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CITIZEN PETITION

The undersigned, on behalf of Gilead Sciences, Inc. (Gilead), submits this petition under 21 CFR 10.30, among other provisions of law, to request that the Commissioner of Food and Drugs (the Commissioner) recognize 5-year exclusivity under sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the Food, Drug, and Cosmetic Act (FDCA) for the new active moieties in STRIBILD®. STRIBILD is a fixed dose combination (FDC) of four drugs for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults. Two of the four drugs in the product, elvitegravir (EVG) and cobicistat (COBI), contain new active moieties, *i.e.*, active moieties that have not previously been approved in any other new drug application (NDA).

Historically, the Food and Drug Administration (FDA) has interpreted sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) to deny 5-year exclusivity to FDCs if *any* active moiety in the drug product as a whole had previously been approved by the agency. This interpretation dates back to the agency's early implementation of the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act). It pre-dates the agency's extensive Hatch-Waxman rulemaking proceeding, which concluded in 1994. And, most important, it pre-dates the significant advances in medicine in which FDC therapies have been recognized as essential for the treatment of HIV/AIDS and other critical diseases, including cancer, cardio-vascular disease, hepatitis C, bacterial infection, malaria, and tuberculosis.

FDA's historical interpretation is not binding. This petition demonstrates that a new interpretation of the exclusivity provisions applicable to new active moieties in FDCs should be adopted and can immediately be put into practice. A new interpretation is fully justified under the statute; is consistent with the agency's regulations; and is necessary to keep pace with advances in medical science.

Basic principles of administrative law permit FDA to change its statutory interpretation without requiring substantive rulemaking, when the existing interpretation has not been memorialized in an express, formal, and definitive policy or rule. In this case, the most prominent statement of an FDA position on the award of exclusivity to FDCs is contained in an internal agency housekeeping document, known as the Exclusivity Summary. The Exclusivity Summary, and other agency documents that recognize the approach taken in the Exclusivity Summary, do not rise to the level of formality and authority needed to bind the agency, such that notice and comment rulemaking would be needed to establish a new approach.

Further, because other sponsors have not detrimentally relied on FDA's existing interpretation – particularly with respect to STRIBILD (where the agency has yet to publish an exclusivity determination) – the agency may apply a new interpretation of the statute to STRIBILD and, going forward, to all other newly approved FDCs that contain one or more new active moieties. Gilead believes such a result is compelled by the regulations that are currently in place.

For these reasons, Gilead submits this petition to request 5-year exclusivity for the two new active moieties in STRIBILD. In light of the evolving approach to the treatment of an array of serious and life threatening diseases, the agency should begin applying the statutory exclusivity provisions in a manner that supports the development of FDCs. This interpretation should be applied to all newly approved FDCs, and the Exclusivity Summary and other related

agency documents may be revised – without notice and comment rulemaking – to conform to this new interpretation.

ACTIONS REQUESTED

The undersigned requests the Commissioner take the following actions:

- recognize 5-year exclusivity under sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FDCA for each of the new active moieties in STRIBILD, namely EVG and COBI; and

- make any necessary conforming changes to FDA's Exclusivity Summary (Form OGD-0113147) and any other affected agency documents, to reflect an interpretation of the governing statute and regulations that recognizes 5-year exclusivity for all new active moieties, whether first approved as single agents or in FDCs with previously approved active moieties.

STATEMENT OF GROUNDS

I. BACKGROUND

A. The Hatch-Waxman Act And FDA's Early Interpretations Of Statutory Exclusivity

When Congress amended the FDCA through the Hatch-Waxman Act, it put in place an incentive structure designed to authorize affordable generic drugs without undermining the development of innovative drugs. *See generally Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 765 (D.C. Cir. 2010) (recognizing that the exclusivity provisions "struck a balance between

expediting generic drug applications and protecting the interests of the original drug manufacturers"). As an incentive for new drug discovery, sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FDCA establish a period of 5-year exclusivity for a "drug, no active ingredient … of which" had previously been approved. *See* 21 USC 355(c)(3)(E)(ii) and 355(j)(5)(F)(ii).

In early 1988, the Director of FDA's Center for Drug Evaluation and Research (CDER) issued a letter offering an interpretation of 5-year statutory exclusivity that was based on whether any active moiety in the *drug product* as a whole – not the "drug" – had previously been approved. Letter from C. Peck, Director, Center for Drug Evaluation and Research, to all NDA or ANDA Holders and Applicants at 3 (Apr. 28, 1988) (referred to herein as the "Peck Letter") ("The Agency considers a drug product eligible for the five-year period if it contains no active moiety that was previously approved by the Agency.") (internal footnote omitted). Consequently, if a drug product contained an active moiety that had previously been approved, FDA denied 5-year exclusivity, without regard to whether any other active moieties in the product had not been previously approved.

Consistent with the Peck Letter, FDA began circulating a checklist-style document, entitled "Exclusivity Summary," to help the various review divisions collect information to be used by the agency's Office of Generic Drugs (OGD) in making exclusivity determinations. *See* Tab 1 attached (FDA Form OGD-011347) (referred to herein as the "Exclusivity Summary" or "Summary").[1] The Exclusivity Summary is an internal document that is published from time to time for specific drug products in the review documents that support individual drug approval

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[1] The earliest version of the Summary we were able to locate is in a set of NDA review documents for a drug product approved in 1994. That version of the Summary indicates that it was "Revised 7-90." We have included, under Tab 1, a redacted version of that Summary, as well as a redacted version of the Summary from a 2012 NDA approval. A comparison of the two Summaries shows that the relevant language relating to 5-year exclusivity has not changed since 1990.

decisions. The Summary is written based on the assumption that 5-year exclusivity for an FDC would be denied if "any one of the active moieties in the drug product" has previously been approved. *Id.* (original emphasis). To our knowledge, the Exclusivity Summary has never been formally published by the agency in the *Federal Register* or any other public docket. Nor has the agency addressed the Summary in a policy document, points to consider document, or guidance.

B. FDA Rulemaking

In 1989, FDA initiated extensive rulemaking to interpret and govern the agency's implementation of the Hatch-Waxman Act. In particular, the agency proposed a rule intended to help the agency and the public resolve which applications are eligible for 5-year exclusivity and which applications will be "blocked" by that exclusivity. *See* 21 CFR 314.108(b)(2) (discussed at greater length in the next section). To implement this operational rule, FDA also created two regulatory terms not present in the statute: "active moiety" and "new chemical entity." *See* 21 CFR 314.108(a).

FDA's rule incorporates two critical interpretations of the statutory provision. First, FDA refined and replaced the statutory phrase "active ingredient (including any salt or ester of the active ingredient)" with the regulatory term "active moiety." *Id.* An "active moiety" is defined as:

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

Id. (emphasis added). Notably, the agency defined "active moiety" in relation to a specific "drug substance," rather than to the drug product as a whole.

Second, FDA provided a carefully drawn interpretation of the statutory term "drug" as used in the 5-year statutory exclusivity provision. The agency immediately recognized in the preamble to the proposed rules that the term "drug" may refer to a "drug product" or, instead, it may refer to something more specific within the product, such as a drug substance or an "active moiety" within a substance. This distinction – between a drug as a specific drug product, or as a drug substance or an active moiety – was central to resolving the scope of an innovator's exclusivity. 54 Fed. Reg. 28872, 28897 (July 10, 1989). Under the "narrower" interpretation:

> exclusivity covers only specific drug products and therefore protects from generic competition only the first approved version of a drug, or change in a drug. Under this interpretation, an innovator's exclusivity could lose its value as soon as FDA approved a second full new drug application for a version of the drug, because an ANDA could be approved by reference to the second approved version of the drug, which would not be covered by exclusivity.

Id. The disadvantages of reading the term "drug" as "drug product" were clear to the agency:

> [I]f FDA adopted the narrower interpretation that exclusivity covers only a specific drug product and does not prevent ANDAs from copying subsequent versions of the innovative product, a manufacturer of a new chemical entity (entitled to 5 years of exclusivity), could not make improvements in the drug, e.g., by making a new dosage form of the drug, without destroying the value of its exclusivity. Approval of a new dosage form, and certain other changes in approved drugs, require[s] the submission of a new drug application; once approved, the new dosage form would become a new drug product that an ANDA application could copy, without being subject to the exclusivity covering the original drug product.

Id. To avoid significantly diluting the value of the exclusivity, FDA adopted a "broader interpretation" in which exclusivity:

> *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 … from generic competition even after FDA had approved subsequent full new drug applications for subsequent versions of the drug. Under this theory, an ANDA or 505(b)(2) application for a drug with the same active

> moiety as the innovator's new chemical entity ... could not be approved until the innovator's exclusivity expired, even if the ANDA or 505(b)(2) application relied on another approved version of the innovator's drug.

Id. (emphasis added).

Thus, FDA interpreted the statutory phrase "the drug" to refer to a "drug substance" or, more specifically, to an active moiety within a drug substance, rather than a "drug product." This decision is consistent with the agency's linking of an "active moiety" to a "drug substance," in the definition of an "active moiety." Even more, this interpretation forms the basis for FDA's fundamental rule for carrying out the 5-year exclusivity statute – namely, that the exclusivity attaches to and follows a specific moiety rather than a specific product:

> Therefore, *when exclusivity attaches to an active moiety* ..., the submission or effective date of approval of ANDA's and 505(b)(2) applications for a drug with that active moiety ... will be delayed until the innovator's exclusivity has expired, whether or not FDA has approved subsequent versions of the drugs entitled to exclusivity, and regardless of the specific listed drug product to which the ANDA or 505(b)(2) application refers.

Id. (emphasis added); *see also id.* at 28898-99. FDA finalized its regulations in 1994, without substantively changing the relevant exclusivity provisions and without reconsidering its interpretation of the term "drug" as used in the statutory 5-year exclusivity provision. 59 Fed. Reg. 50338 (Oct. 3, 1994).

After promulgating its final rule, FDA did not revisit the Exclusivity Summary then in place. Agency reviewers have continued to use the Summary as a guide to implementing the statute as they had before the final rule. Guided by the Summary, agency personnel have, since 1994, denied exclusivity to approximately 10 FDCs containing both new active moieties and previously approved active moieties.[2] To the best of our knowledge, no sponsor has challenged

[2] In all but two of these cases, any 5-year exclusivity that could have been awarded to these products has expired, and FDA need not revisit those exclusivity awards. To our knowledge, the only currently approved

the agency's continued use of the Summary in these instances. Instead, some sponsors appear to have crafted their development strategies in light of the Summary and sought approval first for a new active moiety as a single entity drug product, to secure 5-year exclusivity, and then sought approval of an FDC incorporating that same moiety sometime thereafter.[3] In some cases, the initial approval of (and grant of 5-year exclusivity for) the single-ingredient product has included labeling allowing for, or even *requiring*, co-administration of the drug with other drugs.[4]

C. Medical Policy On The Development Of Fixed Dose Combinations

In the area of HIV treatment, combination therapy has emerged as the standard of care for HIV-1 infected patients. According to the NIH *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* (*Guidelines*), "[a]chieving viral suppression requires the use of ARV regimens with at least two, and preferably three, active drugs from two or more drug classes." *Guidelines* at D-1.

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products whose 5-year exclusivity would still be ongoing, had FDA applied its regulation as discussed here, are Bayer Healthcare's Natazia® (dienogest; estradiol valerate) and Ferring Pharmaceuticals' Prepopik® (sodium picosulfate; magnesium oxide; citric acid). Based on FDA's Paragraph IV Patent Certifications database, at least one ANDA referencing Natazia has already been submitted, in reliance on the publication in the *Orange* Book of 3-year exclusivity for Natazia. *See Approved Drug Products With Therapeutic Equivalence Evaluations* (commonly referred to as "the *Orange Book*") (32nd Edition, 2012), Prescription and OTC Drug Product Patent and Exclusivity List, at 47.

[3] *See, e.g.*, NDA 20-386 for Cozaar® (losartan potassium), approved April 14, 1995, and NDA 20-387 for Hyzaar® (losartan potassium; hydrochlorothiazide), approved April 28, 1995. Cozaar was granted 5-year NCE exclusivity. *See Orange Book* (18th Edition, 1998), Prescription and OTC Drug Product Patent and Exclusivity List, at 42. *See also, e.g.*, NDA 21-995 for Januvia® (sitagliptin phosphate), approved October 19, 2006, and NDA 22-044 for Janumet® (metformin hydrochloride; sitagliptin phosphate), approved March 30, 2007. Januvia was granted 5-year exclusivity. *See Orange Book* (27th Edition, 2007), Prescription and OTC Drug Product Patent and Exclusivity List, at 107.

[4] *See, e.g.*, discussion of Prezista® (darunavir ethanolate), *infra* at II.A.4.

Moreover, the NIH *Guidelines* recognize that FDCs for the treatment of HIV are vital to ensure dosing compliance, *id.* at F-12 and J-17, and compliance in the treatment of HIV is essential to effective care. In fact, FDA's recent announcement of the STRIBILD approval underscores that today's standard in HIV treatment, and the focus of innovation in the field, is the single-tablet regimen. *See* FDA News Release, *FDA approves new combination pill for HIV treatment for some patients,* August 27, 2012 ("Through continued research and drug development, treatment for those infected with HIV has evolved from multi-pill regimens to single-pill regimens.").

Other FDA guidance documents and policy statements are in accord. As early as 2004, the agency made clear the critical role that drug-drug combinations play in the treatment of HIV and other serious diseases:

> *Combination therapy is essential for the treatment of HIV/AIDS.* The goals of HIV therapy are to maximally and durably suppress the virus to allow recovery of the immune system and reduce the emergence of HIV resistance. At least three active drugs, usually from two different classes, are required to suppress the virus, allow recovery of the immune system, and reduce the emergence of HIV resistance. In the United States and developing countries, simplified HIV regimens in the form of co-packaged drugs (such as blister packs) or FDCs may facilitate distribution and improve patient adherence....
>
> FDA recognizes that FDC and co-packaged products may also be valuable in the treatment of other serious infectious diseases such as tuberculosis and malaria.

Draft Guidance, Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV (May 2004) at 2 (emphasis added) (finalized Oct. 2006).

In the years since 2004, FDA consistently encouraged the development of combination therapies in many therapeutic areas, where either broad spectrum coverage or compliance, or both, are at the core of the therapy. *See, e.g., Draft Guidance, Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination* (Dec. 2010) at 2 ("Combination

therapy is an important treatment modality in many disease settings, including cancer, cardio-vascular disease, and infectious diseases."). To take just a few examples in addition to HIV, FDCs have become or are expected to become the standard of care in the following areas:

- Antibiotics: "Some drugs used in combination may potentiate the effects of the other, such as a combination of amoxicillin (a penicillin derivative) and clavulanate (a beta-lactamase inhibitor). Clavulanate increases the effectiveness of amoxicillin against resistant strains that carry the beta-lactamase gene." Y. Terrie, *Monitoring Combination Drug Therapy,* Pharmacy Times, Jan. 2010.

- Cancer: In 2009, several companies collaborated to study combinations of anti-cancer drugs, but the consensus is that progress has been too slow. *See* E. McCallister, *Combo Conundrums,* in BioCentury on BioBusiness, Nov. 21, 2011 (quoting K. Flaherty, director of developmental therapeutics at Massachusetts General Hospital Cancer Center as saying: "We can't wait for each of these agents to find their home as a single agent before we start looking at combinations . . . .").

- HCV: At a recent meeting of the American Association for the Study of Liver Disease, sponsors reported significant progress in developing "all-oral interferon-free drug combinations for hepatitis C, regimens that don't require ribavirin, and the possibility of a one-pill, once-a-day cure," leading to high expectations "that the first interferon-free, all-oral combinations will enter the market before 2016." *See* S. Haley, *Interferon-Free Hepatitis C Regimens Within Reach,* The Pink Sheet, Nov. 19, 2012.

- Malaria: A report on studies of FDCs to treat malaria in India indicates that a need for innovation in this area continues to exist. *See* A. Anvikar, *et al., Artesunate-Amodiaquine Fixed Dose Combination for the Treatment of Plasmodium Falciparum Malaria In India,* Malaria Journal, Mar. 2012, http://www.malariajournal.com/content/11/1/97 ("Fixed dose combination ASAQ proved to be an efficacious and safe treatment for *falciparum* malaria in both the study areas. The study also showed that the partner drug, AQ was effective in the study areas, making it a suitable partner of artesunate. The combination could prove to be one of the viable options in case India opts for fixed dose combination ACT.").

- Tuberculosis: Since at least 1999 the World Health Organization has advocated for replacing single-drug preparations for treating tuberculosis with FDC tablets.

Furthermore, agency experts have recognized that the use of monotherapies can have adverse medical consequences in some circumstances. *See* J. Woodcock, J. Griffin & R. Behrman, *Development of Novel Combination Therapies*, 364 NEW ENG. J. MED. 985 (2011) (noting concerns about reliance on single-agent therapy for certain diseases, including the potential for single-agent therapies to promote drug resistance).[5]

D. STRIBILD

STRIBILD contains four distinct drugs: elvitegravir (EVG) 150 mg, cobicistat (COBI) 150 mg, emtricitabine (FTC) 200 mg, and tenofovir disoproxil fumarate (TDF) 300 mg. EVG is a new HIV-1 integrase strand transfer inhibitor, a drug that interferes with one of the enzymes that HIV needs to multiply. COBI, a pharmacokinetic enhancer, inhibits an enzyme that metabolizes certain drugs. As used in STRIBILD, COBI improves the pharmacokinetic properties of EVG and enables its administration on a once-daily basis. Thus, Gilead combined EVG boosted by COBI with FTC and TDF, which are nucleoside and nucleotide reverse transcriptase inhibitors preferred by the NIH *Guidelines*. By doing so, Gilead has brought to market the first integrase inhibitor that can be administered once-daily in a single-tablet, complete treatment regimen.

FTC and TDF have each been previously approved in other drug products.[6] However, before STRIBILD, FDA had never approved EVG or COBI, or any salt, ester, or other form of

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[5] FDCs are also critical to developing formulations intended to mitigate the side effects of, or the misuse and abuse of narcotic analgesics or anti-addiction drugs. For example, an FDC may combine an opioid agonist with an opioid receptor antagonist, to mitigate misuse of the product. *See, e.g.*, Embeda® (morphine sulfate; naltrexone hydrochloride). In such a case, the opioid agonist is the sole ingredient responsible for the intended use of the product, while the opioid receptor antagonist is only activated if the drug is misused or abused. FDA's historical interpretation discourages sponsors from developing innovative opioids or other therapeutic agents that may need to be co-formulated with a previously approved ingredient to prevent misuse and abuse.

[6] FDA approved Viread® (TDF) in October 2001 and Emtriva® (FTC) in July 2003. The active moieties in both products were awarded 5-year exclusivity.

these moieties, in any other drug product. For this reason, Gilead submitted with its new drug application (NDA 203100) an Exclusivity Request seeking 5-year exclusivity based on the fact that STRIBILD (referred to in the exclusivity request as "the QUAD") contains at least one new active moiety, *i.e.*, EVG. *See* Tab 2 attached (exclusivity request for NDA 203100). On August 27, 2012, the agency approved STRIBILD. *See* Tab 3 attached (approval letter). As of the date of this Citizen Petition, FDA has not determined the exclusivity to which STRIBILD is entitled.

Gilead is also developing EVG and COBI separately as single entity drug products. Currently pending before the agency is NDA 203093 for EVG as an integrase inhibitor for use in combination with a ritonavir-boosted protease inhibitor and other antiretroviral agents for the treatment of HIV-1 infection in antiretroviral-experienced adults. Gilead submitted this NDA on June 27, 2012. Also pending is NDA 203094 for COBI for use as a booster of the protease inhibitors atazanavir and darunavir in adults. Gilead submitted this NDA on June 28, 2012. Consistent with the exclusivity request for STRIBILD, Gilead has requested that the EVG and COBI active moieties in the single entity products should be protected by 5-year exclusivity. *See* Tab 4 attached (exclusivity requests for NDAs 203093 and 203094).

In the case of STRIBILD, it was both beneficial to patients and feasible for Gilead to develop and seek approval for the four-ingredient, single-tablet regimen in the first instance. The agency's historical statutory interpretation, however, strongly discourages such a course of action. If FDA follows its historical approach in this case, all three products – single entity EVG, single entity COBI, and the FDC, STRIBILD – will earn significantly less regulatory protection than is granted to other, similarly innovative products simply because the STRIBILD approval preceded that of the single entity products. STRIBILD would receive 3-year marketing exclusivity. *See* 21 USC 355(c)(3)(E)(iii) and 355(j)(5)(F)(iii). Upon approval, the EVG and COBI products would also receive only 3-year marketing exclusivity. Gilead has developed and will bring to market three new drug products containing two new active moieties. Despite the

innovation and advancement of HIV therapy represented by these three products, none would be protected by 5-year exclusivity.

As discussed below, FDA is not bound to continue on this path. In fact, many factors – including the public health and the agency's own regulations – make it essential for FDA to update its interpretation immediately.

II. ARGUMENT

A. FDA Can And Should Change Its Interpretation To Conform to Medical Policy

1. The exclusivity statute permits the requested interpretation

The Hatch-Waxman Act's statutory exclusivity provision states:

> If an application submitted under subsection (b) of this section for ***a drug***, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application may be submitted under this subsection [505(j)] which refers to ***the drug*** for which the subsection (b) application was submitted before the expiration of five years from the date of approval of the application under subsection (b)....

21 USC 355(j)(5)(F)(ii) (emphases added); *see also* 21 USC 355(c)(3)(E)(ii) (corresponding provision for 505(b)(2) NDAs).[7]

The statutory provision serves two functions: (1) to determine whether an application will qualify for 5-year exclusivity and (2) to determine which subsequent applications will be blocked by that exclusivity. A drug qualifies for the exclusivity if it is "a drug, no active ingredient (including any ester or salt of the active ingredient) of which has [previously] been approved."

[7] The statute provides an exception to allow an applicant to submit an application four years following the date of approval if it contains a patent challenge described in sections 505(b)(2)(A)(iv) or 505(j)(2)(A)(vii)(IV) of the FDCA.

Id. And, the exclusivity will block any subsequent application "which refers to the drug for which the [previous] application was submitted." *Id.*

In both contexts, the term "drug" is ambiguous. The statute speaks of "a drug" and "the drug" in the singular. But, it does not plainly state whether the exclusivity should be recognized as to each drug that is the subject of the 505(b) application or, in the alternative, whether it should be recognized only for the product as a whole. For a product that contains a plurality of active ingredients, this ambiguity is critical. Congress, however, did not resolve this ambiguity by directing an outcome with clear and definitive statutory language. *See, e.g.*, 54 Fed. Reg. at 28897 (noting the ambiguity in the scope of the 5-year exclusivity provision).

The FDCA, in section 201(g)(1), defines "drug" as having several meanings, including both a finished drug product "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles intended for use as a component" of any finished drug product. 21 USC 321(g)(1). Courts have long recognized the flexibility in the definition of the word "drug" in the statute. *See, e.g., Pharmanex v. Shalala,* 221 F.3d 1151 (10th Cir. 2000) (noting that "drug" may mean finished drug product and individual components, and that FDA approves both the finished product and individual active ingredients when it approves an NDA).[8]

Further, the interpretation of "a drug" and "the drug" is dependent on how other ambiguous terms within the exclusivity provision are construed – the most important of which is the term "active ingredient." *See Abbott Labs. v. Young*, 920 F.2d 984, 985, 987 (D.C. Cir. 1990) (finding the term "active ingredient" ambiguous in an analogous exclusivity provision).

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[8] The agency defines the term "drug product" to mean "a finished dosage form, for example, tablet, capsule, or solution, that contains a *drug substance*, generally, but not necessarily in association with one or more other ingredients." 21 CFR 314.3(b) (emphasis added). The term "drug substance" means "an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body." 21 CFR 314.3(b). *See* Glossary at Appendix A to the Petition.

As with the term "drug," and the phrases "a drug" and "the drug," the statute refers to "active ingredient" in the singular, not active ingredients. Again, this may lead to the conclusion that the statutory exclusivity should be analyzed and recognized with respect to each drug and each active ingredient under a given 505(b) application. It is, however, not clear, leaving ample room for interpretation. There is, for example, no express language in the provision evidencing Congressional intent with respect to drug products that combine two or more drugs in a single dosage form. *See* 21 CFR 300.50 (recognizing that "[t]wo or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects....").

Also, as discussed in section II.A.2., *infra*, FDA interpreted the statutory term "active ingredient" to mean "active moiety" and defined active moiety in relation to a "drug substance" rather than a "drug product." *See* 21 CFR 314.108(a) (definition of "active moiety"). And, FDA has made clear that 5-year exclusivity is granted for, and attaches to, active moieties. Thus, FDA itself has shown that the statutory provision is subject to interpretation, and depending on how key terms are interpreted and defined, the operation of the statutory provision may change.

Finally, the interpretation of the statutory provision is dependent on certain policy choices, such as whether the exclusivity should be read broadly to protect active moieties, or narrowly to protect only specific drug products. 54 Fed. Reg. at 28897. As discussed in section II.A.2., *infra*, FDA made a carefully considered policy decision that 5-year exclusivity is specific to an active moiety, rather than to a drug product. *See* 54 Fed. Reg. at 28897 (finding that it would "seriously undermine" 5-year exclusivity if "the drug," as used here, were interpreted to mean "drug product"). That is, the agency concluded that the phrase "*the drug* for which the subsection (b) application was submitted" refers to a specific drug substance that contains a new active moiety. The phrase "the drug" as it appears in the statute clearly refers back to the original drug – "a drug" – that was the subject of a 505(b) application that may be eligible for 5-year exclusivity.

In short, the 5-year exclusivity provision is subject to multiple interpretations. Nevertheless, the best reading of the statute – and the one that best reflects the agency's rulemaking choices – is that for a 505(b) application that contains a fixed dose combination of drugs, the exclusivity must be analyzed and granted as to each drug that is the subject of the application. This reading fits naturally within FDA's governing regulation and definitions, and it fully supports the incentive structure that Congress put in place to reward the development of new active moieties.[9] *See infra* at II.A.3.

2. The existing regulation, 21 CFR 314.108(b)(2), requires the requested actions

In 1994, FDA finalized a comprehensive set of regulations governing the implementation of Hatch-Waxman, including a specific rule on the meaning and operation of the 5-year exclusivity provision. Under 21 CFR 314.108,

> If a *drug product* that contains a *new chemical entity* was approved after September 24, 1984, in an application submitted under section 505(b) of the act, no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for a drug product that contains *the same active moiety* as in *the new chemical entity* for a period of 5 years from the date of approval of the first approved new drug application....

21 CFR 314.108(b)(2) (emphases added). As stated, a drug product will qualify for 5-year exclusivity if it "contains a *new chemical entity*." Further, the agency is precluded from accepting an application for a drug product that contains "the same *active moiety* as in the new chemical entity" until the exclusivity period has expired.

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[9] Such an interpretation also is consistent with a recent decision interpreting the Hatch-Waxman Act. In *Teva Pharmaceuticals, Inc. v. Sebelius*, 595 F.3d 1303, 1315 (D.C. Cir. 2010), the D.C. Circuit rejected FDA's contention that the statute's plain language divested a sponsor of exclusivity. In reaching that conclusion, the court relied on the broader architecture of the Hatch-Waxman Act's incentive provisions to inform its reading of the statute. *See id.* at 1318.

At the core of this provision are three terms – (1) drug product, (2) new chemical entity, and (3) active moiety – that determine the award and scope of 5-year exclusivity. A "drug product" means a "finished dosage form . . . that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients." 21 CFR 314.3(b). Here, instead of using the term "drug substance" in section 314.108(b)(2), the agency used the term "new chemical entity." However, to the extent a new chemical entity is contained within a drug product, a new chemical entity must be on par with a drug substance.

A "new chemical entity" is defined to mean "a *drug* that contains no *active moiety* that has been approved by FDA in any other application submitted under section 505(b) of the act." 21 CFR 314.108(a) (emphases added). Although the agency retained the ambiguous statutory term "drug," in the context of the regulation as a whole, "drug" is more correctly read to mean "drug substance" rather than "drug product."

First, the critical term "active moiety" is itself defined with reference to the molecular structure of an individual *drug substance*:

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

21 CFR 314.108(a) (emphasis added).

Second, the agency defined the term "new chemical entity" specifically to be used in the operational exclusivity provision at section 314.108(b)(2). Section 314.108(b)(2) begins: "If a drug product that contains a new chemical entity...." Plainly, if "new chemical entity" meant the same thing as "drug product," the provision would be needlessly redundant; a drug product cannot "contain" itself. Rather, a drug product contains one or more drug substances. There is a

way to harmonize the definition with the exclusivity provision itself, and that is to read the term "new chemical entity" as referring to an individual drug substance and not a drug product.

Third, related regulations under 21 CFR part 314 reinforce the conclusion that the term "a drug" means something different than the term "drug product" in the exclusivity context. FDA's "refuse to file" regulation, 21 CFR 314.101(e)(2), requires FDA to refuse to file an ANDA or 505(b)(2) NDA during the exclusivity period, if the application is for a "*drug product* [that] contains the same active moiety as a *drug* that … is entitled to a 5-year period of exclusivity…." 21 CFR 314.101(e)(2) (emphases added). Likewise, 21 CFR 314.50(j) carefully distinguishes between a "drug product" that is the subject of an application, and the "drug" that is the focus of an exclusivity determination. Under that regulation, FDA recognizes that "[a] new *drug product*, upon approval, may be entitled to a period of marketing exclusivity under the provisions of § 314.108." 21 CFR 314.50(j) (emphasis added). Immediately following this statement, the agency uses "a drug" and "the drug" rather than "drug product" to frame the standard when an applicant is applying for exclusivity. Specifically:

> If the applicant claims exclusivity under § 314.108(b)(2), [the sponsor must submit] information to show that, to the best of its knowledge or belief, *a drug* has not previously been approved under section 505(b) of the act containing any active moiety in *the drug* for which the applicant is seeking approval.

21 CFR 314.50(j)(3) (emphasis added). Thus, within section 314.50(j), the agency moves from the broader concept of the "drug product" to the more specific concept of a drug substance within the product. It would have been effortless from a drafting perspective for the agency to have used the term "drug product" throughout both 314.101(e)(2) and 314.50(j). But the agency did not do that – just as it chose not to use the term "drug product" in the definition of a "new chemical entity." If FDA had intended to require that all moieties within a proposed drug product must be new for the product to earn the exclusivity, the agency would have used the term

"drug product" in each of these provisions. Instead, the agency used a term that more properly communicates an individual substance, *i.e.*, drug.

Next, as a matter of plain and common usage, the term "new chemical *entity*" communicates the idea of a singular chemical structure, rather than a combination or grouping of structures. If the agency had intended to include combinations of ingredients, it would not have used a singular term. The agency chose a term, "entity," that is commonly understood to mean: a thing with distinct and independent existence, *see Oxford Dictionary*, or something with an independent, separate, or self-contained existence, *see Merriam-Webster Dictionary*. All of these meanings align with the idea of an individual drug substance.

Finally, it is commonly understood that FDA awards 5-year exclusivity for specific ingredients, not groups or combinations of ingredients. FDA made this very clear when it developed the exclusivity regulations:

> Therefore, *when exclusivity attaches to an active moiety* or to an innovative change in an already approved drug, the submission or effective date of approval of ANDA's and 505(b)(2) applications for a drug with that active moiety or innovative change will be delayed until the innovator's exclusivity has expired, whether or not FDA has approved subsequent versions of the drugs entitled to exclusivity, and *regardless of the specific listed drug product to which the ANDA or 505(b)(2) application refers.*

54 Fed. Reg. at 28897 (emphases added). Further, FDA determined that 5-year exclusivity travels with the new active moiety to any drug product subsequently developed by the sponsor that contains that moiety. *See id. at* 28898-99 (describing what FDA now refers to as the "umbrella policy"). This ensures that a sponsor who has developed a new active moiety still has the incentive to further develop drug products containing that moiety. The ingredient- or moiety-specific nature of the award squarely aligns with the conclusion that the phrase "a drug" as used in 21 CFR 314.108 means a specific drug substance, just as it does in the statute. *See supra* at II.A.1.

For all of these reasons, if a drug product contains a new chemical entity – *i.e.*, a drug substance that does not contain a previously approved active moiety – then the agency must award the sponsor with 5-year exclusivity. *See* 21 CFR 314.108(b)(2). As applied to STRIBILD, FDA should not accept another sponsor's ANDA or 505(b)(2) NDA that contains either of the active moieties in EVG or COBI until the exclusivity period expires.

3. The legislative history supports awarding exclusivity to new active moieties

The legislative history of the Hatch-Waxman Act demonstrates three important points relevant to the issue raised in this petition. First, Congress intended to provide a specific and valuable incentive for the development of new active moieties. *See, e.g.*, 130 Cong. Rec. 9114 (daily ed. Sept. 6, 1984) (statement of Rep. Waxman) ("[T]he amendment provides a 5-year period of exclusive market life for drugs approved for the first time after enactment of this legislation. This provision will give the drug industry the incentives needed to develop new chemical entities . . . ."). Second, and closely related to the first, Congress did not want to reward "minor variations" of previously approved active moieties. *See* 54 Fed. Reg. at 28897; *see also id.* at 28896 ("Congress understood that the substantial economic rewards of exclusivity might well encourage drug companies to make minor and unimportant alterations in their marketed drug products . . . ."). The minor variations about which Congress was concerned were new esters or salts of previously approved active moieties. *See* 21 USC 355 (c)(3)(E)(ii) and 21 USC 355(j)(5)(F)(ii) (defining "new active ingredient" as excluding "any ester or salt of the active ingredient"). The goal was to make 5-year exclusivity "limited to new chemical entities, which by definition are innovative . . . ." 54 Fed. Reg. at 28897. Finally, there is no evidence in the legislative history that Congress intended to withhold this valuable incentive where an innovative active moiety is approved in the first instance in an FDC with a previously approved active moiety.

As FDA has acknowledged, Congress relied on the IND/NDA classification system in effect at the time when it developed the exclusivity framework under the Hatch-Waxman Act. *See* 54 Fed. Reg. at 28897-98 (noting that Congress was aware of the IND/NDA classification scheme and relied on that system to ensure that it did not enact legislation that would "confer significant periods of exclusivity on minor variations of previously approved chemical compounds"). Under that system, the agency classified products based on, among other things, whether the product contained a "new molecular entity" (NME). A product that contained at least one NME was classified as a Type 1 IND or NDA.[10] According to the definition in place at the time:

> A new molecular entity is considered *an active moiety* that has not previously been approved (either as the parent compound or as a salt, ester or derivative of the parent compound) in the United States *for use in a drug product either as a single ingredient or as part of a combination.*

Tab 5 attached (FDA Staff Manual Guide No. BD 4820.3 (Aug. 31, 1976) (emphases added), *accord* FDA Staff Manual Guide No. BD 4820.3 (Feb. 19, 1982) (cited in *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392 n.8 (Fed. Cir. 1990))). In other words, an NME is a drug substance that contains a new active moiety. By contrast, a new salt or ester of a previously approved active moiety is not considered to be innovative, and as explained above, Congress did not want to reward their development with 5-year exclusivity.

There is no evidence, however, that Congress considered the development of an FDC, in which a previously approved active moiety is formulated with a new active moiety, to be a "minor variation" of that previously approved moiety, in the same way that a new salt or ester of that moiety would be. For example, there is nothing in the definition of a "new molecular entity"

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[10] Other classifications under the scheme at the time included: Type 2 (new salt, ester or other derivatives of a marketed active moiety), Type 3 (new formulation), Type 4 (new combination), or Types 5 and 6 (already marketed drug products). *See* Tab 5 (FDA Staff Manual Guide No. BD 4820.3) at 2.

as presented to Congress at the time to suggest that an active moiety should be considered any less new or innovative simply because it was first developed as part of an FDC that also contained other, previously approved active moieties. In fact, the definition of an NME recognizes that an active moiety may be approved *either* alone or as part of an FDC, and the novelty of an active moiety depends simply on whether it has previously been approved, *irrespective of its dosage form.* But, once an active moiety is determined not to have been previously approved, the NME definition places no relevance on whether that active moiety is being developed for first approval alone or in an FDC.[11]

The legislative history of the exclusivity provisions is limited. But that which is available confirms that Congress intended to award its most valuable form of exclusivity to sponsors who

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[11] The preambles to the proposed and final rules contain few relevant references. What references there are do not foreclose Gilead's position; in fact, they support it. *See, e.g.*, 54 Fed. Reg. at 28898 ("A drug product is entitled to 10 years of exclusivity only if it does not contain an active moiety that has been part of a drug product previously approved under section 505(b) of the act *either as a single ingredient or as one ingredient of a combination drug product*." (Emphasis added)); 59 Fed. Reg. at 50359 ("For some drug products marketed before 1938 or 1962, the active moiety will have been the subject of an approved application (under prior versions of the act *or as part of a combination product approved under the act*), so the active moiety will be ineligible for 5-year exclusivity." (Emphasis added.)). These statements merely acknowledge the basic rule, based on the agency's system for classifying drugs as new molecular entities, that an active moiety is not new if it has been approved in *any* application under section 505(b) of the FDCA, whether alone or as part of a combination. FDA was, of course, well aware that an active moiety could be approved in an FDC. Nevertheless, the agency made no reference in any other relevant part of the preambles – or in 21 CFR 314.108 itself – to FDCs. There is certainly no express agency statement that a new active moiety first approved as part of an FDC with previously approved moieties cannot be protected by 5-year exclusivity.

FDA was, of course, well aware that an active moiety could be approved in an FDC. Nevertheless, the agency made no reference in any other relevant part of the preambles – or in 21 CFR 314.108 itself – to FDCs. There is certainly no express agency statement that a new active moiety first approved as part of an FDC thereby fails to qualify for 5-year exclusivity.

developed new active moieties, and that Congress rightly understood that the novelty of an active moiety has nothing to do with the dosage form in which it is first approved.[12]

4. FDA's historical interpretation leads to arbitrary results for FDCs

The interpretation outlined by Gilead in this petition differs from the agency's historical interpretation in only one respect: the treatment of FDCs that contain both new and previously approved active moieties. Gilead has proposed an interpretation that is compelled by FDA's own regulation. Gilead's interpretation has the added virtue of harmonizing the treatment of FDCs with the treatment of other products. By contrast, FDA's historical interpretation is not only out of step with the governing regulation, it also leads to illogical and arbitrary results for FDCs such as STRIBILD.

In particular, FDA's approach puts undue weight on the order in which a sponsor's applications are approved in deciding whether to award 5-year exclusivity. If a sponsor develops a new active moiety that can be approved both as a single entity product or as part of an FDC product also containing a previously approved active moiety, the exclusivity award for those products will depend entirely on the order of FDA approval. Thus, if a single entity product containing a new active moiety is approved just one day before – or even on the same day as – the approval of the same moiety in an FDC containing a second, previously approved moiety, the single entity product earns 5-year exclusivity. Moreover, under FDA's umbrella policy, this exclusivity covers the subsequent use of the active moiety in the FDC, so that product would also be covered by the 5-year exclusivity. *See* 54 Fed. Reg. at 28898-99. However, if the approval order of these applications is reversed, FDA does not award 5-year exclusivity to either product. In no other situation does the operation of 5-year exclusivity hinge on such an arbitrary issue of

[12] FDA's historical interpretation does not implement Congress' intent when it does not award 5-year exclusivity to new active moieties first approved in FDCs with previously approved active moieties. *See Teva Pharms., Inc. v. Sebelius*, 595 F.3d at 1316 ("FDA may not … change the incentive structure adopted by Congress" (quoting *Ranbaxy Laboratories Ltd. v. Leavitt*, 469 F.3d 120, 121-22 (D.C. Cir. 2006)).

sequence. There is simply no evidence in the legislative history that Congress intended that a new active moiety would be denied 5-year exclusivity simply because its approval as part of an FDC pre-dated its approval in a single-ingredient dosage form. *See Abbott Labs*, 920 F.2d at 989. As with the interpretation offered by Abbott in that case, FDA's approach to exclusivity for FDCs "fails to serve any conceivable statutory purpose." *Id.*

Similarly, rigid application of FDA's historical interpretation to FDCs also creates inconsistent exclusivity determinations with respect to cross-labeled drug combinations. Compare the exclusivity award for FDCs with the exclusivity determination for Prezista (darunavir ethanolate), an anti-HIV drug that was awarded 5-year exclusivity when it was approved in June 2006.[13] Prezista was approved with a label requirement that it must *always* be co-administered, *i.e.*, used only in combination with a specific dose of the previously-approved drug, Norvir® (ritonavir).[14] However, because darunavir ethanolate was approved not as an FDC with ritonavir, but rather as a separate drug product requiring co-administration, darunavir ethanolate was recognized as an NCE and awarded 5-year exclusivity. Again, there is no evidence that the statute intended to draw such an arbitrary and capricious distinction between an active moiety specifically required by FDA-approved labeling to be used in combination with a previously approved moiety, and those same moieties formulated together as an FDC.

Where an interpretation perpetuates arbitrary and irrational results, it need not – indeed, it should not – be followed. The interpretation embodied in the regulation and proposed by Gilead in this petition would avoid these results for FDCs that contain both new and previously

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[13] *See Orange Book* (27th ed., 2007), Prescription and OTC Drug Product Patent and Exclusivity List, at 28.

[14] *See* package insert (June 2006) at 14 ("PREZISTA, co-administered with 100 mg ritonavir . . . and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains"); *see also id.* at 20-21 ("PREZISTA must always be used with 100 mg of ritonavir (NORVIR®) in combination with other antiretroviral drugs.").

approved active moieties. Instead, this alternate interpretation allows for a sensible result for FDCs that is fully consistent with the incentive structure and legislative intent of the statute. For all other exclusivity determinations, this alternate interpretation does not diverge from FDA's historical approach. For these reasons, Gilead's is the interpretation that should be embraced for FDCs, particularly when the agency and other experts in the community are encouraging sponsors to develop new FDCs to treat serious diseases.[15]

5. Recent legislation and administrative changes to the review process support a change in statutory interpretation

For more than twenty years, the statutory language at issue in this petition – "a drug, no active ingredient ... of which" – appeared only in the Hatch-Waxman exclusivity provisions. However, more recently, Congress has begun to use the identical language in other parts of the FDCA. The new use of this language provides yet another reason for FDA to review and update its 5-year exclusivity interpretation. In fact, FDA has now read the identical language as that found in the exclusivity statute to have the meaning proposed by Gilead, when that language is applied to FDCs.

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[15] Gilead's interpretation is also consistent with how the Patent and Trademark Office analyzes eligibility for patent term extensions on an ingredient-by-ingredient basis for products that contain more than one active ingredient. Gilead recognizes that the statutory language that governs FDA's determinations of NCE exclusivity is distinct from that which governs patent term extensions under 35 USC 156. Although the operational language in the patent statute is different than in the FDCA's exclusivity provision, and the two statutes are subject to independent interpretation, each is amenable to an interpretation that allows the respective agencies to recognize the novelty and newness of individual active moieties, even when approved in an FDC with other active moieties. For patent term restoration, Congress achieved that result through a new section in Title 35 that defines "drug product" to mean active ingredient, whether approved "as a single entity or in combination with another active ingredient." 35 USC 156(f)(2); *see also* Letter from Keith O. Webber, Ph.D., Deputy Director, Office of Pharmaceutical Science, CDER, regarding Torisel Exclusivity Determination, at 11 (May 29, 2012) (Federal Circuit's "interpretation of 'active ingredient' [in 35 USC 156] is inapplicable because it does not pertain to the statutory provisions that govern FDA's determination of NCE exclusivity.") For 5-year exclusivity in the FDCA, Congress worked within the existing definitions to provide FDA with the flexibility to achieve the same result. *See supra* at II.A.1 (discussing how "drug" should be read to mean "drug substance" in the 5-year exclusivity provision, yielding the same outcome).

In the FDA Amendments Act of 2007 (FDAAA), Congress used the language – a "drug, no active ingredient … of which" – to determine when a new drug application triggers the need for additional review, or additional administrative process, due to concerns about the safety of new active moieties. This includes referral to an advisory committee and prompt posting of the action package in support of the approval of all new active moieties. Here, FDA has interpreted the statutory language to apply to every product where at least one drug substance contains a new active moiety, even where that moiety is approved for the first time in an FDC with a previously approved moiety. These interpretations are at odds with FDA's historical approach denying 5-year exclusivity to FDCs containing both new and previously approved active moieties.

Under the first FDAAA provision, "[p]rior to the approval of a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved" in an NDA or biologics license application (BLA), FDA must either refer the drug to an FDA advisory committee for review prior to approval or must state in the action letter its reasons for not doing so. 21 USC 355(s). Congress instituted this and other FDAAA safety provisions in reaction to risks that should have been detected with drugs like Vioxx®, Ketek®, Paxil®, and Avandia®,[16] all of which contained new active moieties. The extra risks of a new active moiety are no less when a sponsor combines them in an FDC with a previously approved moiety.

Accordingly, FDA has interpreted 21 USC 355(s) to apply to FDCs that contain both new and previously approved active moieties. For example, the FDCs Prepopik (sodium picosulfate; magnesium oxide; citric acid) and Natazia (dienogest; estradiol valerate) each contain both a new active moiety and a previously approved moiety. FDA's approval letters for both products conform to 21 USC 355(s) by providing explanations for not referring those drugs to an advisory committee. Consistent with this provision, STRIBILD itself was referred to an advisory committee. To the best of Gilead's knowledge, FDA has thus interpreted the phrase, "drug, no

[16] 153 Cong. Rec. H10596 (daily ed. Sept. 19, 2007) (statement of Rep. Markey).

active ingredient . . . of which" to reach FDCs such as STRIBILD, based on the same language as the Hatch-Waxman exclusivity provisions.

FDA has similarly interpreted the same language in a second FDAAA provision. Section 505(l) of the FDCA requires FDA to publish on its web site the action package of approval for an NDA or BLA not later than 30 days after approval of "a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other [NDA or BLA] . . . ." 21 USC 355(l)(2)(A)(i). For all other drugs, Congress did not require posting unless and until the agency receives three requests for the approval package under the Freedom of Information Act. *Id.* at 355(l)(2)(A)(ii).

The rationale for this provision is that prompt public scrutiny is particularly important for drug approvals involving a new active moiety. No evidence suggests that Congress believed public scrutiny to be any less necessary if a new moiety is approved in an FDC with a previously approved one. In fact, during legislative debate Senator Grassley made clear that what is important when applying the provision is that the drug contains a new active ingredient,[17] not that *all* the active ingredients must be new. Consistent with this expectation, FDA has, to the best of Gilead's knowledge, interpreted this language to require expedited public posting of approval documents for all drug products that contain new active moieties. For example, FDA posted the drug approval package for Natazia exactly 30 days after approval.

Finally, Congress also used the same language in section 524 of the FDCA to determine when a sponsor of a new tropical disease product is eligible for a valuable priority review voucher – that entitles the holder to receive priority review for any application the holder chooses, and which entitlement it may sell. 21 USC 360n. Among the eligibility criteria is the requirement that the application "is for a human drug, no active ingredient (including any ester or

[17] 153 Cong. Rec. S4666 (daily ed. Apr. 18, 2007) (statement of Sen. Grassley) ("This requirement, however, only applies to a drug with an active ingredient that has not been previously approved by the FDA.").

salt of the active ingredient) of which has been approved in any other [NDA or BLA]." 21 USC 360n(a)(4)(C).

Contrary to its interpretation of the two provisions discussed above, FDA has taken a position in draft guidance that if a tropical disease product contains any "active ingredient" that has been previously approved, the application is not eligible for a priority voucher." *See Draft Guidance, Tropical Disease Priority Review Voucher* (October 2008) at 6-7. Nothing in the legislative history of FDAAA suggests that Congress intended this provision to be interpreted differently than the two provisions discussed above, and FDA offered no explanation in this draft guidance for the disparate interpretations. Moreover, Gilead is not aware of any instances in which FDA has applied this interpretation to deny awarding a priority review voucher.[18]

Consistent with Congress' intent in FDAAA, FDA's own policies have increasingly singled out new active moieties for special treatment, whether or not combined with previously approved moieties. For example, NDAs containing previously unapproved active moieties require office-level sign-off. All other approvals may be signed by division-level personnel. *See* 2 FDA Staff Manual Guides §1410.104(1)(C) (granting division directors and deputy directors authority to approve new drug applications other than those that contain "new molecular entities").[19] In applying that policy to FDCs containing both new and previously approved active moieties, FDA requires office-level sign-off. For example, the Office Director signed the approval letter for STRIBILD. *See* Tab 3. Thus, FDA treats STRIBILD similarly to any other product containing a new active moiety, in contrast to the treatment that the agency would give STRIBILD with respect to 5-year exclusivity if the agency followed its historical policy.

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[18] If the Commissioner grants this petition, the agency should update its draft guidance so that its interpretation of section 524 of the FDCA comports with the interpretation of 5-year exclusivity reflected in this petition. Updating the guidance may stimulate development, particularly given that only two tropical disease priority review vouchers have been granted in the more than five years since FDAAA was enacted.

[19] *Available at:* http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm049625.htm.

In addition, FDA also recently announced that an additional two months of review time will be applied to all NDAs containing new active moieties. Specifically, in the PDUFA Reauthorization Performance Goals and Procedures For Fiscal Years 2013 Through 2017 (at 4), the performance goal for standard applications containing a "new molecular entity" – *i.e.*, a previously unapproved active moiety, *see supra* at II.A.3. – is to review and act on 90 percent of submissions "within 10 months of the 60 day filing date." In contrast, for standard "non-new molecular entity" NDAs, the 10-month performance goal runs from the date FDA receives the application, effectively providing two fewer months for the review. *Id.* The obvious reason behind this distinction is the greater amount of review time and effort necessary when a new active moiety is involved. That time and effort is no less when a sponsor seeks approval for that new active moiety in an FDC with a previously approved moiety.

Finally, the recent PDUFA performance goals document establishes a program designed to increase the number of first cycle review approvals for new molecular entities. *Id.* at 5-11. The program seeks to improve communication between the FDA review team and applicants by instituting more interim meetings and exchanges, such as a pre-submission meeting, a mid-cycle communication following the agency's mid-cycle review meeting, early discipline review letters, a late-cycle meeting, and early inspections. *Id.* The PDUFA performance goals document states that the decision to include an application in the program "is distinct from FDA's determination as to whether the drug product contains a 'new chemical entity,' as defined under 21 CFR 314.108(a)," given that new chemical entity exclusivity determinations are made at the time an application is approved. *Id.* at 6 n.2. But the document does not suggest that those determinations are any different for FDCs containing a new active moiety than any other such drug product.

Together, FDA's recent statutory interpretations and policy initiatives demonstrate two important points. First, FDA's interpretation of sections 505(s) and 505(l) of the FDCA

reinforces Gilead's position that the statutory term "drug" can be interpreted to mean drug substance in the Hatch-Waxman Act's exclusivity provisions. Second, most of FDA's recent positions provide further evidence that scientific and medical policy regarding new active moieties has diverged significantly from FDA's historical approach to 5-year exclusivity as applied to FDCs. Adopting the exclusivity approach outlined in this petition will allow the agency to consistently interpret the same statutory language in a manner that (1) advances Congress' interest in providing additional scrutiny to new active moieties; (2) advances the agency's interest in providing more time for review of those new active moieties; and (3) advances medical policy by upholding incentives for development of new active moieties in FDCs, where medically desirable.

B. Administrative Law Permits A Change In Interpretation Without Notice And Comment Rulemaking

As shown, the medical community – including the agency's own experts – have concluded that FDC therapy is "essential for the treatment of HIV/AIDS" and is "an important treatment modality in many disease settings, including cancer, cardio-vascular disease, and infectious diseases." *See supra* at I.C. This evolution in drug development – primarily from "combinations of convenience" to "combinations of necessity" – provides a strong basis for the agency to update its application of the statutory incentive structure. The incentive to develop new active moieties can and should be aligned with patient needs and state of the art medical policy.

The agency's historical interpretation of the statutory exclusivity provisions strongly disfavors developing new active moieties for use in FDCs, unless the new moiety can first be developed in a single entity drug product. This can lead to unnecessary delay in introducing single-tablet solutions for diseases such HIV/AIDS, and can cause sponsors to develop single entity products – and prioritize the submission of the single entity product ahead of an FDC – solely to secure the exclusivity. There is a much better way for the agency to proceed, which is

in the best interest of patients and which can be achieved without a prolonged administrative process.

First, as shown above, the existing regulation (21 CFR 314.108) not only allows FDA to award 5-year exclusivity to individual active moieties in FDCs but, as shown in section II.A.2, *supra*, the best reading of the regulations appears to mandate such an approach. The agency, however, has continued to follow the approach outlined in the pre-regulation Exclusivity Summary. Immediate implementation of the reading of the regulation outlined in this petition would allow the agency to reward sponsors who develop new active moieties, alone or in combination with other drugs, and would eliminate the perverse incentives caused by the current approach.

Second, the agency must recognize a new interpretation of the statute itself, and must conform its own practice to the new interpretation, including revising the Exclusivity Summary. This change can be achieved immediately, in the specific case of STRIBILD, and can be implemented as to all newly approved FDCs that contain new active moieties, without the need for a change to the regulation or other notice and comment proceeding. The existing regulations can readily be applied to FDCs in a manner that protects new active moieties from being referenced in 505(b)(2) NDAs and 505(j) ANDAs during the 5-year exclusivity period.

Finally, even if the regulation is ambiguous, applying a new interpretation to STRIBILD and future products fully comports with established administrative procedure. It is settled law that "an agency is free to alter its past rulings and practices even in an adjudicatory setting." *Airmark Corp. v. FAA*, 758 F.2d 685, 691-692 (D.C. Cir. 1985) (citation omitted); *see also, e.g., SEC v. Chenery Corp. (II)*, 332 U.S. 194, 202-203 (1947). Of course, "[w]hen an agency has given its regulation a definitive interpretation," on which there has been "substantial and justifiable reliance," and the agency "later significantly revises that interpretation, the agency has in effect amended its rule, something it may not accomplish without notice and comment."

Honeywell Int'l, Inc. v. NRC, 628 F.3d 568, 579 (D.C. Cir. 2010) (quoting *Alaska Prof'l Hunters Ass'n v. FAA*, 177 F.3d 1030, 1034 (D.C. Cir. 1999); *MetWest Inc. v. Sec'y of Labor*, 560 F.3d 506, 509-10 (D.C. Cir. 2009)). Neither condition is met in this case because the agency's past interpretation was neither "definitive" nor has it been substantially and justifiably relied upon, particularly for newly approved products such as STRIBILD.

1. FDA has not provided a definitive interpretation of 5-year exclusivity for FDCs

A "definitive" agency interpretation means an "express, direct, and uniform interpretation" of the regulation at issue. *Association of Am. R.Rs. v. DOT*, 198 F.3d 944, 949 (D.C. Cir. 1999). It must be "a definitive and binding statement on behalf of the agency" that "come[s] from a source with the authority to bind the agency." *Devon Energy Corp. v. Kempthorne*, 551 F.3d 1030, 1040 (D.C. Cir. 2008). A definitive agency interpretation also must have "the force of law" in that it "'mark[s] the consummation of the agency's decisionmaking process . . . .'" *Id.* at 1039 (quoting *Bennett v. Spear*, 520 U.S. 154, 177-78 (1997)). An interpretation that "does not cabin agency discretion" is not likely to be definitive. *Hudson*, 192 F.3d at 1035. "'The language actually used by the agency' is often central to making such determinations." *Wilderness Society v. Norton*, 434 F.3d 584, 595 (D.C. Cir. 2006) (quoting *Community Nutrition Inst. v. Young*, 818 F.2d 943, 946 (D.C. Cir. 1987)). But even where the agency "uses mandatory language" in a particular document, the court will view "the document as a whole" to determine whether it "read[s] as a set of rules." *Id.* If it "lacks precision in its directives," then the document is likely just "a statement of policy, not a codification of binding rules." *Id.*

The court has made clear that when it says that an interpretation must be "express, direct, and uniform" in order to bind the agency in the future, it really means it. Indeed, even where an agency's interpretation may be inferred from its actions, that inference does not qualify as a definitive interpretation. For example, the court in *Hudson v. FAA*, 192 F.3d 1031 (D.C. Cir.

1999), rejected such a reading of *Alaska Professional Hunters*, the seminal case from which the rule requiring notice and comment rulemaking for changes to certain agency regulatory interpretations arises:

> Although petitioners argue that *Alaska Professional Hunters* is pertinent because it, like this case, involved a long-term agency practice which constituted an implicit interpretation or application of the relevant regulation, that is not so. In that case, a formal adjudication by an associate agency had adopted an interpretation of the regulation in accord with the informal practice. *See Alaska Professional Hunters*, 177 F.3d at 1031.

Hudson, 192 F.3d at 1036; *see also Devon Energy Corp.*, 551 F.3d at 1041 (explaining that a guidance document is "plainly distinguishable" from "the disputed agency advice" in *Alaska Professional Hunters*, which "had been upheld in a formal adjudication by the Civil Aeronautics Board, FAA's predecessor agency").

No definitive prior interpretation binds FDA here because the agency has not expressly and directly addressed whether 5-year exclusivity applies to FDCs containing both new and previously approved active moieties. Neither the Peck Letter, the agency's internal "Exclusivity Summary," the preambles to the proposed and final regulations, nor past agency practice provides the necessary authoritative and definitive agency interpretation.

The Peck Letter. The 1988 Peck Letter, *see supra* at I.A., cannot be a definitive interpretation for the simple reason that it precedes the promulgation of FDA's final rule in 1994. Even at the time of its issuance, the Peck Letter was not binding on either the agency or the public. Finally, there is little evidence that the Peck Letter expressly considered the operation of 5-year exclusivity in the case of FDCs such as STRIBILD:

> The "active moiety" in a drug product is the molecule or ion, excluding esterified forms, salts, complexes, chelates, or clathrates of the molecule, responsible for the physiological or pharmacological action of the drug substance. A drug product will thus not be considered a "new chemical entity" entitled to five years of

> exclusivity if it contains a previously approved active moiety, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or other non-covalent derivative (such as a complex, chelate or clathrate) has not been previously approved.

Id. at 3, n.*. This explanation presumes that a drug product contains a single active moiety, which is obviously not the case for FDCs. Instead, FDA here seems more concerned with the definition of an "active moiety" rather than a combination in a single dosage form of multiple active moieties.

The Exclusivity Summary. Nor is FDA's internal "Exclusivity Summary" a definitive interpretation. The Summary appears on the agency's website in the approval packages for some, but not all, new drug products. It presents a series of questions agency staff members answer for each new drug application. The relevant language is as follows:

> 2. Combination product.
>
> If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes."
>
> ...
>
> IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
>
> IF "YES," GO TO PART III.

Exclusivity Summary at 3 (underlining in original).

Publicly available information does not reveal who created the Summary. Thus, it is unclear whether the Summary "come[s] from sources who had the authority to bind the agency."

Devon Energy Corp., 551 F.3d at 1041. And to the best of our knowledge, FDA has never published the Summary outside of the review documents for a particular product, such as in the *Federal Register* or in a public docket. Indeed, we were unable to find a blank, non-case-specific version of the Summary that had not already been completed by agency review staff.

It is also unclear *when* the Summary originated. Gilead has obtained a copy that existed at least as of 1990; in more recent versions, the relevant language on combination products remains exactly the same as it was in 1990. This is significant because the regulation was promulgated in 1994, so the Summary predates the regulation. The Summary therefore could not be a regulatory interpretation; it must be an interpretation of the statute. That is important because an agency's statutory interpretation *may* be changed "without notice and comment." *Syncor Int'l Corp. v. Shalala*, 127 F.3d 90, 94 (D.C. Cir. 1997). And as an interpretation contrary to the regulation itself, the Summary cannot stand. *See, e.g., Central Laborers' Pension Fund v. Heinz*, 541 U.S. 739, 748 (2004) (explaining that "neither an unreasoned statement in the manual or allegedly longstanding agency practice can trump a formal regulation with the procedural history necessary to take on the force of law"); *Clean Ocean Action v. York*, 57 F.3d 328, 333 (3rd Cir. 1995) (stating that an "agency guideline or directive that conflicts with the plain meaning of a regulation is invalid") (citing *National Family Planning & Reproductive Health Ass'n v. Sullivan*, 979 F.2d 227, 234-36 (D.C. Cir. 1992)); *see also Actavis Elizabeth LLC v. FDA*, 689 F.Supp.2d 174, 180 (D.D.C. 2010) (finding that FDA's 5-year exclusivity regulation superseded internal agency policy document advocating a contrary interpretation), *aff'd*, 625 F.3d 760 (D.C. Cir. 2010).

Even were the Summary deemed to be an interpretation of the regulation, it plainly is not a *definitive* interpretation. The Summary does not include any express, affirmative language explaining the requirements of 21 CFR 314.108(b)(2) or the ultimate consequences of checking any box "yes" or "no." If the staff member answers "no" to the language from Part II of the

Summary quoted above, he or she is directed "to the signature blocks." If the staff member answers "yes" and continues to Part III, he or she answers questions concerning 3-year exclusivity and then again concludes at the signature blocks. All options end with the staff member being directed to the signature blocks. There, the staff member simply signs the Summary. No "definitive" interpretation can be said to have occurred.

The D.C. Circuit's decision in *Honeywell*, 628 F.3d at 579, is instructive. The court of appeals reviewed the Nuclear Regulatory Commission's denial of a licensee's request for an exemption from the regulatory requirement that licensees have a certain net worth. The Commission had granted the licensee's exemption request in two prior years, and the licensee argued that those two grants had established a definitive interpretation of the exemption provision of the regulation that could be altered only by notice and comment rulemaking. The D.C. Circuit disagreed. *Honeywell Int'l, Inc.*, 628 F.3d at 579. As the court explained, the Commission's prior actions had applied only to the particular exemption request before it, and the court recognized that "conditional or qualified statements, including statements that something 'may be' permitted, do not establish definitive and authoritative interpretations." *Id.* (quoting *MetWest Inc.*, 560 F.3d at 509-510). Just so here. The Summary does not on its face mandate any particular result. It is an internal housekeeping document that aids agency staff members in collecting information and making exclusivity determinations, and it is filled out and signed with respect to a particular application.

The Summary is also like the agency policy manual evaluated by the court in *Wilderness Society v. Norton*, 434 F.3d at 595. There, the court explained: "While the text of the [manual] on occasion uses mandatory language, such as 'will' and 'must,' the document as a whole does not read as a set of rules. It lacks precision in its directives, and there is no indication of how the enunciated policies are to be prioritized." *Id.* The court therefore concluded that the manual "is a nonbinding, internal agency manual intended to guide and inform Park Service managers and

staff. There is no indication that the agency meant for these internal directives to be judicially enforceable at the behest of members of the public who question the agency's management." *Id.* at 596.

The Exclusivity Summary does not itself create enforceable rights or mandate any particular result. Nowhere does it provide an "express" or "direct" interpretation of the requirements for 5-year exclusivity. It is therefore not a binding, definitive interpretation of the regulation with respect to FDCs.

Preambles. The agency at times used broad language in its preambles to the proposed and final regulations indicating that a drug product containing a previously approved active moiety qualifies only for 3-year exclusivity. *See, e.g.*, 54 Fed. Reg. at 28898; 59 Fed. Reg. at 50356. For example, the preamble to the proposed rule states that "[f]or purposes of this proposed rule, FDA interprets the term 'drug' to mean 'drug product' unless otherwise specified." 54 Fed. Reg. at 28877. But as we have explained, the regulatory language *does* "otherwise specif[y]" that, in the specific case of the 5-year exclusivity provisions, "drug" means "drug substance," not "drug product." *See supra* at section II.A.2. As the agency explained in a lengthy discussion of the scope of 5-year exclusivity, if the exclusivity were directed to the drug product that is the subject of the NDA, the exclusivity would be negated by the approval of the same drug substance in a different drug product (such as in a different dosage form). Thus, the agency made the decision that 5-year exclusivity must be directed to the drug substance or, more specifically, the drug substance that contains a new active moiety, in order to give broader effect to the exclusivity, as Congress intended (in the agency's view).

In addition, the agency's preamble statements do not appear to have expressly considered the proper interpretation of the regulation in the context of FDCs. For instance, the preamble often speaks in terms of "*the* active moiety" in the drug product, which suggests that the agency was considering only drug products containing one drug substance, with one active moiety. *See,*

e.g., 59 Fed. Reg. at 50359. At the very least, the agency did not provide any substantive analysis of the regulation's application to FDCs containing both new and previously approved active moieties.

This makes the present matter like that considered by the court in *Association of American Railroads*, 198 F.3d at 948. In that case, the Association of American Railroads (AAR) challenged the Federal Railroad Administration's (FRA) issuance of a technical bulletin, which the AAR claimed was inconsistent with the FRA's prior, definitive interpretation of the Roadway Worker Protection Rule. The court explained: "The AAR detects this definitive interpretation in the Roadway Worker Protection Rule's Preamble, in an email and two letters from agency personnel, and in the agency's own safety manual." *Association of Am. R.Rs.*, 198 F.3d at 948. The court rejected the AAR's argument, finding "nothing in these materials, individually or taken together, that comes even close to the definitive interpretation that triggered notice and comment rulemaking in *Alaska Professional Hunters*." *Id.* This was true even though, the court observed, "the AAR has unearthed some documents that seem, albeit sometimes vaguely, to support its argument that the agency—or at least some of its employees—may have interpreted paragraph (c)(5)" in a particular way. *Id.* at 949. But the court nevertheless concluded that none provided an "express, direct, and uniform interpretation" of the specific interpretive question at issue. *Id.* at 949.

So too here – the language in the preambles is not specific or definitive enough to constitute a direct, express agency interpretation of the regulation with respect to FDCs such as STRIBILD.

Past Exclusivity Decisions. In the years following the promulgation of 21 CFR 314.108(b)(2), FDA has denied 5-year exclusivity to approximately ten products that contained one or more new active moieties in combination with a previously approved active moiety. *See supra* at I.B. To the best of our knowledge, there are no publicly available decisions in any of

these cases that explain FDA's reasoning in arriving at these exclusivity determinations. The most that can be said about these prior determinations is that there exists some "implicit" interpretation that led the agency to refuse to recognize 5-year exclusivity for these FDCs. But as the court of appeals explained in *Hudson*, 192 F.3d at 1036, an "implicit interpretation" is not enough to constitute a definitive interpretation. And as further demonstrated by *Honeywell*, 628 F.3d at 579, the court will not infer a binding regulatory interpretation from agency decisions absent some express statement from the agency. So even if one could infer a uniform agency practice based on the agency's prior exclusivity decisions, the publicly available information does not provide an "express" or "direct" interpretation of the regulation, *Association of Am. R.Rs.*, 198 F.3d at 949, and certainly not one that reflects "a definitive and binding statement on behalf of the agency," *Devon Energy Corp.*, 551 F.3d at 1040. This makes these circumstances quite unlike those present in *Alaska Professional Hunters*, where the court concluded that the agency was bound by "administrative common law." *See* 177 F.3d at 1035. For as the D.C. Circuit later clarified in *Hudson*, the dispositive fact in *Alaska Professional Hunters* was that "a formal adjudication by an associate agency had adopted an interpretation of the regulation in accord with the informal practice." *Hudson*, 192 F.3d at 1036 (citing *Alaska Prof'l Hunters*, 177 F.3d at 1031); *accord Devon Energy Corp.*, 551 F.3d at 1041. There has been no such formal adjudication here.

In sum, the agency has not yet provided an express and direct interpretation of the specific question posed here. Therefore, the agency has not yet issued a "definitive interpretation" of 21 CFR 314.108(b)(2) as it applies to FDCs that contain both new and previously approved active moieties. The agency is thus "free to adopt the interpretation at issue in this case without providing an opportunity for notice and comment." *Devon Energy Corp.*, 551 F.3d at 1041.

2. Even if there had been a definitive interpretation, there has been no substantial and justifiable reliance

Even if there had been a definitive prior interpretation, moreover, and *even if* the requested action would constitute a substantial departure from that prior interpretation, notice and comment rulemaking is not required if there has been no "substantial and justifiable reliance on a well-established agency interpretation." *MetWest Inc.*, 560 F.3d at 511; *accord Honeywell Int'l, Inc.*, 628 F.3d at 579-80. As the court explained in *MetWest*, the "substantial and justifiable reliance" requirement "is a crucial part of the analysis." 560 F.3d at 511 n.4. "To ignore it is to misunderstand *Alaska Professional Hunters* to mean that an agency's initial interpretation, 'once informally adopted, freezes the state of agency law, which cannot subsequently be altered without notice and comment rulemaking.'" *Id.* (quoting Peter L. Strauss, *Publication Rules in the Rulemaking Spectrum: Assuring Proper Respect for an Essential Element*, 53 Admin. L. Rev. 803, 844 (2001)).

An agency is not bound by a prior interpretation just because there has been *some* reliance on that interpretation; rather, the reliance must be both "substantial" and "justifiable." So, for instance, in *Alaska Professional Hunters*, the court recognized that "[p]eople in the lower 48 states had pulled up stakes and moved to Alaska. They and others within Alaska had opened hunting and fishing 'lodges and built up businesses dependent on aircraft, believing their flights were [not] subject to' certain commercial flight regulations." *MetWest Inc.*, 560 F.3d at 511 (quoting *Alaska Prof'l Hunters*, 177 F.3d at 1035). "Their reliance on the FAA's advice was, as we said, 'justifiable.'" *Id.* at 511 n.5 (quoting *Alaska Prof'l Hunters*, 177 F.3d at 1034). It was also substantial: "Forcing guide pilots to comply with regulations developed for commercial airlines would have driven Alaska's hunting and fishing tourism operations out of business." *Id.* at 511.[20]

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[20] "Furthermore, during this 30-year span, the 'guide pilots and lodge operators had no opportunity to participate in the development of the … regulations' that the FAA had abruptly decided to apply to them. As a

There has been no similar reliance on any prior agency interpretation of 21 CFR 314.108(b)(2) with respect to FDCs such as STRIBILD. *See, e.g., Association of Am. R.Rs.*, 198 F.3d at 950. Neither innovator sponsors – who may have staged their applications based on FDA's position – nor generic sponsors – who may wish to develop a generic FDC – have substantially and justifiably relied on FDA's historical position. To the extent innovator sponsors have in the past elected to develop single entity products first, they did so for each discrete new drug application. There is no evidence that these companies built their businesses around such a strategy, as in *Alaska Professional Hunters*. But even if these companies had in fact modeled their business operations to develop single entity products before FDCs, they may continue that practice unimpeded; the only difference under Gilead's proposed interpretation is that they now *also* have the option of developing the FDC product first.

Plainly, no generic sponsor has built its business around an expectation that FDA will only award 3-year exclusivity to FDCs containing both new and previously approved active moieties. Exclusivity determinations under 21 CFR 314.108(b)(2) are prospective in effect, making it unlikely in the extreme that *any* competitor could "rely" on hypothetical, forward-looking exclusivity determinations. Exclusivity operates on *future* new drug applications, usually ANDAs for generic drugs, and determines when the agency may accept for filing applications that refer to the active moiety in a previously approved drug product. Thus, the reliance interests in any given case are quite limited. If STRIBILD is deemed to have 5-year exclusivity instead of 3-year exclusivity, a generic drug manufacturer may not submit an application until the end of that 5-year period. The timing of the application and approval might change, but the resources that the generic manufacturer would have to expend to submit an ANDA would not differ. And the "feasibility" of manufacturers delaying their applications for

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result, they were deprived of any opportunity to request changes or exceptions to accommodate the unique circumstances of Alaskan air travel." *MetWest, Inc.*, 560 F.3d at 511 (quoting *Alaska Prof'l Hunters*, 177 F.3d at 1035-36).

two years "is clear." *MetWest Inc.*, 560 F.3d at 511. Unlike the guiding and hunting industry described in *Alaska Professional Hunters*, the generic industry is in no way founded upon the FDA treatment of FDCs described in this petition.

3. Policy considerations amply support a "new" interpretation

Because there has been no definitive agency interpretation of the regulation with respect to FDCs, and certainly not one on which there has been substantial and justifiable reliance, the agency may apply a "new" interpretation of the regulation in this proceeding. All that is required is that "the agency … acknowledge and provide an adequate explanation for its departure from established precedent." *Dillmon v. NTSB*, 588 F.3d 1085, 1089-90 (D.C. Cir. 2009). No heightened standard applies. *Id.* at 1089 (citing *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 514-516 (2009)). A petition response from FDA, after consideration of views submitted to the public docket, is sufficient here.

Moreover, the agency has many valid reasons to depart from its presumed prior practice. The recent evolution in medicine and public health policy favoring FDC therapies discussed above is itself an adequate explanation. *See supra* at I.C. And as we also have explained, the opportunity to harmonize 5-year exclusivity with FDA's recent interpretations of identical statutory language in FDAAA provides further justification for implementing a new interpretation at this time. *See supra* at II.A.5.

An agency practice that interprets the statute and 21 CFR 314.108(b)(2) to grant 5-year exclusivity to FDCs containing at least one new active moiety is the right practice under the law, under the regulations, and as a matter of public health policy. Applying this interpretation will preclude arbitrary exclusivity determinations based on the order that applications are approved. It will protect the investments of a drug pioneer that has developed new active moieties that happen to be best used with other existing drugs. It will eliminate the disparate treatment between new moieties approved with co-administration labeling, and those first approved in

FDCs. And it will promote the development of combination drug therapies where they are needed the most.

III. CONCLUSION

For the reasons stated, Gilead requests FDA recognize 5-year exclusivity under sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) for the new active moieties in STRIBILD. On that basis, the proper coding of the exclusivity in the *Orange Book* for STRIBILD should be "NCE," with an expiration date of August 27, 2017. This exclusivity should also be carried over to the single ingredient EVG and COBI products, currently under review, based on the agency's "umbrella" exclusivity policy. The award of 5-year exclusivity for EVG and COBI is the only award that adequately protects the substantial investment Gilead made in the development of these two new active moieties that offer new and important treatment for HIV patients and clinicians. Finally, FDA should update its Exclusivity Summary to conform to this interpretation, ensuring that similarly situated products, *i.e.*, FDCs containing at least one new active moiety, will be awarded 5-year exclusivity in the future.

ENVIRONMENTAL IMPACT

The actions requested in this petition are not within any of the categories for which an environmental assessment is required pursuant to 21 CFR 25.22.

ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted if requested by the Commissioner.

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: August 27, 2012. 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.

Respectfully submitted,

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