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**BY HAND**

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**CITIZEN PETITION**

This citizen petition is submitted on behalf of Bayer HealthCare Pharmaceuticals Inc. ("Bayer") under Section 505 of the Federal Food, Drug, and Cosmetic Act (the "Act") and 21 C.F.R. § 10.30 to request that the Food and Drug Administration ("FDA") 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 dienogest, the new active moiety in NATAZIA®.

Bayer holds New Drug Application ("NDA") number 022252 for NATAZIA, an oral contraceptive. NATAZIA is a fixed-dose combination ("FDC") of two active moieties, dienogest and estradiol valerate. Prior to approval of NATAZIA, FDA had never approved an NDA for any drug substance containing any dienogest or any of its esters or salts as an active moiety. FDA had, however, previously approved drugs containing estradiol valerate as an active moiety.

FDA has historically denied 5-year exclusivity to FDCs that contain a new active moiety and a previously approved active moiety. This approach is contrary to the 5-year exclusivity provision in the FDCA, Congress's intent, and FDA's own regulations concerning 5-year exclusivity. Moreover, the approach produces arbitrary outcomes that disfavor FDCs. Accordingly, FDA should recognize 5-year exclusivity for drugs that contain *any* active moiety that has not been approved previously. This would include FDCs such as NATAZIA that contain drug substances with a previously approved active moiety (estradiol valerate) in combination with a drug substance with a new active moiety (dienogest). Because FDA's current approach to FDCs has never been formally adopted, and is, in fact, inconsistent with FDA's own formally adopted regulations, FDA could adopt this proposed approach without notice and comment rulemaking.

Two other citizen petitions have been submitted to FDA concerning the proper exclusivity period that should be granted to FDCs that contain both previously approved active moieties and

entirely new active moieties. One petition was submitted on behalf of Gilead Sciences, Inc. on January 8, 2013 (Docket No. FDA-2013-P-0058) (the "Gilead Petition") and the other was submitted on behalf of Ferring Pharmaceuticals, Inc. on January 29, 2013 (Docket No. FDA-2013-P-0119) (the "Ferring Petition"). The Gilead Petition makes explicit reference to NATAZIA, stating that it is one of a only a few products for which 5-year exclusivity would still be ongoing, if FDA had applied its regulation as written and as required by the FDCA. Bayer fully endorses the arguments set forth in the Gilead Petition and the Ferring Petition.

### **Actions Requested**

Bayer requests that FDA recognize 5-year exclusivity for dienogest, the new active moiety in NATAZIA, pursuant to Sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FDCA.

### **Statement of Grounds**

#### **I. NATAZIA BACKGROUND**

On May 6, 2010, FDA approved NATAZIA for use as an oral contraceptive. FDA granted 3-year exclusivity to NATAZIA. NATAZIA contains estradiol valerate, an estrogen, and dienogest, a progestin. A package of NATAZIA consists of 28 tablets, to be taken once per day. The package contains two placebo tablets and tablets contain varying amounts of estradiol valerate (4 tablets) or estradiol valerate and dienogest (22 tablets). NATAZIA is the first drug product approved by FDA that contains dienogest.

Bayer began its development program for NATAZIA in 1993, intending to develop an estradiol-based, rather than ethinylestradiol-based, oral contraceptive. It had been shown that reductions in ethinylestradiol improve tolerability; however, such reductions also resulted in less favorable outcomes with respect to bleeding. These results prompted efforts to develop oral contraceptives utilizing estradiol or estradiol valerate rather than ethinylestradiol.

Most previous attempts to develop an estradiol-based mono-phasic oral contraceptive failed due to unacceptable outcomes with respect to bleeding. Accordingly, Bayer developed a unique four-phasic regimen incorporating an estrogen step-down and a progestin step-up, meaning that the estrogen dose (i.e., the estradiol valerate dose) decreases during the cycle while the progestin dose (i.e., the dienogest dose) increases. This regimen allows for early estrogenic dominance, ensuring initial endometrial proliferation and sensitivity to midcyclic progestin action. In addition, the use of dienogest during the middle to late parts of the cycle helps to ensure endometrial stroma stability. Dienogest was selected as the progestin component due to its particularly strong endometrial effect.

Estradiol valerate was approved in the form of DELESTROGEN in 1954. Accordingly, at the time Bayer was developing NATAZIA forty years later, estradiol valerate had not only been approved, but had also undergone significant marketing experience. This prior approval and

experience would generally reduce the burden for applicants seeking approval of a subsequent drug product containing only estradiol valerate. Indeed, various generic versions of estradiol valerate were approved pursuant to abbreviated new drug applications (“ANDAs”). Because Bayer was combining estradiol valerate with dienogest, an entirely new active ingredient, however, Bayer was required to conduct numerous animal and human studies to establish the safety and effectiveness of dienogest.

Bayer’s pre-clinical testing included a complete nonclinical pharmacology/toxicology program for dienogest. This program included pharmacology studies, pharmacokinetic and toxicokinetic studies, general toxicology studies, genotoxicity studies, reproductive toxicity studies, and carcinogenicity studies. General toxicology studies included single and repeat dose toxicity studies in various species. Specific studies included, for example, 104-week carcinogenicity studies conducted in rats and mice.

With respect to human testing, Bayer included data from 37 clinical studies in the NATAZIA NDA, 32 of which were biopharmaceutical and clinical pharmacology studies that evaluated dose linearity, absolute bioavailability, single and multiple-dose pharmacokinetics, metabolism, food effect, and drug-drug interaction. Among these were two prospective, randomized, Phase II studies to obtain information on the ovulation-inhibition potency of four different combinations of estradiol valerate and dienogest. The regimen that was identified as having the lowest effective dose of dienogest for efficient ovulation inhibition was selected.

After 11 years in development, Bayer initiated phase III trials of NATAZIA in 2004 for the purpose of obtaining regulatory approval of the product. Approval of NATAZIA was supported by five Phase III studies involving more than 2,400 subjects who received the study drug. This included two safety and efficacy studies of NATAZIA for use as a contraceptive, one supportive comparative study, and two safety and efficacy studies of NATAZIA for treatment of dysfunctional uterine bleeding. These studies provided safety and efficacy data from more than 30,000 28-day treatment cycles.

In total, from the start of the first dose-finding study in 1993, Bayer spent 16 years and nearly \$200 million to bring NATAZIA to market.

FDA was informed that NATAZIA included dienogest, an active ingredient that had never before been approved. Indeed, FDA was aware that dienogest was a new active ingredient long before Bayer even submitted the NDA for NATAZIA: during a pre-investigational new drug application meeting with Bayer, FDA stated that “[b]ecause dienogest is a new molecular entity (NME), we will require two adequate and well-controlled studies for efficacy and safety.”<sup>1</sup> This

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<sup>1</sup> FDA defines the term “new molecular entity” as an active ingredient that has never before been marketed in the United States in any form. *See, e.g.,* FDA, Drugs@FDA Glossary of Terms, *available at* <http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm>.

statement acknowledged the increased burden that sponsors must bear when bringing to market a drug product containing a new active ingredient. FDA's summary basis of approval ("SBA") for NATAZIA also makes reference to dienogest as a new molecular entity. For example, the SBA states that "[a]lthough [dienogest] is a new molecular entity, the large clinical trial database did not raise any concerns regarding the safety or efficacy" of the product. In addition, the SBA notes that "[t]he Applicant conducted a thorough QT (TQT) study because [dienogest] is a NME [new molecular entity]."

## II. LEGAL FRAMEWORK

The legal framework created by the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Amendments") represents a delicate balance between allowing consumers access to affordable drugs and encouraging the development and commercialization of new medicines. To promote better access to affordable drugs, the Hatch-Waxman Amendments created abbreviated approval pathways for drug approval, namely, ANDAs and 505(b)(2) applications. And to promote research and development, the Hatch-Waxman Amendments included provisions to protect innovation through patent term restoration and various forms of regulatory exclusivity.

One type of exclusivity created by the Hatch-Waxman Amendments is 5-year exclusivity for new chemical entities ("NCEs"). The statutory provision governing 5-year exclusivity states that if an application is approved for "a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved" previously, no ANDA or Section 505(b)(2) application may be submitted referring to such drug for a 5-year period. 21 U.S.C. § 355(j)(5)(F)(ii); *See also* 21 U.S.C. § 355(c)(3)(E)(ii). By regulation, FDA has interpreted this exclusivity to attach to "active moieties," which are 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.

21 C.F.R. § 314.108(a). What this exclusivity period means is that, for 5 years following approval of a drug containing a new active moiety, no person may submit an ANDA or 505(b)(2) application for a drug containing that active moiety. If the ANDA or 505(b)(2) application includes a certification of patent invalidity or noninfringement, however, the application can be submitted 4 years after approval. 21 C.F.R. § 314.108(b)(2).

By contrast, a 3-year exclusivity period is available for new drug products that contain previously approved active moieties, provided that the applications for such drug products contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval

of the application and conducted or sponsored by the applicant.” 21 U.S.C. §§ 355(c)(3)(E)(iii) and 355(j)(5)(F)(iii). During this exclusivity period, FDA will not make approval effective for any ANDA or 505(b)(2) application that relies on such studies conducted by the original applicant, unless the ANDA or 505(b)(2) applicant has obtained a right of reference to such studies. *Id.*

FDA has historically interpreted 5-year exclusivity to be available only when every active moiety in a finished drug product is a new active moiety, or, in other words, when none of the active moieties in the drug product have been previously approved. The first public reference to this interpretation of which Bayer is aware is an “informal notice” letter from 1988 stating that “[t]he Agency considers a drug product eligible for the five-year period if it contains no active moiety that was previously approved by the Agency.” Letter from C. Peck, Director, CDER, to all NDA or ANDA Holders and Applicants (Apr. 28, 1988) (the “Peck Letter”). Although the letter does not expressly contemplate FDCs including a previously approved active moiety and a new active moiety, Bayer understands that it has been FDA’s approach since that time to deny 5-year exclusivity to such products.

This approach is also reflected in FDA’s “Exclusivity Summary,” which is an internal agency checklist used to support exclusivity determinations. The Exclusivity Summary asks: “[i]f the product contains more than one active moiety . . . , 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.’” (emphasis in original). The presumption of the Exclusivity Summary seems to be that a combination product with even one previously approved active moiety would not be eligible for 5-year exclusivity. Thus, FDA has not granted 5-year exclusivity to FDC drugs, such as NATAZIA, that include one previously approved active moiety and one new active moiety. Rather, FDA has only granted 3-year exclusivity to these kinds of combination drug products. To our knowledge, the Exclusivity Summary has never been publicly announced, and copies of it are available to the public only as completed documents in NDA packages.

### III. ARGUMENTS

#### A. The FDCA Requires That Dienogest Receive 5-Year Exclusivity

The FDCA’s 5-year exclusivity provision states:

[i]f 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 which refers to *the drug* for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section . . . . (emphasis added).

21 U.S.C. § 355(j)(5)(F)(ii); *See also* 21 U.S.C. § 355(c)(3)(E)(ii). Thus, exclusivity applies in the case of a “drug,” no active ingredient of which has been previously approved.

The FDCA defines the term “drug” as an article that is “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man” or “intended to affect the structure or function of the body of man.” 21 U.S.C. § 321(g)(1)(B)-(C). But the term is *also* defined as “articles intended for use as a component” of those articles described in the previous sentence. 21 U.S.C. § 321(g)(1)(D). Accordingly, the term “drug” can refer either to a finished drug product or to a component of a finished drug product (e.g., a drug substance). In the case of NATAZIA, the term “drug” could refer to the entire finished tablet or it could refer separately to each of the drug substances, estradiol valerate or dienogest.

Determining which definition of the term “drug” is applicable to the 5-year exclusivity provision is critical. If “drug” means “finished drug product,” then, consistent with FDA’s historical position, NATAZIA is not eligible for 5-year exclusivity because there is one active ingredient in the finished drug product that has been previously approved (estradiol valerate) and the statute requires that “no active ingredient” of the finished drug product have been previously approved. If, on the other hand, “drug” means “a component of a finished drug product, or a drug substance,” then dienogest is eligible for 5-year exclusivity because no active ingredient within the drug substance dienogest has previously been approved.

As will be shown, it is clear from the statutory language and FDA’s own regulations that the term “drug” in the context of the 5-year exclusivity provision means a component of a finished drug product, or a drug substance, rather than a finished drug product. This conclusion is based on the fact that the term “drug” is used twice in the statutory provision. The provision first refers to “a drug” with no previously approved active ingredient as that which is potentially eligible for 5-year exclusivity. The provision then states that, if exclusivity is granted, no application may be submitted which refers to “the drug.” The use of the indefinite article “a” before “drug” in the first instance and the use of the definite article “the” before “drug” in the second instance conveys a particular meaning – namely, that the second occurrence of the word “drug” specifically refers to the “a drug” that first appears in the provision. Accordingly, the two references to “drug” must have the same meaning in the 5-year exclusivity provision.

The second occurrence of the term “drug” refers to that to which exclusivity attaches and FDA has made clear in its regulations that 5-year exclusivity attaches to active moieties, *not* to finished drug products. *See* 21 C.F.R. § 314.108(b)(2) (stating that when exclusivity attaches, no 505(b)(2) application or ANDA may be submitted for a product “that contains the same active moiety.”). Because the second occurrence of the term “drug” refers to active moieties, and because the first and second occurrences of that term as discussed above, must refer to the same thing, the first instance of “drug” must also refer to active moieties rather than to finished drug products.

When read in this light, the 5-year exclusivity provision states that if an application is submitted for “a drug substance or active moiety” that includes no previously approved active ingredient, then no ANDA or 505(b)(2) application may be submitted that references “the drug substance or active moiety” for a period of five years. Because dienogest includes no previously approved active ingredient, dienogest is entitled to 5-year exclusivity.

**B. Congress Intended That New Active Moieties Such As Dienogest Be Granted 5-Year Exclusivity**

The legislative history of the Hatch-Waxman Amendments indicates that Congress intended to reward the development of new drug substances with 5 years of exclusivity. By contrast, Congress intended to reward new clinical studies concerning previously approved drug substances with 3 years of exclusivity. As explained by Representative Waxman, 5-year exclusivity “will give the drug industry the incentives needed to develop new chemical entities whose therapeutic usefulness is discovered late when little or no patent life remains.” Cong. Rec. H9113-H9114 (Sep. 6, 1984). By contrast, 3-year exclusivity “is afforded to nonnew chemical entities” to “encourage drugmakers to obtain FDA approval for significant therapeutic uses of previously approved drugs.” *Id.*

Congress’s intent in implementing the Hatch-Waxman Amendments further suggests FDA’s current statutory interpretation is unreasonable.

Based on this Congressional intent, a combination drug that contains at least one drug substance that has not yet been approved deserves 5 years of exclusivity. Development of such a combination drug requires much more research, development, and effort than that required to change the formulation of an existing drug product or to add a new indication. Getting such a product to market usually requires the kind of soup-to-nuts development program that is required of products that consist of entirely new chemical entities – i.e., a robust preclinical track record that supports clinical study, and a phase I - III clinical program to support regulatory approval. The development of NATAZIA, as described previously, evidences the significant time, effort, and expenditure necessary to bring a combination drug to market, even when one of the drug substances in the drug This is exactly the type of innovation and committal of resources that Congress intended to reward the costs with 5 years of exclusivity.

**C. FDA’s Regulations Require That Dienogest Receive 5-Year Exclusivity**

FDA’s regulations concerning 5-year exclusivity state that

[i]f 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, except that the 505(b)(2) application or abbreviated application may be submitted after 4 years if it contains a certification of patent invalidity or noninfringement described in 314.50(i)(1)(i)(A)(4) or 314.94(a)(12)(i)(A)(4). 21 C.F.R. § 314.108(b)(2)

The key terms “drug product” and “new chemical entity,” are defined as follows:

- Drug product: “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 C.F.R. § 314.3(b).
- New chemical entity: “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 C.F.R. § 314.108(a).

Notably, the definition of “new chemical entity” references the term “drug,” which, as discussed above, could either mean a finished drug product or a component of a finished drug product. In this instance, however, only one meaning of the term “drug” makes sense. If the term “drug” in the definition of “new chemical entity” were interpreted to mean “drug product,” then the 5-year exclusivity provision under 21 C.F.R. § 314.108(b)(2) would be nonsensical: it would apply in the case of a drug product that contains a “new chemical entity,” i.e., a drug product that contains “a [drug product] that contains no active moiety that has been approved by FDA in any other application.” To avoid this absurd result, the term “drug” in the definition of “new chemical entity” must mean a component of a drug product, or a drug substance. Accordingly, any drug product that contains a new chemical entity, i.e., a drug substance with no previously approved active moiety, should be granted 5 years of exclusivity.

In the case of NATAZIA, the entire tablet is considered the “drug product”. The drug product clearly does contain “a new chemical entity” because it contains a drug substance with no previously approved active moiety (i.e., dienogest). Thus, according to FDA’s own regulation, NATAZIA must be granted 5 years of exclusivity.

**D. FDA’s Current Approach To 5-Year Exclusivity And FDCs Containing A Previously Approved Active Moiety Leads To Inconsistent and Inequitable Results**

As described in Section II, despite the language of FDA’s own regulation, FDA has traditionally taken the approach that if an FDC contains any previously approved active moiety, it is not eligible for 5-year exclusivity. Yet, in certain instances, FDCs that contain a previously approved active moiety are, in fact, eligible for 5-year exclusivity pursuant to FDA’s “umbrella policy”:

[T]he agency interprets [5-year NCE exclusivity] to cover any subsequent approval of an application or supplemental application for a different ester, salt, or other



noncovalent derivative, or a different dosage form, strength, route of administration, or new use of a drug with the same active moiety. Any modification to the product will be protected for the period of exclusivity remaining on the original application, unless the change occurs after or toward the end of the initial 5 years of exclusivity and independently qualifies for exclusivity under another exclusivity provision.

54 Fed. Reg. 28872, 28898-99 (July 10, 1989).

What this means is that if a drug product containing only one new active moiety is approved and granted 5 years of exclusivity, an FDC containing that new active moiety in combination with another, previously approved active moiety could benefit from the longer exclusivity period if approved soon after the original drug product. In that instance, because the 5-year exclusivity attaches to the new active moiety, it prevents the filing of ANDA and 505(b)(2) applications referencing the first drug product or the subsequent FDC (because both contain the new active moiety). By contrast, if the FDC were approved *first*, it would not be eligible for 5-year exclusivity because it contains a previously approved active moiety.

For example, on March 5, 2007, FDA approved Novartis's TEKTURN (aliskiren hemifumarate). Aliskiren hemifumarate had not been approved previously, so it received 5 years of exclusivity. Novartis subsequently sought approval of a combination of aliskiren hemifumarate with valsartan, which had been approved as an active ingredient in the 1990s. FDA approved that combination drug, known as VALTURN, in September 2009. Because VALTURN contained aliskiren hemifumarate and because VALTURN was approved within five years of the original approval of aliskiren hemifumarate, VALTURN was protected under FDA's "umbrella policy" for the full remainder of aliskiren hemifumarate's 5-year exclusivity period, or until March 5, 2012. Thus, both TEKTURN and VALTURN benefited from 5-year exclusivity. (Indeed, even if VALTURN had been approved on March 6, 2007, it would have benefited from exclusivity until five years later, on March 5, 2012.)

Consider the result, however, if VALTURN had been first, e.g., on March 4, 2007, and TEKTURN approved the day later. In this scenario, VALTURN would have included a previously approved active ingredient, valsartan, and a new active ingredient, aliskiren hemifumarate. Because the product included valsartan, FDA would not have granted 5-year exclusivity to VALTURN. Nor would FDA have granted 5-year exclusivity to the subsequent approval of aliskiren hemifumarate alone, in the form of TEKTURN. Thus, whether both products benefit from 5-year exclusivity or receive no 5-year exclusivity depends solely upon the order in which the applications are approved. Such an outcome cannot be rationally explained, nor is it consistent with any legislative purpose.

In a similarly arbitrary manner, FDA's current policy favors a drug product with one active moiety that is labeled for use in combination with another drug product over a drug product that combines the active moieties of the two drug products into a single drug product. For example, on

April 28, 2011, FDA approved Janssen Biotech's ZYTIGA (abiraterone acetate). The approval of ZYTIGA requires that the product be administered with prednisone -- use of ZYTIGA alone is not an approved use. When approved, FDA granted ZYTIGA five years of exclusivity because abiraterone acetate was not a previously approved active moiety. But if Janssen had combined abiraterone acetate with prednisone in a single dosage form, and sought approval of the combined product, FDA would not have granted five years of exclusivity to the product because prednisone was a previously approved active moiety.

There is no plausible reason why FDA should incentivize sponsors to obtain approval for a drug product that contains a single new active moiety prior to obtaining approval for an FDC that incorporates that active moiety in combination with other active moieties. There is also no reason why FDA should encourage sponsors to seek separate approvals for each active ingredient of a combination product rather than to seek approval of a FDC. But these outcomes are precisely what FDA's interpretation of the 5-year exclusivity provision with respect to FDCs promotes. As discussed in Section III.B., the objective of 5-year exclusivity is to reward research and development relating to new chemical entities. Regardless of whether the new chemical entity is first approved as part of a FDC with a previously approved chemical entity, significant time and effort was undoubtedly invested in developing that new chemical entity. Due to the substantial investment required, a 5-year exclusivity period is appropriate.

**E. Public Policy Considerations Weigh In Favor Of Recognizing 5-Year Exclusivity For Dienogest**

As discussed in the previous section, FDA's current approach encourages sponsors to seek approval for a new active moiety alone rather than for a FDC that contains a new active moiety in combination with a previously approved active moiety. FDA's approach thus discourages development and approval of new active moieties in FDCs. But FDCs have a demonstrated value to the public in a variety of contexts.

One advantage of FDCs is that they can significantly reduce patients' pill burden, thereby facilitating compliance with dosing regimens. A 2007 review of studies involving FDCs showed that FDCs decreased the risk of non-compliance by 26% compared to free drug combination regimens. Bangalore et al, *Fixed Dose Combinations Improve Medication Compliance: A Meta-Analysis*, Am. J. of Med. 120, p. 713-719 (2007). And in a 2006 guidance document, FDA explained the value of FDCs and other forms of combination therapy for treatment of HIV:

Combination antiretroviral 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 achieve the above mentioned therapeutic goals. In the United States and developing countries,

simplified HIV regimens in the form of FDC or co-packaged drugs (such as blister packs) may facilitate distribution and improve patient adherence.

FDA, *Guidance for Industry: Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV* (Oct. 2006).

The ability of a FDC to facilitate patient adherence is particularly beneficial with drugs such as NATAZIA that have complicated dosing regimens. NATAZIA's regimen is complicated because the dose of each of its active ingredients varies throughout the month. NATAZIA's 28 color-coded pills are comprised of the following:

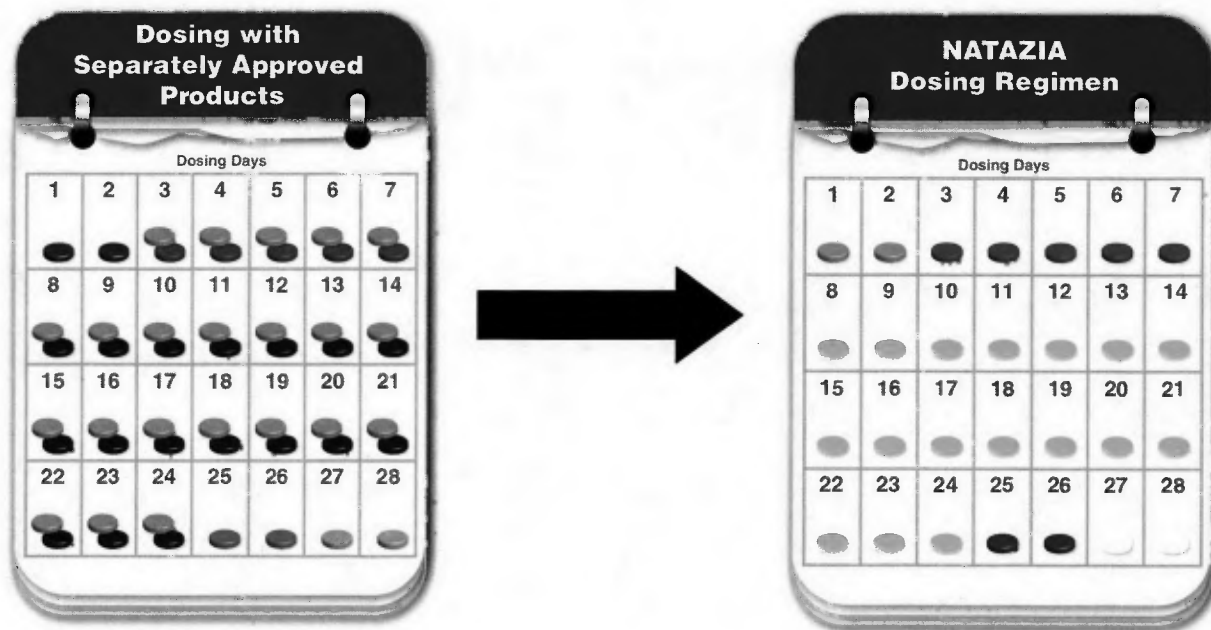
- 2 dark yellow tablets containing 3 mg estradiol valerate
- 5 medium red tablets containing 2 mg estradiol valerate and 2 mg dienogest
- 17 light yellow tablets containing 2 mg estradiol valerate and 3 mg dienogest
- 2 dark red tablets containing 1 mg estradiol valerate
- 2 white placebo tablets

Patients are instructed to take one tablet at the same time each day, and patients are to take the tablets in a pre-determined order.

If estradiol valerate and dienogest were not combined in a single dosage form, patients would be forced to take two different tablets each day, and would need to ensure that both tablets are being taken in the correct order. Patients would need to keep up with the following six different types of tablets:

- 3 mg estradiol valerate (purple in graphic below)
- 2 mg estradiol valerate (pink)
- 1 mg estradiol valerate (orange)
- 3 mg dienogest (green)
- 2 mg dienogest (blue)
- Placebo (gray)

Requiring patients to keep up with six different types of pills and five different combinations of those pills is an unnecessary burden, easily avoided by combining the ingredients into a single dosage form. Indeed, the following graphic illustrates how the 28-day dosing scheme is simplified by combining estradiol valerate and dienogest in NATAZIA, rather than having them approved as separate products that are labeled for combination use:



NATAZIA thus represents significant innovations on many fronts. Not only does it incorporate an entirely new active ingredient, dienogest, but it also simplifies a complicated dosing schedule into a single pill. The effort expended by Bayer in developing this innovative product should be appropriately rewarded with 5-year exclusivity, as required by the statute, Congressional intent, FDA's own regulations, and public policy considerations.

#### **F. FDA Can Change its Interpretation without Notice and Comment Rulemaking**

In general, "an agency is free to alter its past rulings and practices even in an adjudicatory setting." *Honeywell Int'l v. Nuclear Regulatory Commission*, 628 F.3d 568, 579 (D.C. Cir. 2010) (internal citation omitted). An agency is, however, required to engage in notice and comment rulemaking if it "has given its regulation a definitive interpretation," there has been "substantial and justifiable reliance" on the interpretation, and the agency later "significantly revises" its interpretation. *Id.* (quoting *Alaska Professional Hunters Ass'n v. FAA*, 177 F.2d 1030, 1034 (D.C. Cir. 1999); *MetWest v. Sec'y of Labor*, 560 F.3d 506, 511 (D.C. Cir. 2009)). As discussed in more detail below, FDA has not given its relevant regulation a "definitive interpretation." Furthermore,

even if FDA's interpretation were considered definitive, there has not been substantial or justifiable reliance on that interpretation. Accordingly, notice and comment rulemaking is not required prior to FDA's adoption of the interpretation of 5-year exclusivity proposed in this petition.

1. *FDA Has Not Made a "Definitive" Interpretation of its Regulation*

A "definitive" interpretation should be an "express, direct, and uniform" interpretation. *Honeywell*, 628 F.3d at 579 (quoting *Ass'n of Am. Railroads v. Dep't of Transp.*, 198 F.3d 944, 949 (D.C. Cir. 1999)). None of the Peck Letter, the Exclusivity Summary, or the preambles to FDA's proposed and final rules regarding product exclusivity can be considered "definitive" interpretations of 5-year exclusivity as applied to FDCs like NATAZIA. Although statements in these documents hint at a policy of denying 5-year exclusivity for FDCs that incorporate a previously approved active moiety, none of these documents can be considered definitive interpretations of FDA's exclusivity regulations for the reasons stated below.

- The Peck Letter. This letter is dated April 28, 1988. FDA's final rule regarding new drug product exclusivity was not published for another six years, in 1994. Clearly, the Peck Letter cannot be an interpretation of a rule that did not yet exist at the time the letter was issued. Moreover, the Peck Letter is self-described as an "informal notice." This qualifying language regarding the letter's significance further demonstrates that it cannot be considered a definitive interpretation of anything.
- The Exclusivity Summary. The Exclusivity Summary is an *internal* FDA checklist that asks, among other things "[i]f the product contains more than one active moiety . . . , has FDA previously approved an application under section 505 containing *any one* of the active moieties in the drug product?". The Exclusivity Summary goes on to state that if the combination "contains one never-before-approved active moiety and one previously approved active moiety, answer 'yes.'" As far as we are aware, the Exclusivity Summary is not even available publicly in its uncompleted form. The Gilead Petition attaches a version of the Exclusivity Summary that was available in 1990, but it is otherwise only available as a completed form as part of an NDA package. Like the Peck letter, the Exclusivity Summary cannot be considered a definitive interpretation because it pre-dates the final regulation.

Moreover, no explicit policy is set forth in the Exclusivity Summary – the checklist does not explain the significance of answering "yes" to the question noted above regarding combination products. Indeed, nowhere in the checklist is there an express statement regarding FDA's position with respect to 5-year exclusivity for FDCs such as NATAZIA that contain one previously approved active moiety and one new active moiety. Without an express statement of policy, the Exclusivity Summary cannot be considered a "definitive" interpretation of FDA's regulations.

- Preambles. Similarly, the preambles to the proposed and final regulations concerning new product exclusivity do not directly address 5-year exclusivity determinations for FDCs that

contain a previously approved active moiety and a new active moiety. Indeed, the preambles usually refer to a singular active moiety – “the” active moiety – which suggests that FDA was not actively considering the issues associated with FDCs, which contain more than one active moiety.

To our knowledge, FDA has not otherwise made public statements regarding its position with respect to 5-year exclusivity for FDCs that contain one previously approved active moiety and one new active moiety. Although FDA has previously denied exclusivity for such products, we are unaware of any publicly available documents explaining the rationale for these determinations. A definitive interpretation cannot be based on an inference from agency action. *See Hudson v. FAA*, 192 F.3d 1031, 1036 (D.C. Cir. 1999) (“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.”).

## 2. *There Has Not Been Substantial and Justifiable Reliance*

Even if FDA is considered to have given a definitive interpretation of its policy, FDA would still be able to change its policy without notice and comment rulemaking due to the absence of substantial and justifiable reliance on that interpretation. *See MetWest v. Sec. of Labor*, 560 F.3d 506, 511 n.4 (describing substantial and justifiable reliance as a “crucial part of the analysis”). As an example of substantial and justifiable reliance, in *Alaska Professional Hunters*, the Federal Aviation Administration had a 30-year history of advising entities that a regulation did not apply to them. In reliance on this, “[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.” *Id.* (quoting *Alaska Prof’l Hunters*, 177 F.3d at 1035). By contrast, any reliance in the present situation would be neither substantial nor justifiable.

If FDA were to recognize 5-year exclusivity rather than 3-year exclusivity for NATAZIA, this would simply cause a 1-2-year delay in the submission of ANDAs and 505(b)(2) applications referencing NATAZIA, depending on the type of patent certifications contained in the applications. Any currently pending submissions could be resubmitted at the appropriate time (or FDA could even deem them to be submitted on the appropriate date). Recognizing the 5-year exclusivity to which NATAZIA is entitled under the statute and regulation would not increase or otherwise alter the investment required to develop and seek approval of a generic product. Unlike the case in *Alaska Professional Hunters* where companies designed their businesses around FAA’s historical position, a generic manufacturer’s drug development program would not turn on whether FDA grants 3-year exclusivity or 5-year exclusivity to NATAZIA. Accordingly, any reliance by a generic manufacturer would not be substantial.

Furthermore, any such reliance would not be justifiable. As demonstrated above, the controlling statutory and regulatory language indicates that NATAZIA should receive 5-year exclusivity because it contains a new active moiety. Although there are documents that suggest an FDA policy of granting 3-year exclusivity for products containing any previously approved active moieties, any reliance on these documents is seriously undermined by the conflicting statutory and regulatory language, which compels resolution in favor of 5-year exclusivity.

### **Conclusion**

As demonstrated above, the statutory language regarding 5-year exclusivity requires that 5-year exclusivity be granted for a FDC that contains *any* active moiety that has not been approved previously. This outcome is consistent with Congress's intent and required by FDA's own regulations. In addition, this approach avoids the arbitrary results associated with FDA's historical practice of denying 5-year exclusivity to these types of products. Furthermore, this approach advances the public interest by encouraging development of FDCs through an appropriate reward for the substantial investment associated with the development of FDCs containing new active moieties, such as the 16 years and nearly \$200 million spent by Bayer to develop NATAZIA. Administrative law permits FDA to adopt this interpretation without engaging in notice and comment rulemaking.

Thus, for the reasons stated, FDA should recognize 5-year exclusivity for dienogest, the new active moiety in NATAZIA.

### **Environmental Impact**

Under 21 C.F.R. §§ 25.30(h) and 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

### **Economic Impact**

Information regarding the economic impact of this proposal will be submitted upon request by FDA following review of this petition.


### **Certification**

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 dates: May 6, 2010, the date of FDA's approval of NATAZIA, and

April 19, 2013

December 22, 2010, the date Bayer first received notice of an ANDA referencing NATAZIA as its reference listed drug. 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: Bayer. 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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