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SmithKline Beecham
Pharmaceuticals

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

Re: Marketing Exclusivity and Patent Provisions
for Certain Antibiotic Drugs
Docket No. 99N-3088
65 Fed. Reg. 3623 (January 24, 2000)

SmithKline Beecham (SB) submits these comments on the proposed rule published by the Food and Drug Administration (FDA) on January 24, 2000, concerning marketing exclusivity and patent provisions for antibiotic drugs under the Food and Drug Administration Modernization Act of 1997 (FDAMA).

SB is one of the world's leading healthcare companies. SB discovers, develops, manufactures, and markets pharmaceuticals, vaccines, over-the-counter medicines and health-related consumer products. SB's products include Augmentin, a leading broad-spectrum antibiotic. SB employs over 5000 scientists and support specialists worldwide to research and develop pharmaceutical products.

SB strongly disagrees with the proposed rule. FDA's proposed exclusion of pre-FDAMA active moieties (rather than specific pre-FDAMA antibiotic drug products) from eligibility for patent listing and exclusivity protections is inconsistent with FDAMA and does not promote the public health. Some of the most significant advances in the development of antibiotic drug products involve continued research on previously developed active moieties. Indeed, the active moieties in currently marketed antibiotic products provide a well-established safety profile on which to build. FDA's exclusion of pre-FDAMA active moieties from any patent listing and exclusivity protections defeats Congress's intent to encourage antibiotic research and development.

Introduction

Before the enactment of FDAMA in 1997, the approval of antibiotics was regulated separately from the approval of other drugs. Antibiotics were certified under section 507 of the FD&C Act, whereas other new drugs were approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

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In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act).[1] The Hatch-Waxman Act facilitated the marketing of generic versions of pioneer products originally approved under section 505 of the FD&C Act (through abbreviated new drug applications, or ANDAs). The Hatch-Waxman Act also afforded certain patent listing and limited exclusivity protections to pioneer manufacturers for drug products approved under section 505. The manufacturer of a new drug product may be eligible for two types of exclusivity: five years of exclusivity for a new chemical entity (in other words, a new active moiety) and three years of exclusivity for new drug product containing the same active moiety (e.g., a salt or ester or a combination). Before FDAMA, antibiotics were not subject to these exclusivity protections because they were approved under section 507.

FDAMA repealed section 507 of the FD&C Act and treated antibiotics as "new drugs" subject to section 505.[2] As a result, antibiotics became eligible for the patent and exclusivity protections applicable to new drugs under the Hatch-Waxman Act. To encourage research and development of new antibiotic drugs without granting windfall protections for older ones, Congress provided that "new" antibiotic drugs would be eligible for patent and exclusivity protections, while "old" antibiotics would not. Under the "transition" rule, FDAMA itself establishes the statutory dividing line between "new" and "old" antibiotic drugs:

> The following subsections of section 505 (21 U.S.C. 355) shall not apply to any application for marketing in which the *drug that is the subject of the application* contains an antibiotic drug and *the antibiotic drug was the subject of any application* for marketing received by the Secretary of Health and Human Services under section 507 of such Act (21 U.S.C. 357) before the date of the enactment of [FDAMA].[3]

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

2 Section 125(d) of FDAMA, Pub. L. No. 105-115, 111 Stat. 2295, 2326-2327 (1997).

3 *Id.* (emphasis added).

The statute indicates that Congress defined an "old" antibiotic as an antibiotic drug product (containing a specific active ingredient) that was deemed to be the "subject" of an NDA. FDA, however, has expanded the class of "old" antibiotics to include all antibiotics containing the same active moiety as a pre-FDAMA antibiotic drug product, regardless of whether those specific antibiotic drug products actually were the subjects of pre-FDAMA NDAs. The net effect is to expand the universe of antibiotic drug products that are not eligible for patent listing and exclusivity to include products that were not and which could not have been marketed before FDAMA.

1. The Proposed Rule Is Inconsistent With the Language of the Statute and With Congress's Intent

FDA's proposed rule implements the FDAMA transition provision quoted above. In so doing, it purports to elaborate on the statutory distinction between "new" antibiotic drugs, which are eligible for exclusivity and patent protections, and "old" antibiotic drugs, which are not. The statute distinguishes between "an antibiotic drug that is the subject of an application" before FDAMA and after FDAMA. The proposed rule, however, distinguishes between a "new active moiety" and an "old active moiety."[4] As FDA put it: "the agency is proposing to implement section 125(d)(2) of [FDAMA] by relying on a comparison of active moieties to determine whether the drug that is the subject of an NDA contains a pre-repeal antibiotic drug."[5] Under FDA's interpretation of the antibiotic transition rule, the Hatch-Waxman Act's patent listing and exclusivity provisions "do not apply to any application or abbreviated application in which the drug that is the subject of the application or abbreviated application contains an antibiotic drug that has the same active moiety . . . as an antibiotic drug that was the subject of a marketing application received by FDA under former section 507 of the [FD&C Act] before November 21, 1997." [6]

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[4] The Hatch-Waxman Act exclusivity regulations define "active moiety" as:

> *Active moiety* means 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 CFR 314.108(a).

[5] 65 Fed. Reg. 3623, 3625 (January 24, 2000).

[6] 65 Fed. Reg. at 3626 (*proposed* 21 CFR 312.109(a)).

This interpretation has a substantial impact. The exclusivity and patent protections available under the Hatch-Waxman Act are vital incentives for research and development of innovative new products. Under the plain language of FDAMA, as confirmed by its legislative history, a new active ingredient -- which could be a salt or ester of an active ingredient contained in a previously approved drug product or a combination that includes an active ingredient of a previously approved drug product -- is a new antibiotic that *is* eligible for patent listing and exclusivity. Under FDA's approach, however, a new active ingredient or new combination of active ingredients is not eligible for exclusivity notwithstanding the fact that it has not been the subject of a pre-FDAMA NDA. Gordon Johnston, Deputy Director of FDA's Office of Generic Drugs and co-chair of FDA's Antibiotic Regulation Repeal Working Group, acknowledged this in a February 1998 speech to a trade association of generic drug manufacturers:

> "We are working on [a list of 'old' antibiotics that will not be eligible for patent or exclusivity protection in the future] now and. . . *it appears the definition for old antibiotic will be active moiety as opposed to active ingredient*" Johnson said. The distinction is "significant because that would preclude an old antibiotic from gaining patent or exclusivity privileges based on addition of a new salt." [Johnston] claimed that "if we get that list defined by active moiety, it will be a small victory in this overall process."[7]

This result is at odds with the plain language of the transition provision of FDAMA and with the drug approval provisions under section 505 of the FD&C Act. Section 125(d) of FDAMA treats pre-FDAMA antibiotic drugs as if they had been the subject of an approved application under section 505 of the FD&C Act. Those antibiotic drugs are "old" antibiotics which are ineligible for exclusivity protections. FDA's proposed rule takes the position that the entire active moiety is ineligible for exclusivity. It follows that FDA now treats the active moiety as the "subject" of a pre-FDAMA section 505 application. This is flatly inconsistent with the section 505 approval process and with the way FDA has historically interpreted section 505.

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[7] *FDA Antibiotic Regulation Repeal Group Co-Chaired by Lumpkin, Johnston; Agency to Meet with PhRMA, Generics Trade Groups on Pediatric Exclusivity,* THE PINK SHEET, February 9, 1998, at 3 (quoting Gordon Johnston's speech to the National Association of Pharmaceutical Manufacturers) (emphasis added).

An NDA is submitted to obtain approval of a specific drug product. For this reason, a "listed drug" is defined as a "new drug product that has an effective approval under section 505(c) of the [FD&C Act] or under section 505(j) of [the FD&C Act]."[8] A "drug product" is a "finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance." [9] A "drug substance" is the "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."[10] The definitions of the terms "drug product" and "drug substance" do not include the terms "salt" or "ester." In other words, the "subject of an application" for marketing is a drug product containing a specific active ingredient in a finished dosage form. If the "subject of an application" were an active moiety, a pioneer manufacturer would be free to market other drug products containing other drug substances (e.g., salts or esters of the active ingredient) without submitting a full NDA or supplemental NDA and without performing the clinical studies necessary to support such an application. Thus, the term "drug" as used in the drug approval provisions means "drug product" not "active moiety." [11]

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8 21 CFR 312.3(b).

9 *Id.*

10 *Id.*

11 In the unique context of pediatric exclusivity, FDA has construed the term "drug" to refer to an entire active moiety. That should be attributed to the particular circumstances of FDAMA's pediatric exclusivity provision. First, in the Hatch-Waxman context, FDA has taken the position that the term drug refers to a drug product rather than to an active moiety. *Pfizer, Inc.* v. *Food and Drug Administration,* 753 F. Supp. 171, 174 (D. Md. 1989) (magistrate's report and recommendation), *adopted* 753 F. Supp. 171 (D. Md. 1990). Second, in the pediatric context, the grant of exclusivity to an active moiety is plainly a better way to achieve Congress's objective of encouraging research on pediatric uses. The grant of exclusivity to a single drug product would not have that effect. Third, the language of the antibiotic transition provision is much more clearly tied to the concept of an application than is the language of the pediatric exclusivity provision.

That is the position that FDA has taken in litigation concerning the interpretation of section 505 in the Hatch-Waxman context. In *Pfizer, Inc.* v. *Food and Drug Administration*, the federal district court stated clearly:

> The FDA interprets the word "drug" as used in [section 505(b)(1) and (c)(2) of the FD&C Act] to mean the "drug product" for which the new drug application. . .was filed. Pfizer contends that the term "drug" in this context refers to both the drug substance (active ingredient) and the drug product. . . .Pfizer's argument is without merit.[12]

The district court adopted the recommendation of the magistrate, which focused on the fact that the statutory provisions at issue, like the antibiotic transition provisions, referred specifically to a new drug *application*:

> The relevant statutory section in this case, however, modifies the word "drug" by attaching the phrase "for which the applicant submitted the application." In that context, the FDA's interpretation of drug as meaning drug product is consistent with and indeed required by the statute.[13]

Under FDA's new interpretation, FDA approval of a pre-FDAMA antibiotic drug product would permit the manufacturer to market other antibiotic drug products containing the same active moiety without further approval by FDA. Similarly, under FDA's approach, a new combination of "old" antibiotics would be an old antibiotic rather than a new one. This would allow a manufacturer to market a new product which contains two previously approved active moieties on the basis of separate pre-FDAMA NDAs. Even under the pre-FDAMA antibiotic monograph system, there were separate monographs for each individual antibiotic drug and for combinations of those individual antibiotics; a combination was a distinct antibiotic that was not encompassed by the monographs of either (or any) of its component antibiotics. Thus, the statutory language and FDA's interpretation of that language unambiguously indicate that an interpretation of the transition rule that treats an "active moiety" as the "subject of an application" under section 505 cannot stand.

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[12] 753 F. Supp. at 171 (denying Pfizer's motion for summary judgment and granting FDA's cross-motion for summary judgment as recommended in the report of the magistrate).

[13] 753 F. Supp. at 176.

2. The Legislative History Confirms that an "Antibiotic Drug" is a Drug Product Rather than an Active Moiety

The FDAMA transition provision states that the product not eligible for exclusivity is "*the antibiotic drug was the subject of any application* for marketing received . . .before the date of the enactment of [FDAMA].[14] The legislative history of the transition provision confirms that section 125 means what it says, and no more. The House of Representatives report stated very clearly:

> The repeal of section 507 [of the FD&C Act] also results in applications for new antibiotic products being submitted to the FDA under all the requirements and benefits of section 505, including the granting of market exclusivity to all new drugs under the so-called Waxman-Hatch provisions. The Committee intends that the granting of market exclusivity be limited to products that achieve the policy objective of increasing research toward the development of new antibiotics. Thus, the granting of market exclusivity to new antibiotic drugs is limited to those products that are New Chemical Entities *and to products for which a New Drug Application has not been submitted prior to the date of enactment.*[15]

Had Congress intended to provide that no post-FDAMA application containing a pre-FDAMA antibiotic active moiety would be eligible for any form of exclusivity, it could simply have stated that "the granting of market exclusivity to new antibiotic drugs is limited to those products that are New Chemical Entities."

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[14] Section 125(d) of FDAMA (emphasis added).

[15] H.R. Rep. No. 105-310 (1997) (emphasis added).

But Congress added to the end of that sentence the words "*and to products for which a New Drug Application has not been submitted prior to the date of enactment.*"[16] In fact, during the FDAMA hearings, the generic industry conceded that the repeal of Section 507 would make antibiotics eligible for both the five-year exclusivity for new chemical entities and the three-year period applicable to new products containing old active moieties.[17]

In May 1998, only a few months after the enactment of FDAMA in November 1997, the principal drafters of FDAMA expressly confirmed that antibiotics would be eligible for either five-year or three-year exclusivity. They described the exclusion of derivatives of old antibiotics from the Hatch-Waxman exclusivity provisions as "unsupportable" and "clearly inconsistent with Congress' intent."[18] They wrote:

> In the transition provision, Congress provided that the Hatch-Waxman exclusion applied to: any application for marketing in which the drug that is the subject of the application contains an antibiotic drug was the subject of any application received [by FDA]. . . before the date of enactment of [FDAMA].
>
> This unambiguous transition provision is application-oriented. By its own term, it covers applications for "antibiotic drug[s]." It plainly does not cover new molecular entities that are indirectly or directly related to the antibiotic drug that is the subject of an excluded application for an "old antibiotic." According to traditional tools of statutory construction the transition provision cannot be read or interpreted to cover derivatives of "old antibiotics."

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16 *Id.* (emphasis added).

17 Examining Proposals to Reform the Performance, Efficiency, and Use of Resources of the Food and Drug Administration, Senate Committee on Labor and Human Resources, S. Hrg. 105-23, at 228 (March 19 and April 11, 1997)(Statement of the National Association of Pharmaceutical Manufacturers).

18 Letter from Rep. Tom Bliley, Chairman, House Commerce Committee, Rep. Michael Bilirakis, Chairman, House Commerce Subcommittee on Health and Environment, and Richard Burr, member of the House Commerce Committee, to Michael A. Friedman, M.D., Lead Deputy Commissioner, United States Food and Drug Administration (May 21, 1998), *reprinted in* FDA WEEK, January 28, 2000, at 4.

> Moreover, such an interpretation is clearly inconsistent with Congress' intent. Through FDAMA, Congress has ensured that, for any new molecular entity that is an antibiotic for which FDA requires a full NDA, Hatch-Waxman's research incentives will be available to s[t]imulate product development. In reaching that result, Congress carefully balanced the short-term interests of the generic drug industry (which wanted no impediments to generic drug approvals for old antibiotics) and the long-term interests of the research-based pharmaceutical industry (which sought Hatch-Waxman's powerful research incentives to spur development of new antibiotics -- whether derived from old antibiotics or newly invented -- to fight the public health crisis caused by antibiotic resistance.[19]

This interpretation makes sense as a policy matter. FDA's objectives should be to provide incentives for pioneer manufacturers to develop drugs. This is the sole point of the legislative history of FDAMA's antibiotic provision, quoted above. Further, this interpretation is consistent with the balance struck by the Hatch-Waxman Act itself. The application-based interpretation of the FDAMA transitional provision does not prejudice generic manufacturers: it does not grant any Hatch-Waxman protections to antibiotic products that already were approved when FDAMA was enacted and thus were available for abbreviated applications at that time. Nor is there any windfall grant of unearned protection to the pioneer manufacturer for salts, esters, and other derivatives of previously approved antibiotics. The manufacturer would not receive five years of exclusivity because no NCE or new active moiety is involved. Instead, where the manufacturer would be obligated to perform clinical studies on the new product to show that it is safe and effective, it would become eligible for three years of exclusivity -- the same period that is available under the Hatch-Waxman Act for salts and esters of previously-approved non-antibiotic drugs and synthetic anti-infective drugs.

Congress did not intend the repeal of Section 507 of the FD&C Act to put salts or derivatives of *synthetic* antibiotics, i.e., those not derived from a micro-organism, in a better position than salts or derivatives of well-established non-synthetic antibiotic drugs subject to Section 507.[20] FDA's proposed construction would unjustifiably favor salts or derivatives of synthetic antibiotics over those of Section 507 antibiotics by retaining the pre-FDAMA differential

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[19] *Id.* (emphasis in original).

[20] Synthetic anti-infectives did not fit within the definition of "antibiotic" under former Section 507 and thus were eligible for Hatch-Waxman protections even prior to FDAMA.

treatment of these products, which FDAMA itself was intended to eliminate. Moreover, the public health rationale for providing Hatch-Waxman protections (to encourage the further development of safe and effective drugs in an environment of ever-increasing resistant bacteria) applies equally to synthetic and non-synthetic antibiotics. Congress intended that both forms of anti-infectives should be eligible for patent listing and exclusivity protections.

For all these reasons, the antibiotic transition provision as written preserves the balance struck in the Hatch-Waxman Act between innovation and limited exclusivity, on the one hand, and facilitating generic competition, on the other. FDA's broader interpretation upsets that balance and defeats Congress's "policy objective of increasing research toward the development of new antibiotics."

3. FDA's Attempted Justifications Are Not Supported by FDAMA or by Congress's Policy Objectives.

FDA justifies its overbroad interpretation of the transition provision by relying on the following definition of "antibiotic drug" under the FD&C Act:

> The term "antibiotic drug" means any drug . . . composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a microorganism and which has the capacity to inhibit or destroy microorganisms in dilute solution (including a chemically synthesized equivalent of any such substance) or *any derivative thereof.*[21]

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[21] Section 201(jj) of the FD&C Act, 21 USC 321(jj) (emphasis added).

FDA combines this definition with the transition provision to conclude that an antibiotic drug that was the "subject of an application" before FDAMA, together with any "derivatives" of that antibiotic drug, are ineligible for exclusivity. In so doing, FDA ignores the fact that the "antibiotic drug" definition originally appeared in section 507 and was not added by FDAMA to shed light on the antibiotic transition provision. It therefore does not compel the conclusion that the term "derivatives" was included in transition provision to deny exclusivity to any drug product that contains a previously approved active moiety. As used in section 507, the term "derivatives" indicated merely that derivatives of antibiotic drugs also were considered antibiotic drugs subject to section 507 rather than subject to section 505.[22] Thus, the inclusion of derivatives simply ensured that a salt or ester of an antibiotic drug would be regulated as an antibiotic under section 507. The definition does not bear on the "old" versus "new" dividing line under FDAMA at all.[23]

FDA also argues that its approach to antibiotic exclusivity is consistent with FDA's interpretation of the Hatch-Waxman Act: "FDA has consistently looked at active moieties to determine if the exclusivity protection granted to a drug product would allow a subsequent ANDA or application described in section 505(b)(2) of the [FD&C Act] to be submitted or approved."[24] In fact, however, the statutory language is different, and thus provides no support for FDA's position here. The Hatch-Waxman Act's exclusivity provisions refer specifically to a prior approval of "an active ingredient (*including any ester or salt of the active ingredient*)"[25] in determining eligibility for five years of exclusivity rather than three years. The FDAMA transitional provision for antibiotics does not contain this wording or the term "active moiety." It therefore directs FDA to look to the specific active ingredient rather than the active moiety. The salt or ester of a previously-approved antibiotic active moiety would receive three years of exclusivity under the Hatch-Waxman Act. This is the true "consistency" between application of FDAMA and the Hatch-Waxman Act. By so doing, FDA would promote research and development of new antibiotic drugs based on modifications or combinations of previously approved active ingredients.[26]

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[22] Section 507(a) provided, "The Secretary . . . shall provide for the certification of batches of drugs . . . composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any antibiotic drug, *or any derivative thereof.*" 21 USC 357(a) (emphasis added).

[23] Indeed, if the reference to derivatives in the definition applied more broadly, it would lead to the absurd result that approval of any "antibiotic" also encompassed approval of all its derivatives.

[24] 65 Fed. Reg. at 3625.

[25] Section 505(j)(5)(D)(ii) and (iii), 21 USC 355(j)(5)(D)(ii) and (iii) (emphasis added).

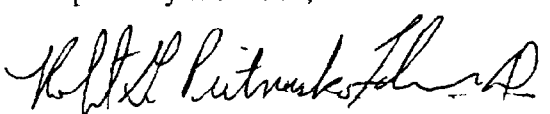
[26] FDA has in fact *granted* exclusivity to an active moiety where the manufacturer performed pediatric studies in connection with one product within that active moiety. This interpretation of the Section 505A of the FD&C Act was upheld by the federal district (continued...)

Conclusion

Encouraging the development of new antibiotic products from all potential sources is even more important today and for the future public health. Great needs exist to develop new products and improved old products as micro-organisms develop ways to overcome the effectiveness of older products. The NIH, CDC, and FDA have held public meetings to discuss how best to combat resistant infections and encourage antibiotic research through incentives and otherwise.[27] The proposed rule runs afoul of the publicly stated goals for the advancement of public health as stated at the Atlanta meeting.

SB therefore urges FDA to interpret FDAMA's antibiotic transition provision to exclude from the Hatch-Waxman protections only specific antibiotic drug products (not active moieties) that were the subjects of previously submitted applications. Any post-FDAMA application for an antibiotic product that differs from one subject to a pre-FDAMA application in terms of the specific active ingredient or combination of active ingredients, dosage form, strength, or other relevant characteristic should be eligible for Hatch-Waxman protections. Such an interpretation would be consistent with the statute and with congressional intent in enacting it. The interpretation set forth in the proposed rule is not.

Respectfully submitted,



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court for the District of Columbia over the objections of generic manufacturers. *National Pharmaceutical Alliance* v. *Henney*, 47 F. Supp. 2d 37 (D.D.C. 1999).

[27] *Meeting on Development of a Public Health Plan to Combat Anti-Microbial Resistance*, sponsored by CDC, FDA, and NIH, Atlanta, GA, July 19-21, 1999.