

October 10, 2016

Electronic Submission

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this petition under sections 505(c)(3)(E) and 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act (FDCA) and the related regulations 21 C.F.R. §§ 10.30 and 314.108 to request the Commissioner of Food and Drugs grant five-year new chemical entity (“NCE”) exclusivity to Stribild® (cobicistat; elvitegravir; emtricitabine; tenofovir disoproxil fumarate) and to apply such exclusivity to all subsequently approved drug products that contain any of the new active moieties (elvitegravir and cobicistat) approved in the Stribild product.

I. ACTION REQUESTED

In light of the recent district court’s decision in Ferring v. Burwell,¹ Gilead requests that FDA promptly award five-year NCE exclusivity to Stribild, which was approved on August 27, 2012, and extend such exclusivity under FDA’s “umbrella policy” to later-approved Gilead products containing the new active moieties, specifically Tybost® and Vitekta®. Additionally, because all of these drug products should have been protected against the receipt of an Abbreviated New Drug Application (ANDA) before August 27, 2016, Gilead requests that FDA withdraw its January 2016 receipt of the Mylan ANDA 208982 referencing Tybost, as well as any other ANDA filed before August 27, 2016 that references a drug containing elvitegravir or cobicistat.

II. STATEMENT OF GROUNDS

FDA denied Gilead NCE exclusivity for its fixed-combination drug product, Stribild (NDA 203100), based on FDA’s since-revised policy that a fixed-combination product containing both previously approved and new active moieties are not eligible for such exclusivity. FDA revised this NCE policy in February 2014 in response to, in part, a Citizen Petition filed by Gilead, but nonetheless, refused to apply its new policy to Stribild and other similarly-situated fixed combination drug products.

¹ Memorandum Opinion, Ferring v. Burwell, No. 1:15-cv-00802 (D.D.C. Sept. 9, 2016).



In Ferring v. Burwell, the District Court in D.C. reviewed FDA’s pre-February 2014 NCE policy for fixed-combination products, determined that such policy was arbitrary and capricious, and remanded the exclusivity determination for the fixed-combination product Prepopik® back to FDA for further review. In light of this decision, Gilead requests that FDA also review and revise its NCE exclusivity denial for Stribild, a fixed-combination drug product that, like Prepopik, contains a combination of approved and new active moieties. Gilead also requests that FDA extend, under its umbrella policy, such five-year NCE exclusivity to the subsequently-approved products that contain the new active moieties in Stribild: namely, Tybost, and Vitakta. Finally, in accordance with these NCE exclusivity determinations, Gilead also requests that FDA withdraw the receipt of any ANDAs referencing these products prior to the expiration of their NCE exclusivity periods.²

A. Statutory and Regulatory Background

i. NCE Exclusivity for Fixed-Combination Drug Products and FDA’s Umbrella Policy

Congress enacted the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) in 1984 as a system to both protect the interests of innovative drug manufacturers and provide consumers access to more affordable medicines.³ To that end, Hatch-Waxman put in place exclusivity provisions as an incentive to innovators to develop new products while authorizing an abbreviated approval process to reduce the cost of drugs for consumers. ANDA applicants could rely on FDA’s findings of safety and efficacy for a previously approved version of the drug as long as the applicant could demonstrate that the proposed generic is “the same as” the reference listed drug (“RLD”).⁴ At the same time, as a reward for undertaking the onerous clinical studies needed for full NDA approvals, Hatch-Waxman awarded periods of exclusivity to successful NDA applicants.⁵ The scheme was designed to strike “a balance between expediting generic drug applications and protecting the interests of the original drug manufacturers.”⁶

Congress and, by extension, FDA have made several forms of exclusivity available to NDA sponsors. New drug products that contain active ingredients that have never received approval are eligible for NCE exclusivity, which provides five years of protection for the RLD.⁷

Sections 505(c)(3)(E)(ii) and 505(j)(5)(F) of the FDCA provide a five-year exclusivity period for approved new chemical entities “no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under” 505(b). FDA

² In January 2016, Mylan filed an ANDA with a Paragraph IV certification referencing Tybost. Gilead filed a patent infringement suit within the 45-day period required to trigger the statutory 30-month stay of FDA approval. Under FDA’s umbrella policy, NCE exclusivity for Tybost would have precluded FDA receipt of the Mylan ANDA prior to August 27, 2016.

³ Pub. L. No. 98-417, 98 Stat. 1585 (1984).

⁴ Id.

⁵ Id.

⁶ Abbott Labs. v. Young, 920 F.2d 984 (D.C. Cir. 1990).

⁷ 21 U.S.C. § 355(c)(3)(E)(ii); 21 C.F.R. § 314.108(b)(2).



interpreted this provision to extend exclusivity based on whether any active moiety in the drug product as a whole had been approved; therefore, FDA extended exclusivity for a drug only if it contained no active moiety previously approved by FDA.⁸ Thus, NCE exclusivity was systematically denied to any combination product containing a moiety that had previously been approved regardless of whether it also contained one or more new active moieties.

FDA also adopted an “umbrella policy,” which attaches five-year NCE exclusivity to both the first approved drug product that was eligible for NCE exclusivity and to any products containing the same active moiety.⁹ The five-year exclusivity travels with the new active moiety to any subsequent products to ensure that a sponsor who develops an active moiety has incentive to further develop drug products containing that moiety.¹⁰ Thus, under FDA policies, only drug products containing no previously approved active moieties were eligible for five-year exclusivity, and any later-approved products containing those active moieties would be similarly protected for the duration of the original five-year exclusivity period.¹¹

In February 2014, FDA changed its NCE exclusivity policy for fixed-combination products.¹² In response to a Citizen Petition filed, followed by two others filed by Ferring and Bayer, FDA decided that drug products containing any new active moiety now qualify for NCE exclusivity.¹³ However, FDA refused to apply the new policy to approved products like Stribild, irrespective of whether a generic had been filed at the time of the new policy.¹⁴

As a result of FDA’s policy change, fixed-combination products with new active moieties that had not been approved as of October 2014 were eligible for NCE exclusivity even if they contain previously approved active moieties; whereas products that had been approved before that date were not eligible regardless of whether the product had received an exclusivity determination.¹⁵ After the announcement of this policy change, Gilead and Ferring filed Petitions for Reconsideration on the issue of retroactivity.¹⁶ FDA denied these Petitions, concluding that the arguments were adequately considered in the original Citizen Petition

⁸ Letter from Carl C. Peck, M.D., Director, Center for Drug Evaluation and Research, to all NDA or ANDA Holders and Applicants, at p. 2 (April 28, 1988) (Peck Letter) (emphasis added), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075014.pdf>; FDA, “Abbreviated New Drug Application Regulations,” Proposed Rule, 54 Fed. Reg. 28872 at 28898 (Jul. 10, 1989).

⁹ 54 Fed. Reg. at 28898-99.

¹⁰ *Id.*

¹¹ See Memorandum Opinion, *Ferring v. Burwell*, No. 1:15-cv-00802 (Sept. 9, 2015).

¹² See Guidance for Industry: New Chemical Entity Exclusivity Determinations for Certain Fixed Combination Drug Products, n.32 (CDER, Oct. 2014); FDA Response to Citizen Petitions, Docket Nos. FDA-2013-P-0058, FDA-2013-P-0119, FDA-2013-P-0471 (Feb. 21, 2014).

¹³ See Citizen Petition re Stribild, Docket No. FDA-2013-P-0058 (Jan. 8, 2013) and Citizen Petition re Prepopik, Docket No. FDA-2013-P-0119 (Jan. 29, 2013).

¹⁴ FDA Response to Citizen Petitions, Docket Nos. FDA-2013-P-0058, FDA-2013-P-0119, FDA-2013-P-0471 (Feb. 21, 2014); no ANDA had been filed containing elvitegravir or cobicistat as of October 2014.

¹⁵ *Id.*

¹⁶ Petition for Reconsideration, Docket No. FDA-2013-P-0058 (Mar. 21, 2014); Petition for Reconsideration, Docket No. FDA-2013-P-0119 (Mar. 21, 2014).



proceeding and that Petitioners did not demonstrate sound public policy grounds supporting reconsideration.¹⁷

Subsequently, Ferring filed suit against FDA in the D.C. District Court alleging that its actions were contrary to the FDCA and the agency's own regulations, as well as arbitrary and capricious in violation of Section 706(2)(A) of the Administrative Procedures Act.¹⁸ Initially, the Court held that FDA's interpretation of NCE exclusivity for fixed-combination products was not arbitrary and capricious, rejecting Ferring's argument that FDA's fixed-combination NCE and umbrella policies created circumstances in which a drug's eligibility for five-year exclusivity arbitrarily relied on the order in which NDAs were approved.¹⁹ The Court explained that Ferring failed to show any evidence in support of its assertions; however, the Court also declined to determine whether FDA's refusal to retroactively apply exclusivity was arbitrary and capricious and asked the parties for supplemental briefing on the issue.

Ferring moved for reconsideration of the Court's determination that FDA's prior interpretation of the NCE exclusivity provision was not arbitrary and capricious. In its motion, Ferring listed examples in which the order of approvals in fact determined whether a product would qualify for NCE exclusivity. Notably, Ferring cited Stribild as an example for the court to show that "if . . . the fixed-dose combination drug product had been approved just hours before the single-ingredient product, none of the products would have been awarded NCE exclusivity, because each would have contained a previously approved active ingredient."²⁰ While no new single agent product in Prepopik has ever been approved, it relied on drugs like Stribild to show how the temporal nature of the guidance was arbitrary and capricious.

Based on Ferring's new examples of the temporal relationship between approval and exclusivity, the Court determined that FDA's NCE exclusivity policy in effect prior to the February 2014 revision treated similar cases differently. The Court observed that products lost out on five-year exclusivity solely because they had been first approved as part of a fixed-combination drug product. The Court went on to state that under administrative law principles, an agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so; here, FDA's policy as applied to fixed-combination products treated similar cases differently, and FDA could not provide a legitimate reason. Thus, the Court held that the policy was arbitrary and capricious and remanded it back to FDA for further review consistent with the Court's ruling.²¹

ii. ANDA Considerations

¹⁷ See FDA Response to Petitions for Reconsideration, Docket Nos. FDA-2013-P-0058 and FDA-2013-P-0119 (Oct. 10, 2014).

¹⁸ Complaint, *Ferring v. Burwell*, No. 1:15-cv-00802 (June 1, 2015).

¹⁹ Memorandum Opinion, *Ferring v. Burwell*, No. 1:15-cv-00802 (Mar. 15, 2016).

²⁰ *Id.*

²¹ *Id.*



Under the FDCA, FDA makes available an abbreviated approval process for manufacturers of generic drugs.²² The ANDA relies on the data of a previously approved NDA containing full clinical trials.²³ The ANDA applicant must certify to any patents listed for the NDA in FDA’s compendium Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book.²⁴ If an ANDA applicant seeks FDA approval to market a copy of a brand drug before all of the patents listed in the Orange Book have expired, it must challenge the unexpired patents by filing a Paragraph IV certification.²⁵ A Paragraph IV certification requires the ANDA applicant to provide notice of its FDA filing to both the NDA holder and the patent owner.²⁶

When a generic applicant submits an ANDA, FDA reviews the application for completeness and notifies the applicant that its application is substantially complete and has officially been “received” by the agency.²⁷ Only when the application is received by FDA, and no earlier, can the ANDA applicant send its notice to the NDA holder and the patent holder.²⁸ Either or both of these parties must file a patent suit based on the notification within 45 days to trigger a 30-month stay, which delays FDA approval of the ANDA for 30 months unless a court finds the patent invalid or not infringed prior to the expiration of the stay.²⁹ The first ANDA applicant to include a Paragraph IV certification for a particular RLD is eligible for 180-day marketing exclusivity, in which FDA may not approve any other ANDA referencing the same product.³⁰

Exclusivity can affect the timing of an ANDA submission. If an NDA has received five-year NCE exclusivity, an ANDA cannot be accepted or received by FDA for the duration of the five-year exclusivity period unless it contains a Paragraph IV certification.³¹ An ANDA with a Paragraph IV certification may be accepted only after four years of exclusivity have elapsed, called the NCE-1 period.³² Conversely, if a product has three-year exclusivity, FDA may accept an application at any time, including before the expiration of the three-year period.³³

Because NCE exclusivity prevents the submission or receipt of an ANDA prior to the NCE-1 date, it delays any Paragraph IV certifications, the subsequent 45 days for filing a patent infringement suit, and the commencement of the 30-month stay. For products with NCE exclusivity, FDA extends the 30-month stay for patent infringement suits for an additional 2.5

²² 21 U.S.C. § 355(j).

²³ *Id.*

²⁴ 21 C.F.R. § 314.94(a)(12).

²⁵ In the case of method of use patent, the ANDA applicant can seek to omit the patented use from its label by filing a section viii statement.

²⁶ 21 C.F.R. § 314.95.

²⁷ 21 C.F.R. § 314.95(3)(b).

²⁸ *Id.*

²⁹ 21 U.S.C. § 355(j)(5)(B)(iii).

³⁰ 21 U.S.C. § 355(j)(5)(B)(iv).

³¹ 21 U.S.C. § 355(c)(3)(E)(ii).

³² *Id.*

³³ *Id.*



years after the expiration of exclusivity.³⁴ In other words, products with NCE exclusivity receive the full five years of exclusivity, and the 30-month stay runs from expiration of the NCE exclusivity.

B. Factual Background

Stribild is a fixed dose combination drug product indicated for the treatment of human immunodeficiency virus type 1 (HIV) in adults. Stribild is comprised of two distinct drug substances that had received prior FDA approval and two distinct drug substances that were new active moieties. The two previously approved substances, emtricitabine (“FTC”) and tenofovir disoproxil fumarate (“TDF”), received NCE five-year exclusivity upon initial approval as single-ingredient drugs while the two remaining substances, elvitegravir (“EVG”) and cobicistat (“COBI”), were approved for the first time as part of the fixed combination Stribild product.

Stribild was approved under NDA 203100 on August 27, 2012. While Gilead properly requested an exclusivity determination for the fixed-combination product, FDA deferred making an exclusivity decision. Concurrently, Gilead submitted separate single-ingredient NDAs for EVG (as Vitekta) and COBI (as Tybost) on June 27, 2012.³⁵ Consistent with its exclusivity request for Stribild, Gilead requested that EVG and COBI be protected under Stribild’s five-year NCE exclusivity.

On January 8, 2013, Gilead filed a Citizen Petition requesting five-year NCE exclusivity for Stribild and asking the agency to reevaluate its approach to NCE exclusivity determinations for fixed-combination products. In February 2014, FDA denied Gilead’s Citizen Petition and released a draft guidance document explaining changes to the NCE exclusivity policy for fixed-combination drugs containing previously approved moieties. FDA awarded Stribild three-year exclusivity in March of 2014. Gilead filed a Petition for Reconsideration in March 2014, which FDA denied in October 2014 while finalizing its new guidance document. FDA approved Tybost and Vitekta with three-year exclusivity in September 2014.

III. ARGUMENT

A. FDA must revise its arbitrary and capricious fixed-combination NCE exclusivity policy to comply with Ferring v. Burwell

As explained, Ferring v. Burwell unambiguously held that FDA’s temporally-based NCE exclusivity policy was arbitrary and capricious.³⁶ The Court was clear that FDA provided no sound explanation as to why the timing of or the order in which drugs were approved should alter the assessment of whether the active moiety is sufficiently novel to warrant protection under a five-year exclusivity period. This policy inherently treated similar products differently, as new

³⁴ Id.

³⁵ NDA 203093 for EVG and NDA 203904 for COBI.

³⁶ Memorandum Opinion, Ferring v. Burwell, No. 1:15-cv-00802 (Sept. 9, 2015).



active moieties receiving five-year NCE exclusivity would share such exclusivity with later-approved fixed-combination drug products containing such moieties while the same products approved in the reverse order would receive disparate treatment by being denied NCE exclusivity altogether.

The Court remanded the Prepopik exclusivity determination back to FDA to revise its policy such that similar products receive similar treatment. To do so, FDA must grant five-year NCE exclusivity to Prepopik, as well as to all similarly situated fixed-combination drug products for which NCE exclusivity has previously been denied, including Stribild.

B. In conformity with Ferring v. Burwell, Stribild and its progeny should receive NCE exclusivity

The Court's determination was broadly based on the nature of FDA's NCE policy rather than specific facts relevant to Prepopik. Indeed, the Court explicitly relied on the Stribild fact pattern in reaching its decision in Ferring v. Burwell that FDA's NCE exclusivity policy failed to treat similar products the same. This is despite the fact that Prepopik had no subsequent single agent approval and thus did not fail to treat single agent products the same. However, referring to Stribild, the Court stated that "[t]hese newly highlighted examples now show that, even if the FDA's prior interpretation is reasonable under Chevron Step Two from a conceptual standpoint, that interpretation produces circumstances that fail to treat 'similar cases in a similar manner.'"³⁷

Clearly then, the Court's findings apply even more directly to Stribild as they do Prepopik, entitling Stribild to five-year NCE exclusivity. In addition, under FDA's long-standing umbrella policy, the exclusivity applied to Stribild should follow and protect the new active moieties EVG and COBI. Accordingly, Tybost and Vitekta are entitled to the remaining NCE exclusivity protection awarded to Stribild, which is due to expire on August 27, 2017.

C. FDA must withdraw "receipt" of any filed ANDAs

As noted above, the FDCA prohibits FDA from "receiving" any ANDA application prior to the NCE-1 date; thus, no ANDA application referencing any of these Gilead products should have been received prior to August 27, 2016. Nonetheless, because NCE status had been initially denied, FDA received an ANDA with a Paragraph IV certification referencing Tybost in January 2016 — over 8 months prematurely. Gilead was then forced to bring an infringement suit within 45 days of receiving notice of the ANDA filing in order to trigger a 30-month stay and prevent premature launch of generic product onto the market.

Because none of these events should have occurred when then they did, FDA must withdraw receipt of the ANDA referencing Tybost and, along with it, the Paragraph IV certification. The ANDA filer would incur no harm, as it can refile its ANDA at any time now

³⁷ Memorandum Opinion, Ferring v. Burwell, No. 1:15-cv-00802 (Sept. 9, 2015).



that the NCE-1 date has expired; and Gilead is not required to file suit to trigger the 30-month stay until the end of the five-year NCE exclusivity period.

D. In the interest of fairness, FDA should make this determination promptly

FDA's initial denial of NCE exclusivity, now held to be arbitrary and capricious, has caused Gilead to incur significant costs. Gilead is currently involved in what is now a premature Paragraph IV litigation and could be facing generic competition 18 months earlier than it should.³⁸ Additionally, as this NCE debate ensues, potential ANDA applicants face uncertainty as to the exclusivity of Gilead drugs, and those involved in premature litigation are incurring unnecessary and wasteful expenditures. It is therefore in the best interest of the industry, as well as the public for FDA to make a swift determination and award NCE exclusivity *nun pro tunc* for Stribild, along with "umbrella exclusivity" for Tybost and Vitekta.

IV. ENVIRONMENTAL IMPACT

This petition is categorically exempt from the requirement for an environmental assessment or an environmental impact statement pursuant to 21 C.F.R. §§ 25.30 and 25.31.

V. ECONOMIC IMPACT

Information on the economic impact of the petition will be provided upon request.

VI. 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.

A handwritten signature in black ink, appearing to read "Dana Pizzuti", is written over a horizontal line.

Dana Pizzuti
Vice President, Regulatory Affairs
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
(650) 574-3000

³⁸ Under the current litigation, the 30 month stay expires in September 2018. Under NCE exclusivity, if suit is brought at the end of the five year period, the 30 month stay will not expire until February 2020.