interpretation to STRIBILD, Natazia, and Prepopik. Instead, FDA issued a Level 1 *Draft Guidance* setting forth its new interpretation and stating that it would apply the new interpretation only to products approved after the *Draft Guidance* is finalized.[9]

II. ARGUMENT

A. FDA's Reasons for Declining to Recognize 5-year NCE Exclusivity for COBI and EVG Are Not Applicable to STRIBILD

New chemical entity (NCE) exclusivity determinations need not be made at the time that a new drug application is approved. In fact, the exclusivity has no legal effect until the agency is asked to receive a competing 505(b)(2) or 505(j) application. Thus, in the case of STRIBILD, and in several other cases, FDA has exercised its discretion and deferred making an exclusivity decision for a newly approved drug. As of the date of the petition response, the agency had not made an exclusivity determination for STRIBILD or the two new chemical entities, COBI and EVG.

As the agency has done numerous times, it could have issued its petition decision and immediately applied the framework or policy developed in the petition response to the product at issue.[10] Instead, the agency insisted on holding STRIBILD to the interpretation in place as of the date the agency approved the product. The reasons the agency gave for doing this do not fit the circumstances surrounding STRIBILD and, thus, we ask the agency to reconsider.

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[9] *Draft Guidance for Industry, New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products* (Feb. 2014) (*Draft Guidance*).

[10] On the same day as the STRIBILD decision, the agency also issued a letter decision establishing a new framework for analyzing complex mixtures for NCE exclusivity purposes. *See* Vascepa (icosapent ethyl) Capsules (NDA 202057) Exclusivity Determination, Letter from J. Woodcock to R. Dormer (Feb. 21, 2014). The agency immediately applied that framework to a specific drug product, even though that product – like STRIBILD – had been approved about 18 months earlier.

First, FDA states that it is not recognizing 5-year NCE exclusivity for STRIBILD, Natazia, and Prepopik because it would burden sponsors of ANDAs that had already been filed for those products. According to FDA, "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 application."[11] FDA's concern is not relevant to STRIBILD because, to Gilead's knowledge, FDA had not filed any ANDAs or 505(b)(2) NDAs that reference STRIBILD as of the time of the Petition Response.[12]

Second, FDA indicates that it is not applying 5-year NCE exclusivity to STRIBILD, Natazia, and Prepopik because each was approved when FDA's old interpretation was in effect. However, the date of approval is not the relevant date for STRIBILD because FDA made the decision to defer the exclusivity determination for STRIBILD. Gilead raised the 5-year NCE exclusivity issues early during STRIBILD's NDA process. In accordance with 21 CFR 314.50(j), Gilead requested 5-year NCE exclusivity at the time of submission of the STRIBILD NDA and reiterated its request in a letter submitted to the agency immediately following STRIBILD's approval.

Although FDA typically determines exclusivity at the time of approval, FDA specifically deferred STRIBILD's exclusivity determination due to Gilead's actions. As FDA explained, "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."[13] FDA did not list any exclusivity determination for STRIBILD in the *Orange Book* until after its

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11 Petition Response at 17.

12 FDA generally maintains the existence of a pending application, including an ANDA, as confidential. However, pending ANDAs typically become publicly known through press releases, paragraph IV notice letters, and FDA's paragraph IV database. Based on the available information, Gilead is not aware of any pending ANDA for STRIBILD.

13 Petition Response at 3.

Petition Response. Thus, for as long as STRIBILD has been approved, FDA made it known that the exclusivity for the product would be dependent on future deliberations. Accordingly, STRIBILD should benefit from the new interpretation. Indeed, by granting the deferral, FDA presumably intended that STRIBILD should be eligible for 5-year NCE exclusivity if FDA ultimately changed its interpretation.

The deferral of STRIBILD's exclusivity determination also mitigates FDA's concern that recognizing 5-year NCE exclusivity for STRIBILD would unnecessarily disrupt regulated industry and deprive the public of a notice and comment period.[14] The exclusivity deferral for STRIBILD has provided regulated industry with more than 16 months of notice that STRIBILD may have 5-year NCE exclusivity. In particular, stakeholders have been on notice of the exclusivity issues since mid-September 2012, when FDA publicly listed STRIBILD in the *Orange Book* without an exclusivity determination. There is no reason to believe that recognizing 5-year NCE exclusivity for STRIBILD would unnecessarily disrupt regulated industry.

Furthermore, Gilead's citizen petition, which was submitted within months of the approval of STRIBILD, provided stakeholders with a detailed explanation of the underlying exclusivity issues and an opportunity to comment. As further evidence that FDA's fear is unfounded, there was only one comment submitted in opposition to Gilead's citizen petition. On December 17, 2013, almost a year after Gilead submitted its petition, Mylan Inc. submitted a comment opposing Gilead's petition.[15] Similarly, there were no comments submitted in

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[14] *Id.* at 17

[15] Mylan also submitted its comment to the dockets for the Ferring Petition and the Bayer Petition. Docket Nos. FDA-2013-P-0119-0005 and FDA-2013-P-0471-0005 (Dec. 17, 2013). Notably, Mylan's comment was submitted more than five months after the 180-day anniversary of the STRIBILD petition and three months after the statutory deadline for FDA to take final agency action on the Bayer Petition, which was subject to section 505(q) of the FDCA.

opposition to the Natazia and Prepopik citizen petitions. The scarcity of comments belies FDA's belief that applying 5-year exclusivity to STRIBILD would disrupt regulated industry.

Third, FDA states that recognizing 5-year NCE exclusivity for STRIBILD, Natazia, and Prepopik would not advance the goals of the Hatch-Waxman Act because exclusivity is intended to encourage development of novel drugs, and those products have already been developed. FDA's rationale misses the mark with respect to STRIBILD. Gilead developed the new active moieties in STRIBILD with the expectation that they would have 5-year NCE exclusivity. Gilead recognized during development that pursuing the combination product first would be more beneficial to patients and scientifically feasible. Accordingly, the NDA for STRIBILD was submitted before the NDAs for COBI and EVG. The novel drugs in STRIBILD were, however, developed with the full expectation that they would be eligible to receive NCE exclusivity.

Finally, the agency states that if it were to recognize NCE exclusivity for COBI and EVG, it would amount to "additional exclusivity" because the novel drugs in STRIBILD have already been developed.[16] Gilead strongly disagrees. Awarding the exclusivity in this instance represents the appropriate statutory recognition for having developed these novel drugs. Nothing additional or gratuitous is being requested.

B. FDA Must Refuse to Receive 505(b)(2) and 505(j) Applications for Products that Contain COBI or EVG until August 2016/2017

Gilead agrees with FDA's conclusion that "the word 'drug' is ambiguous in both the eligibility and bar clauses of the 5-year NCE exclusivity statutory provisions."[17] There is certainly ample room for interpretation. However, two key points of interpretation – which pre-date the Petition Response – require the agency to recognize NCE exclusivity for COBI and

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16 Petition Response at 17.

17 *Id.* at 14.

EVG. Because Gilead formally requested NCE exclusivity for both drug substances under 21 CFR 314.50(j), and because Gilead based its request on these pre-existing interpretations, FDA must reconsider its decision and grant the exclusivity in this instance to COBI and EVG.

First, FDA agreed that under the so-called "bar clause" in the statute, the term "the drug" in the clause "*the drug* for which the subsection (b) application was submitted" has been interpreted to mean *a specific active moiety*, rather than a drug product.[18] This interpretation is essential to FDA's "umbrella policy" in which exclusivity awarded to a drug product that contains a new active moiety extends to any subsequent products that also contain that active moiety.[19] In light of that clear and appropriate interpretation, it is not plausible that the term "a drug" in the clause "an application submitted under subsection (b) for *a drug*" could mean something different. The terms "a drug" and "the drug" appear in the same sentence and *refer to the same physical entity*. Gilead appreciates that the same word may have different meanings within the same statute. There are, however, limits to that principle of construction, and those limits clearly have been exceeded in this instance. The same word, in the same sentence, referring to the *exact same thing*, must be given the same meaning.[20] Here, the meaning specifically adopted by the agency is that the "drug" at issue in the exclusivity provision is a specific active moiety.

Second, the agency incorporated this interpretation into the operational regulation that bars the submission of certain 505(b)(2) and 505(j) applications. The regulation bars the

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18 *Id.* at 8.

19 *Id.* (quoting 54 FR 28872, 28898-99 (July 10, 1989)).

20 FDA relies on two cases to say it is "permissible to interpret the same word in two different clauses [of the same sentence] to mean different things." Petition Response at 11, n.51 (citing *Abbott Labs. v. Young*, 920 F.2d 984, 987 (D.C. Cir. 1990) and *Atlantic Cleaners & Dyers, Inc. v. U.S.*, 286 U.S. 427, 433 (1932)). These cases, however, address whether the same word in different sections of the same statute may be given a different meaning. They do not address whether the same word in the same section, let alone the same sentence, may carry a different meaning.

submission of an application that references "a drug product that *contains* a new chemical entity" until five years after that drug product's approval.[21] As with the FDA's interpretation of the bar clause in the statute, the regulatory bar protects individual new chemical entities rather than products. The plain language here is unambiguous. A drug product cannot "contain" another drug product; it may contain drug substances and moieties, but not other drug products. Thus, FDA's operational regulation is designed to provide the same scope of protection – namely, moiety-specific protection – as the bar clause in the statute, based on FDA's clear and reasonable interpretation of the statute. The Petition Response recognizes this argument but offers no response.[22]

On reconsideration, the agency must resolve that its longstanding "umbrella exclusivity" policy[23] – in which the term "the drug" is interpreted to mean a specific drug substance or moiety – and its operational rule for applying the exclusivity, together require the agency in this instance to refuse to accept 505(b)(2) and 505(j) applications for products that contain COBI or EVG until the NCE exclusivity period has expired. Gilead reserved its right to this exclusivity by specifically requesting it under 21 CFR 314.50(j) and by supporting its request with the very argument offered throughout this proceeding.

C. Petition for Reconsideration Standards

FDA regulations provide that FDA must grant a petition for reconsideration if: (1) relevant information or views were not 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 the petition; and (4) reconsideration is not outweighed by public

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21 21 CFR 314.108(b)(2) (submission permitted after four years if it contains a patent challenge) (emphasis added).

22 Petition Response at 12.

23 54 FR at 28897-99

health or other public interests.[24] As described below, Gilead's petition for reconsideration meets those standards.

First, Gilead does not believe that FDA has adequately considered the relevant information. As shown above, the factors cited by FDA to support its decision not to recognize 5-year NCE exclusivity for COBI and EVG are not relevant to the facts surrounding STRIBILD. Furthermore, FDA did not address the plain language of its operational regulation (21 CFR 314.108(b)(2)), which bars the submission of 505(b)(2) and 505(j) application that reference drug products that contain a new chemical entity.

Second, Gilead's position is not frivolous and is being raised in good faith. Gilead carefully and consistently presented to the agency its position that legal, regulatory, and medical policy considerations supported an award of NCE exclusivity for COBI and EVG. Gilead formally requested the exclusivity, briefed the agency on the subject, and then agreed to initiate a petition process to allow for public consideration of the issue. The agency generally has agreed that Gilead's position is permissible and desirable, except with respect to STRIBILD.

Third, there are sound public policy grounds supporting reconsideration. FDA acknowledged that public policy supports Gilead's interpretation of NCE exclusivity:

> 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…irrespective of whether the fixed-combination also includes a drug substance that contains a previously approved active moiety or moieties.[25]

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[24] 21 CFR 10.33(d).

[25] Petition Response at 16.

Public policy also supports encouraging members of the public, like Gilead, to initiate medically important policy changes such as this. Here, not only did Gilead develop a product that met the federal government's goal of developing a "single pill regimen" for the treatment of HIV,[26] but Gilead also advanced a significant structural change to the development of medically important fixed-combination products. There are, therefore, sound reasons for reconsidering the original decision refusing exclusivity for the new ingredients in STRIBILD to reinforce the public policy and public health benefits that the petition helped to achieve.

Finally, reconsideration is not outweighed by public health or other public interests. To the contrary, Gilead's request benefits the public health. As the agency itself acknowledges, Gilead's requested interpretation will "align the exclusivity incentives more closely with FDA's public health goals."[27]

Even if FDA determines that the four factors described above are not satisfied, FDA's regulations also authorize FDA to grant a petition for reconsideration when FDA determines it is in the public interest and in the interest of justice.[28] Based on the same reasons described above, Gilead believes that its request meets this standard, and FDA therefore should grant Gilead's request. Additionally, applying the new interpretation immediately to protect the novel active moieties in STRIBILD is in the interest of justice. In particular, Gilead should be recognized for successfully bringing this issue to the agency's attention.

CONCLUSION

For the foregoing reasons, Gilead respectfully requests that FDA grant this petition for reconsideration.

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26 Gilead Petition at 9.

27 *Draft Guidance* at 7.

28 21 CFR 10.33(d).

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: February 21, 2014. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Gilead. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Sincerely,

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