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

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

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America ("PhRMA") 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").

PhRMA is a voluntary, non-profit association that represents the country's leading research-based pharmaceutical and biotechnology companies. These companies are devoted to research on medicines that allow patients to lead longer, healthier, and more productive lives. PhRMA member companies invest approximately $24 billion annually to discover and develop new medicines. These companies are the source of nearly all new drugs – including antibiotic drugs – that are discovered and evaluated throughout the world.

PhRMA believes FDA's Proposed Rule is inconsistent with any rational interpretation of the relevant provisions of FDAMA and contradicts the intent of Congress to promote innovation in the field of antibiotic drugs. Accordingly, PhRMA requests FDA to revise its Proposed Rule.

I. FDA'S PROPOSED RULE IS INCONSISTENT WITH ANY RATIONAL INTERPRETATION OF THE FDAMA PROVISIONS.

Section 125(b) of FDAMA repealed Section 507 of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") (21 U.S.C. 357 (1996)). Section 507 was the section of the FD&C Act under which the agency certified antibiotic drugs.

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Section 125(d)(1) of FDAMA provides that marketing applications for antibiotic drugs that were approved under former Section 507 of the FD&C Act will be considered to have been submitted and approved under the new drug application ("NDA") submission and approval provisions found at Section 505(b) and (c) of the FD&C Act (21 U.S.C. 355(b) and (c)). If the marketing application was an approved abbreviated antibiotic drug application, it will be considered to have been submitted and approved under the abbreviated new drug application ("ANDA") provisions found in Section 505(j) of the FD&C Act.

FDAMA also exempts certain antibiotic-related drug marketing applications from the marketing exclusivity and patent provisions found in Section 505 of the FD&C Act.[1] Under former Section 507 of the FD&C Act, antibiotic drug applications were not subject to the patent listing and exclusivity provisions in Section 505 of the FD&C Act.

Section 125 of FDAMA preserves this distinction by providing that "[d]rugs that were approved and marketed under former Section 507 of the FD&C Act, as well as those that were the subject of applications that may have been withdrawn, not filed, or refused approval under Section 507 of the FD&C Act are excluded from the patent listing and exclusivity provisions." 65 Fed. Reg. at 3624.

Specifically, FDAMA provides that:

> [t]he following subsections of Section 505 (21 U.S.C. 355) [concerning market exclusivity and patents] 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]. Section 125(d) of FDAMA.

Pub. L. No. 105-115, 111 Stat. 2295, 2326-2327 (1997) (emphasis added).

A. FDA Erroneously Focuses On The Definition Of "Antibiotic" To Support The Rationale Of Its Proposed Rule.

In the Proposed Rule, FDA has erroneously concluded that the determination under Section 125(d) of FDAMA of whether a drug contains a pre-repeal antibiotic depends on whether the drug that is the subject of a marketing application contains an active moiety that can be found in a pre-repeal antibiotic drug. 65 Fed. Reg. at 3625. FDA's conclusion is inconsistent with any rational interpretation of FDAMA.

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[1] The FDAMA does not affect whatever rights patent holders may have regarding patent term extensions under 36 U.S.C. 156 for patents claiming antibiotic drug products.

FDA's error begins with its focus on the term "any derivative" in the definition of antibiotic drug that appeared in former Section 507 of the FD&C Act and was repeated in Section 125(d) of FDAMA. The term "antibiotic drug," as used in Section 125(d) of FDAMA, is defined as:

> ". . . any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlorictracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof. 21 U.S.C. 321(jj).

FDA first asserts that "any derivative" means derivatives such as salts or esters of a substance. By limiting "any derivative" to salts or esters, FDA then uses this language to support its rationale for the use of "active moiety" as the standard for the determination of pre-repeal antibiotics. FDA's regulations define an active moiety as "the molecule or ion responsible for physiological or pharmacological action, excluding appended portions that would cause the drug to be an ester, salt, or other noncovalent derivative of the molecule." 21 C.F.R. 314.108(a).

The problem, however, is that the "active moiety" definition is limited to "***non-covalent***" derivatives of the molecule. FDA does not and cannot provide an explanation for arbitrarily excluding covalent derivatives from its determination of pre-repeal antibiotic drugs that is based on the term "***any*** derivative." Although, under FDA's incorrect interpretation, the FDAMA language would require the exclusion of covalent derivatives from the benefits of the Hatch-Waxman Act, the exclusion of such derivatives from patent listings and market exclusivity would eviscerate all incentives for the great majority of antibiotic innovations that are likely to occur in the foreseeable future. FDA's erroneous focus on the term "any derivative" to support its rationale makes this result both statutorily required and logically absurd.

B. FDA's Proposed Rule Would Provide Fewer Incentives For Antibiotic Innovation Than Are Provided For Innovation In Other Drug Categories.

According to the Proposed Rule, "FDA has consistently looked at active moieties to determine whether the exclusivity protection granted to a drug product would allow a subsequent ANDA or application described in Section 505(b) of the FD&C Act to be submitted or approved." 65 Fed. Reg. at 3625. Although this statement accurately reflects FDA's practices with respect to approvals of ANDAs and applications described in 505(b)(2) of the FD&C Act, FDA is erroneously applying the same standard in the context of the antibiotic provisions of FDAMA. Application of the same standard in this context produces markedly different consequences.

In the Hatch-Waxman context, the term "active moiety" is used exclusively for a determination of whether the NDA product receives five years of data exclusivity as a new chemical entity ("NCE") or three years of data exclusivity as a non-NCE. The concept of "active moiety" is not used to determine whether patents can be listed for the modification to the original drug. Similarly, the concept of active moeity is not used to prevent three-year exclusivity if the subsequent NDA or NDA supplement for the modification otherwise meets the criteria for non-NCE data exclusivity.

In contrast, under FDA's interpretation of the antibiotic rule, the concept of "active moiety" will both prevent patent listings for the new NDA or NDA supplement, and it will prevent non-NCE data exclusivity, even when clinical studies are required to support approval of the modification. As the Proposed Rule states:

> NDA's for products that contain, for example, a salt of a pre-repeal antibiotic drug, or that propose such things as a new manufacturing process, new dosage form, or new use of a pre-repeal antibiotic drug, will be subject to the exceptions listed in Section 125(d)(2) of [FDAMA] and proposed § 314.109(a).

65 Fed. Reg. at 3625. According to FDA's Proposed Rule, these changes would neither be eligible for patent listings nor eligible for non-NCE data exclusivity. However, under the operation of the Hatch-Waxman Act for other drugs, each of these changes would be eligible for patent listings for relevant patents and data exclusivity if they rely on new studies. Therefore, FDA's approach creates fewer incentives for innovation for antibiotics than exist for other drugs.

Congress intended the repeal of Section 507 of the FD&C Act to place antibiotic drugs that are the subject of post-repeal marketing applications in a position to have the same incentives for innovation as other drugs. FDA's Proposed Rule, however, will place post-repeal antibiotics in a less favorable position than other drugs. This was not the intent of Congress, and FDA cannot assert that it was.

II. A "DRUG" THAT WAS THE SUBJECT OF A PRE-REPEAL APPLICATION MUST BE INTERPRETED TO MEAN "DRUG PRODUCT"

The definition of antibiotic drug in Section 125(d) of FDAMA[2] merely defines the types of drugs that are "antibiotic." As described above, it does not and cannot define the scope

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[2] The term "antibiotic drug," as used in Section 125(d) of the Modernization Act, is defined as:

> ". . . any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlorictracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof.

21 U.S.C. 321(jj).

of products that are excluded from the benefits of the Hatch-Waxman data exclusivity and patent listing requirements.

The FD&C Act defines "drug" broadly to cover both a finished drug product and its active ingredient or ingredients and delegates to FDA the task of determining how to apply that definition in particular instances. Any interpretation of the relevant language in the FDAMA exclusion for pre-repeal antibiotic drugs must focus on the word "drug."

A. "Drug Product" Is The Only Meaning Of Drug That Avoids An Absurd Result.

"Drug product" means a finished dosage form, *e.g.*, tablet, capsule, or solution, that contains the active drug ingredient, generally, but not necessarily, in association with inactive ingredients. 21 C.F.R. § 320.1(b). "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, but does not include intermediates used in the synthesis of such ingredient. *Id.* In this regard, the ester form is a different active ingredient from the salt form. Accordingly, "Drug Product" is the only meaning of drug that will provide post-repeal antibiotic products with the same incentives for innovation under the Hatch-Waxman Act as other drug products.[3]

Indeed, in a nearly identical statutory construction, FDA interpreted the word drug to mean "drug product." *Pfizer, Inc.* v. *Food and Drug Administration*, 753 F. Supp. at 171, 174 (D. Md. 1989) (magistrate's report and recommendation), adopted 753 F. Supp. at 176. The *Pfizer* court adopted the magistrate's recommendation that, in the context of Section 505 of the FD&C Act, "FDA's interpretation of drug as meaning drug product is consistent with and indeed required by the statute."[4]

Section 505(b)(1) and (c)(2) of the FD&C Act refers to a "drug for which the applicant submitted the application." 21 U.S.C. §§ 355 (b)(1) and (c)(2). This statutory language is substantively the same as "a drug that is the subject of the application" that is described in Section 125(d) of FDAMA. The interpretation of "drug" as "drug product" is equally compelled in the language of Section 125(d) of FDAMA.

B. "Drug Product" Is The Only Meaning Of Drug That Complies With The Legislative History.

Section 125(d) of FDAMA states that the product is not eligible for exclusivity if "the antibiotic drug was the subject of ***the subject of any application*** for marketing received . . .

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[3] The "drug substance" definition would still preclude modifications such as new manufacturing process, new dosage form and new uses of a pre-repeal antibiotic drug from patent listings in all cases and from non-NCE data exclusivity in the circumstances when these modifications rely on new clinical studies for approval.

[4] *Id* at 176, (district court referring to and adopting the recommendation of the magistrate).

before the date of the enactment of [FDAMA]."[5] The legislative history shows that this provision is application-specific. It also follows that "drug product" is the only meaning of "drug" that will achieve the application-specific intent of the legislative history.

> The House of Representatives Report states that:
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> "[t]he 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."[6]

The House Report confirms that the FDAMA provision is application-specific: "The repeal of Section 507 [of the FD&C Act] also results in ***applications . . . being submitted*** under all the requirements and benefits of Section 505, . . ." The 505 benefits accrue to applications, and applications refer to drug products. Similarly, the House Report discusses "applications for new antibiotic ***[drug] products;***" it does not discuss applications for new antibiotic ***active moeities***.

Moreover, in May 1998, only a few months after the enactment of FDAMA in November 1997, the principal drafters of FDAMA expressly confirmed that the exclusion from the benefits of the Hatch-Waxman Act were application-specific.[7] According to the drafters of the 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."[8]

Thus, the exclusion from Hatch-Waxman benefits is application-specific, and the term antibiotic "drug" must mean antibiotic "drug product" to achieve the application-specific intent of Congress.

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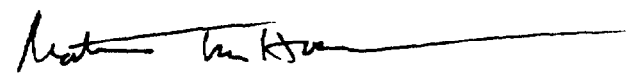
[5] Section 125(d) of FDAMA (emphasis added).
[6] H R. Rep. No. 105-310 (1997) (emphasis added).
[7] Letter from Rep. Tom Bliley, Chairman, House Commerce Committee, Rep. Michael Bilirakis, Chairman, House Commerce Subcommittee on Health and Environment, and Richard Burr, member of the House Commerce 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.
[8] *Id.* at 1-2.

III. CONCLUSION

For the reasons described above, PhRMA urges FDA to withdraw its erroneous interpretation of Section 125(d) of FDAMA. Instead, FDA must interpret Section 125 to provide the benefits of the Hatch-Waxman to post-repeal antibiotics to the same extent as those benefits are available to other drugs under Section 505 of the FD&C Act. This approach is both consistent with the statutory language and furthers the congressional intent of encouraging innovation in antibiotic drug products.

Sincerely yours,



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