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PETITION FOR STAY OF ACTION

BOSTON
DALLAS
DELAWARE
NEW YORK
SAN DIEGO
SILICON VALLEY
TWIN CITIES
WASHINGTON, DC

The undersigned submits this Petition for Stay of Action under 21 C.F.R. § 10.35, on behalf of Allergan, Inc., requesting FDA to stay its approval of all Section 505(j) Abbreviated New Drug Applications (“ANDAs”) and Section 505(b)(2) New Drug Applications for generic versions of Restasis®, Ophthalmic Emulsion 0.05%, pending disposition of Allergan’s pending Citizen Petition in Docket No. 2003P-275/CP-1. In addition, Allergan requests that FDA immediately list Allergan’s patents for Restasis® in the Orange Book. Allergan seeks a decision on this stay petition as soon as possible and no later than thirty days after it has been received by the FDA. Allergan will consider any failure to grant such relief in that period of time a final decision of the FDA for purposes of seeking judicial review.

A. Decision Involved

On June 13, 2003, Allergan filed a Citizen Petition requesting that it be accorded three years of market exclusivity along with Orange Book patent listing rights for Restasis® (NDA 21-023), approved on December 23, 2002, under Section 505 of the Food Drug & Cosmetic Act (“FDCA”). Allergan’s Citizen Petition was necessitated by FDA’s subsequent and improper reclassification, on March 3, 2003, of Restasis® as an antibiotic drug product (NDA 50-790). This reclassification occurred some three months after Restasis® was approved by FDA under Section

2003P-0275

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505, some ten years after development first began and after Allergan spent over \$47 million dollars in Research and Development costs. By reclassifying Restasis® in this manner, FDA rendered the drug ineligible for Hatch-Waxman benefits pursuant to a proposed, but yet to be adopted, rule implementing Section 125(d) of the Food and Drug Administration Modernization Act of 1997 (FDAMA). FDA has not yet acted on Allergan's Citizen Petition.

B. Action Requested

FDA is requested to stay its approval of all ANDAs and Section 505(b)(2) applications for generic versions of Restasis® until it has ruled on Allergan's pending Citizen Petition and, if FDA denies that petition in whole or in part, until twenty days after that decision to permit Allergan to seek a judicial stay. Allergan believes that the need for a stay in this case is particularly compelling because of the streamlined regulations set forth in 21 C.F.R. § 320.22 (b) which apply to bioequivalency determinations for generic ophthalmic solutions. In particular, Section 320.22(b) requires that FDA "shall" waive the requirement for evidence of *in vivo* bioequivalency upon a showing that a generic ophthalmic solution contains the same active and inactive ingredients in the same concentration as the reference listed drug. Generic manufacturers of Restasis®, therefore, are in a position to receive rapid approval of their ANDAs and Section 505(b)(2) applications.¹ Without the right to list Restasis® patents in the Orange Book, Allergan will not receive any notice that generic applications have been submitted to FDA nor will it be able to take advantage of the thirty month stay provisions should patent litigation ensue. To avoid irreparable harm to Allergan, FDA is requested to adhere to its initial and correct classification and approval of Restasis® as a non-antibiotic drug product eligible for Hatch-Waxman benefits or, in the alternative, to find that Restasis® is a new

¹ In a companion filing to this Petition, Allergan is amending its Citizen Petition to provide evidence of its current U.S. investment in Restasis® -- a sum which exceeds \$47 million.

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antibiotic drug product that does not fall within the Hatch-Waxman ineligibility provisions of Section 125 of FDAMA.

In either event, Allergan further requests that FDA immediately list Allergan's patents for Restasis® in the Orange Book, at least until such time as the Citizen Petition has been decided and Allergan has an opportunity for judicial review of that decision. Accordingly, Allergan is resubmitting the patent information for Restasis® as Exhibit A to this petition. FDA improperly refused to list the patent information for this drug at the time of its approval. That listing should now occur, at least provisionally during the pendency of the requested stay. FDA's failure to grant Allergan patent listing rights along with the right to receive notice of generic drug applications and approvals under 21 U.S.C. §§ 355(b), (c), and (j) will prejudice Allergan's ability to enforce its patents pursuant to Section 271(e)(2) and protect its investment in Restasis®.

C. Statement Of Grounds

1. Mandatory Stay

Under 21 C.F.R. § 10.35(e), FDA must grant a stay of action if all of the following apply:

- (a) the petitioner will otherwise suffer irreparable injury
- (b) the petitioner's case is not frivolous and is being pursued in good faith;
- (c) the petitioner has demonstrated sound public policy grounds supporting the stay; and
- (d) the delay resulting from the stay is not outweighed by public health or other public interests.

As demonstrated below, all of these criteria are met.

a. Allergan will suffer irreparable injury

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If this Petition for stay is denied by FDA and generic versions of Restasis® are approved and enter the market, it is axiomatic that Allergan will immediately lose significant sales and market share. Even if a court should subsequently overturn the FDA's denial of this Petition, Allergan will be unable to recoup such losses; thus, it will be irreparably harmed.

Such harm is not a remote possibility. Restasis® has been hailed as "the first prescription treatment that has been shown to help improve the quality and quantity of tears" for treating dry eye syndrome, a common ailment.² Absent a favorable ruling on the Citizen Petition and this Petition to Stay, Restasis® will not receive three years of market exclusivity and Allergan will not be given the opportunity to enforce its patents under Hatch-Waxman. Manufacturers of low cost generics will be able to cash in quickly on the tremendous market potential for this new drug, putting Allergan's investment of more than \$47 million in Restasis® at risk. Because such losses can never be recovered once generic products enter the market, there can be little doubt that Allergan will be irreparably harmed by a denial of this Petition.³

b. Allergan's case is not frivolous and is being pursued in good faith

² Stefanie Weiss, *How Dry Eye Am*, Washington Post, July 1, 2003, at F5 (attached as Exhibit B). See also Lynda Charters, *Restasis Approval A Milestone For Dry Eye*, Ophthalmology Times, February 1, 2003, at 1 ("The FDA approval of cyclosporine ophthalmic emulsion 0.05% (Restasis, Allergan) Dec. 26 marked a landmark for ophthalmology. The eye drop therapy for moderate to severe keratoconjunctivitis sicca is unique in that it treats the inflammatory process that causes the condition, and not just its symptoms.") (attached as Exhibit C); Laurie Barber, M.D., *Clinical Experience with Cyclosporine (Restasis) for Dry Eye*, March 2003, available at <http://www.eyetowncenter.com/eyetc/11.541/0.21/0.22/0.145/0.1/0.0/0.0/articles.htm> ("There is considerable pent-up demand among dry eye patients who have simply given up on the medical profession.") (attached as Exhibit D); Michelle Stephenson, *The Flap's Important Role In LASIK-Induced Dry Eye/Restasis: Getting beyond the dry facts*, Eye World, July 2003 (available at <http://www.eyeworld.org/july03/0703p36.html>) ("When Restasis (Allergan, Irvine, Calif.) gained Food and Drug Administration approval last December, for the first time ophthalmologists found that they were able to get at the underlying cause of dry eye disease rather than simply offering patients palliative options.") (attached as Exhibit E).

³ See *CollaGenex Pharmaceuticals, Inc v. Thompson*, CV 03-1405 (D.C.D.C. July 22, 2003), in which the court discusses the devastating impact of generic entry on pioneer drugs.

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Allergan's Citizen Petition makes a compelling case for the relief requested. As explained in the Citizen Petition, Allergan is suffering the consequences of repeated FDA errors concerning the historic regulation of cyclosporine (CSA), the active ingredient in Restasis®.

FDA's first error occurred in 1983 when CSA was inappropriately classified as an antibiotic drug despite the fact that CSA does not function as an antibiotic and had never been approved for any antibiotic indications. In point of fact, CSA has been shown to be an immunosuppressive compound that functions essentially as an "anti-antibiotic."⁴ For this reason, Restasis® is contraindicated for patients with eye infections -- conditions that are commonly treated with antibiotic drugs.⁵

Significantly, one court recently held that the FDA cannot classify a drug product as an antibiotic if, in fact, it exhibits no antibiotic properties. *See CollaGenex Pharmaceuticals, Inc. v. Thompson*, CV 03-1405 (D.C.D.C. July 22, 2003) (attached as Exhibit F). In *CollaGenex*, the district court enjoined FDA from approving any ANDAs for a generic version of Periostat® (doxycycline hyclate 20 mg) because, at the concentration of the active ingredient authorized, the drug product did not have the capacity to inhibit or kill microorganisms as required of an antibiotic drug under 21 U.S.C. § 321(jj). Similar to the situation here, CSA, in the concentration approved for Restasis® (0.05%), has never been shown to have any capacity to inhibit or kill microorganisms. Based on the holding in *CollaGenex*, Restasis® cannot be properly classified as an antibiotic drug.

At the time of FDA's decision in 1983, its consequences were minimal because antibiotic drugs were not then discriminated against for purposes of Hatch-

⁴As Allergan's Citizen Petition explains, an immunosuppressive reagent is essentially the opposite of an antibiotic, which inhibits or destroys microorganisms. In contrast, an immunosuppressive reagent enables microorganism growth because it suppresses the immune system by blocking activation of the phosphorylase enzyme calcineurin. *See* Citizen Petition at 10.

⁵ *See* Restasis® product information sheet, available at www.restasis.com ("RESTASIS™ is contraindicated in patients with active ocular infections.").

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Waxman as they are today. In any event, Allergan was not a party-in-interest to that early determination.

FDA's second error occurred in 2000 when it construed FDAMA's so-called "antibiotic repeal" provisions in a manner that penalizes pioneer drug manufacturers, contrary to Congressional design. As Allergan explains in its Citizen Petition, Section 125 of FDAMA was intended to stimulate research and investment in new antibiotic drugs by making pioneer antibiotics newly eligible for Hatch-Waxman benefits.⁶ To avoid any unintended windfalls to manufacturers of "old" antibiotics, Congress placed restrictions on certain drug approvals. Thus, Section 125(d)(2) provides that any antibiotic drug that was "the subject of any application for marketing received [by FDA] under Section 507 . . . before [passage of FDAMA]" would be ineligible for Hatch-Waxman benefits (*e.g.*, market exclusivity, patent certification and Orange Book listing).⁷

Restasis®, however, had not previously been the subject of a Section 507 application received by FDA and, therefore, Allergan was operating under the clear assumption that FDAMA's "exception" to Hatch-Waxman had no applicability. Allergan's assumption squared with the statutory language, the clear Congressional intent and the public comments of several of the drafters.⁸ Accordingly, Allergan had every reason to expect that Restasis® would be eligible for Hatch-Waxman benefits upon approval – an expectation that was confirmed by FDA's initial classification of Restasis® as a 20,000-series (non-antibiotic) application (NDA 21-023) in February 1999, and subsequent approval in December 2002.

⁶ House Rep. No. 105-310, 105th Cong., 1st Sess. 77 (1997). Prior to 1997, antibiotics were regulated under Section 507 and thus, ineligible for Section 505 Hatch-Waxman benefits.

⁷ This "exception" to Hatch-Waxman was in recognition of the fact that any antibiotic drug product that had been "received" by FDA prior to FDAMA was, by definition, one which already had been fully developed and clinically tested and therefore, was not in need of new "research and investment" which Hatch-Waxman was designed to stimulate.

⁸ See 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, U.S. FDA (May 21, 1998), reprinted in *FDA WEEK*, January 28, 2000.

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In January 2000, however, FDA released a “proposed rule” which construed Section 125(b)(2) as *denying* Hatch-Waxman benefits to any NDA containing an “active moiety” of any antibiotic drug that had ever been the subject of an application received under Section 507.⁹ FDA prepared a list of such pre-FDAMA antibiotic drugs that included CSA. Under FDA’s novel and arbitrary interpretation of Section 125, Restasis® would fall within the Hatch-Waxman exception if it were classified as an antibiotic drug product.

FDA’s third and most recent error was its post-approval reclassification of Restasis® as an antibiotic drug product. After having already approved Restasis® as a 20,000-series nonantibiotic drug on December 23, 2002, after many years of treating Restasis® as an immunosuppressive drug for purposes of approval, FDA unexpectedly changed course and reclassified it as a 50,000-series antibiotic drug on March 3, 2003, making it ineligible for Hatch-Waxman benefits under FDA’s enforcement of its proposed rule. Allergan relied on FDA’s previous classification when it continued investing tens of millions of dollars into the research and development of Restasis®. FDA should therefore be estopped from changing course so late in the process. FDA’s action unfairly denies Restasis® the Hatch-Waxman rights to three years of market exclusivity and Orange Book patent listing which are vital to its commercial success. For these reasons, Allergan’s cause of action is non-frivolous and is being pursued in good faith.

c. Sound public policy grounds support the stay

Hatch-Waxman represents a carefully balanced compromise between pioneer and generic drug manufacturers. It is intended to encourage the costly research and development efforts that lead to the discovery of new drugs while, at the same time, expedite the availability of safe, effective, and less expensive versions of approved

⁹ See Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs, 65 Fed. Reg. 3623-02, Notice 99N-3088, proposed January 24, 2000 (Proposed Rule).

drugs. FDA's arbitrary classification of the immunosuppressive drugs CSA and Restasis® as antibiotic drugs not eligible for Hatch-Waxman benefits significantly deprives Allergan, as the NDA holder, of the benefits of the carefully crafted Hatch-Waxman bargain. Moreover, such improper classification confers a potential windfall on ANDA and 505(b)(2) applicants who are now in a position to obtain rapid approvals of generic versions of Restasis® based on Allergan's clinical data. Such windfall is especially unfair in the case of ophthalmic solutions where bioequivalency may be determined to be self-evident under 21 C.F.R. § 320.22. Because Hatch-Waxman benefits are critical to stimulating research and development of costly new drug products, any action which threatens the balance struck by Congress between pioneer drug manufacturers and generics also threatens the public interest. A stay in this case, therefore, is supported by sound policy goals.

d. Any delay will not harm the public interest

Allergan plans to seek court review if FDA denies its Citizen Petition or this Petition for Stay. Allergan anticipates that a court would view this case as raising significant public policy concerns and would decide the case quickly, minimizing the impact of any delay in generic approvals.

Indeed, Allergan is not the only company to have strongly disagreed with FDA's proposed rules interpreting of Hatch-Waxman's impact on antibiotic drugs. Several other drug manufacturers, as well as Pharmaceutical Research and Manufacturers of America ("PhRMA"), filed extensive comments on the FDA's proposed rule, challenging its unusual and arbitrary interpretation of FDAMA.¹⁰

¹⁰ See Comment from PhRMA of April 24, 2000 (arguing that FDAMA applies only to antibiotic drug products, not active moieties) (attached as Exhibit G); Comment from SmithKline Beecham of April 14, 2000 (same) (attached as Exhibit H); Comment from Merck of April 21, 2000 (disagreeing with FDA's interpretation of "active moiety") (attached as Exhibit I); Comment from Alcon of April 21, 2000 (arguing that "old" antibiotics still receive Hatch-Waxman benefits under 35 U.S.C. § 271(e)(2)) (attached as Exhibit J); and Comment from AstraZeneca of January 24, 2001 (arguing that FDA improperly classified meropenem as an antibiotic, not an anti-infective agent) (attached as Exhibit K).

These comments provide powerful evidence that the legislative drafters of Section 125 did not intend to exclude new antibiotic drug products from receiving Hatch-Waxman benefits under Section 505.¹¹

There is no public health benefit or other issue of public interest in sustaining arbitrary and capricious drug classifications that deprive NDA holders of their exclusivity and marketing rights under the applicable statutes and regulations. Nor is there any public interest in allowing approval of generic drugs under an illegitimate classification system. “The public’s interest in ‘the faithful application of the laws’ outweigh[s] its interest in immediate access to [a competing] product.” *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060, 1066 (D.C. Cir. 1998).

2. Discretionary Stay

Finally, even if FDA finds that the criteria for a mandatory stay set forth above are not met, FDA may nevertheless grant a discretionary stay if it is “in the public interest and in the interest of justice.” 21 C.F.R. § 10.35(e). The issues raised by Allergan’s Citizen Petition are both novel and important. In *CollaGenex*, a case involving similar questions of drug classification, the pioneer drug manufacturer obtained a court-imposed stay much like Allergan is seeking. FDA, therefore, should grant this stay request pending resolution of these issues for all similarly situated manufacturers. Such issues are far from being settled, as evidenced by the pendency of FDA’s three year old proposed rules dealing with antibiotic drug classifications, yet the FDA has proceeded to enforce those rules prematurely. The public interest and the interests of justice demand expeditious, certain, and even-handed resolution of the issues.

D. Conclusion

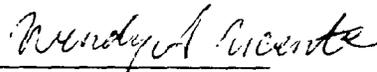
¹¹ *Id.*

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Allergan's Citizen Petition asks that FDA remove CSA from the list of proposed antibiotics that are ineligible for marketing exclusivity and patent listing, or alternatively to find that Restasis® is not an antibiotic drug product. The FDA has erred in its classification of CSA as an antibiotic compound and its interpretation of FDAMA as excluding Restasis® from eligibility for Hatch-Waxman benefits. These errors have stripped away Allergan's rights to market exclusivity and Orange Book patent listing for Restasis® after an expenditure of over \$47 million dollars in costs and years of reliance on FDA's previous position that the drug was not an antibiotic.

For the reasons provided herein, FDA should, within thirty days of this petition, grant a stay of approval of all ANDA and 505(b)(2) applications for generic forms of Restasis® pending a final determination on Allergan's pending Citizen Petition. In addition, at least until FDA makes a decision on the Citizen Petition, FDA should list the patents for Restasis® in the Orange Book to alleviate the current harm being done to Allergan under FDA's enforcement of its proposed rule. Should FDA ultimately deny the relief requested herein, Allergan asks that it be given sufficient time (at least twenty days) to seek a judicial stay before FDA approves any generic drug applications.

Respectfully submitted,



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Counsel for Petitioner

A



July 30, 2003

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-610
Orange Book Staff
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773

RE: NDA 50-790 (formerly 21-023)
RESTASIS™ (cyclosporine ophthalmic emulsion) 0.05%

Dear Orange Book Staff:

Allergan is notifying your office that the current Orange book shows no patent protection for Allergan's RESTASIS™ (cyclosporine ophthalmic emulsion) 0.05%. The following information is being supplied so that the omission can be corrected.

Trade Name: RESTASIS™
Active Ingredient: cyclosporine
Strength: 0.05%
Dosage Form: Ophthalmic emulsion
Approval Date: December 23, 2002

The following patents are placed for RESTASIS™ (cyclosporine ophthalmic emulsion) 0.05%:

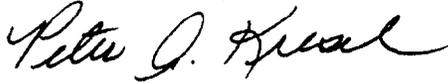
Patent Number	Patent Title	Expiration Date
US 4,649,047	Ophthalmic Treatment by Topical Administration of Cyclosporin	March 19, 2005
US 4,839,342	Method of Increasing Tear Production by Topical Administration of Cyclosporin	August 2, 2009
US 5,474,979	Nonirritating Emulsion for Sensitive Tissue	May 17, 2014

Our original NDA stated an expiration date of June 13, 2006 for patent number 4,839,342. Please note the term of this patent has been extended to the date listed in the table above. Allergan is requesting that this patent information be included in the Orange Book at your earliest opportunity.

The undersigned declares that the above stated United States Patent Numbers 4,649,047; 4,839,342 and 5,474,979 cover the formulation, composition, and/or method for use of cyclosporine A. This product is currently approved under section 505 of the Federal Food, Drug and Cosmetic Act.

Should you require additional information, you may contact me by telephone at 714-246-4391, by fax at 714-246-4272, or E-mail at bancroft_elizabeth@allergan.com.

Sincerely,



Elizabeth Bancroft
Senior Director
Regulatory Affairs

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c

Factiva

Dow Jones & Reuters

Restasis approval a milestone for dry eye. (Increased tear production).

Lynda Charters

1,797 words

1 February 2003

Ophthalmology Times

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ISSN: 0193-032X; Volume 28; Issue 3

English

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Reviewed by Eric D. Donnenfeld, MD, and Peter J. McDonnell, MD

The FDA approval of cyclosporine ophthalmic emulsion 0.05% (**Restasis**, Allergan) Dec. 26 marked a landmark for ophthalmology. The eye drop therapy for moderate to severe keratoconjunctivitis sicca is unique in that it treats the inflammatory process that causes the condition, and not just its symptoms. Allergan estimates that the product will be commercially available this spring.

The three-arm study of cyclosporine for the treatment of dry eye began about 5 years ago and included two concentrations of cyclosporine (0.1% and 0.05%) that were compared with a novel lipid emulsion vehicle (placebo). Moderate to severe dry eye was defined as the presence of corneal staining, Schirmer scores less than 5 mm, and frank conjunctival and corneal staining.

Investigators were masked as to which eye drop the patients instilled twice daily for 6 months. The eyes were evaluated by global assessment of the severity of the dry eye at 1, 3, and 6 months after the onset of treatment. Schirmer tests, corneal and conjunctival staining, and tear breakup time tests were repeated at each follow-up visit.

The frequency of the use of adjunctive artificial tears to relieve dry eye symptoms was also recorded as a measure of the efficacy of cyclosporine. A small subgroup of patients underwent biopsy of the conjunctiva before and after 6 months of treatment to detect inflammatory cells; the results with the two concentrations of cyclosporine were then compared with the controls.

Therapy significance

Cyclosporine is eagerly awaited by members of the ophthalmic community who treat patients with chronic dry eye resulting from ocular inflammation, because it is the only therapy that increases tear production and tear quality, according to Eric D. Donnenfeld, MD, a principal investigator in the multicenter **Restasis** study.

"In the more than 800 patients who participated in the **Restasis** study, a statistically significant number of patients who received cyclosporine had more tear production documented by increased Schirmer scores, decreased corneal and conjunctival staining, and more importantly, there was a global improvement in the patients' assessment of their dry eye symptoms compared with the controls," said Dr. Donnenfeld emphasized. He is also a founding partner of Ophthalmic Consultants of Long Island, Rockville Centre, NY, and associate professor of ophthalmology, New York University Medical Center, New York.

"From a pathologic perspective, the most exciting finding was that when the conjunctival biopsies were performed there was a significant increase in the numbers of goblet cells, indicating that the patients who received cyclosporine made more goblet cells and produced more mucin, and there was a decrease in the inflammatory markers in the conjunctiva, indicating that there was less inflammation there," he added.

"**Restasis** allows patients to make their own physiologically normal tears," he said. "The availability of this drug is a landmark event that is equivalent to the advent of phacoemulsification or antiviral therapy."

Peter J. McDonnell, MD, professor and chair, department of ophthalmology, University of California, Irvine, and colleagues Roy Chuck, MD, PhD, and Ramin Pirnazar, MD, principal investigator, tested cyclosporine according to the same or similar protocols in about 100 patients at the University of California, and a control group of patients received the placebo formulation.

"One measure of efficacy of **Restasis** was the less frequent use of adjunctive tears, which was certainly apparent in many of our patients," Dr. McDonnell said. "Other measures of efficacy were that a high percentage of our patients generally believed that their condition had improved and at the end of the study wanted to continue receiving cyclosporine.

"In addition, our patients typically had less corneal staining, and in some patients the Schirmer test scores actually increased substantially," he said. "Unfortunately, there is no single test that is considered the single standard for patients with dry eye and the results can vary."

Dr. McDonnell noted that 75% to 80% of patients who received cyclosporine had improvement.

The drug appears to be very safe; 17% of patients reported transient ocular burning after instillation of the drops, and from 1% to 5% reported conjunctival hyperemia, discharge, epiphora, eye pain, foreign-body sensation, pruritus, stinging, and visual disturbance (mostly blurring). Cyclosporine is not known to cause cataract or infections, and it does not inhibit wound healing.

Dr. McDonnell said despite that fact that many patients reported stinging and burning upon instillation, none of his patients left the study for this reason, because the positive effect of the drug was substantial. He also noted that the drug is contraindicated in patients with herpetic disease because of its possible effect on lymphocytes. Herpetic disease was an exclusion criterion for these trials.

The mechanism by which cyclosporine improves tear production is unclear. In dry eye the lymphocytes that normally pass through the lacrimal gland instead aggregate in the gland and cause inflammation. Cyclosporine reverses the inflammatory process and allows lymphocytes to pass through the lacrimal gland and not cause damage, Dr. Donnenfeld explained.

An interesting result of this study, but one whose ultimate outcome is presently unknown, is that cyclosporine may cure dry eye in some patients rather than having to be used chronically.

"Although the trial did not allow this type of experimentation, after patients completed the study some reported that their condition stabilized without cyclosporine," Dr. McDonnell said. "I think this result may depend on the point in the disease at which we begin to treat. If it is possible to eliminate the inflammation completely, my hope is that some patients will experience a 'cure.' I hope we will be able to eliminate the need for treatment or be able to taper the treatment so that they no longer have to use the drug twice a day.

"I believe that historically we have waited far too long to diagnose dry eye disease and treat our patients," he added. "We are now treating patients who are perhaps considered to have 'mild' or 'moderate' dry eye, but who have been suffering for a long time and the inflammation and dryness have been allowed to progress. We should consider intervening much earlier in the process, instead of waiting for postmenopausal women, especially, to develop severe debilitating disease, with significant limitation of quality of life. Perhaps we should be testing tear production when patients reach age 30 to detect early manifestations of dry eye disease, when we have a window of opportunity to prevent progression."

Dr. Donnenfeld echoed that sentiment.

"I believe that the patients who are the best candidates for treatment with cyclosporine have not yet been identified," Dr. Donnenfeld commented. "Patients should be treated with cyclosporine at the onset of the development of dry eye. In the early acute inflammatory process, **Restasis** can reverse the process and allow the patient to produce his or her own tears. We do not want to postpone treatment until the lacrimal gland becomes fibrotic and not sustainable."

Dr. McDonnell also pointed out that the efficacy of cyclosporine was not assessed in patients with punctal plugs.

"Intuitively, **Restasis** should be effective in these patients, but it has not specifically been established to be safe

and effective in these patients," Dr. McDonnell said. "The dosing may have to be adjusted and there is a question about whether the drop would last as long in the tear film. Perhaps the dose could be decreased to once daily in some patients, but those with especially severe disease might have to be treated aggressively, with twice-daily dosing. More patients need to be tested to answer these questions."

Dr. McDonnell is eager to begin treating his patients with dry eye who did not meet the inclusion criteria.

"Dry eye is one of the most common and debilitating diseases that ophthalmologists see in clinical practice," Dr. Donnenfeld said. "Tens of millions of patients in the United States have dry eye."

"For the first time, we can offer these patients a drug that might reverse their dry eye and help resolve the disease," he concluded. "The advent of this drug acknowledges for the first time that dry eye is an inflammatory disease that should be treated with immunomodulation and not just tear supplementation."

Marketing approach

Regarding marketing, David Power, director of global pharmaceutical marketing, Allergan, explained that the drug will be marketed to physicians in March and April, but not directly to consumers. Public relations initiatives are being planned to raise awareness of dry eye disease in the general public and the availability of cyclosporine so that individuals with symptoms can seek help from ophthalmologists. He said Allergan will be working closely with patient support groups.

"[The approval offers] a great opportunity to serve probably one of the greatest unmet medical needs in ophthalmology," said David E.I. Pyott, chairman, president, and chief executive officer, Allergan. "If you talk with anterior segment specialists, they say dry eye is a very frustrating disease to treat because we really don't have the perfect answer. It's very tedious, and those patients have been clamoring for [such a product]."

Pyott pointed out that the dry eye market today is huge and difficult to define. Allergan believes the market in the next 3 to 5 years will be somewhere between \$350 million and \$550 million worldwide.

"The current market for artificial tears worldwide is just under \$500 million--so you will almost double the size of that total for therapeutic relief products, which is very exciting," he said. "The other thing that is exciting is that Allergan will be the one and only company [with a therapeutic product] for up to 3 years."

"Allergan is very excited about the FDA approval of **Restasis**," said Lester J. Kaplan, PhD, president/research and development, Allergan. "This is a culmination of Allergan's research and development team's pioneering work in the field of ocular surface disease. Allergan ... is pleased about the ability to address this unmet need of both patients and ophthalmologists by offering the first therapeutic option for the treatment of chronic dry eye disease."

RELATED ARTICLE: Take-home message.

Cyclosporine ophthalmic emulsion 0.05% (**Restasis**, Allergan) is the first therapy that treats the inflammatory process that causes dry eye and not just the symptoms of dry eye. The product will be launched this spring.

RELATED ARTICLE: FYI.

Eric D. Donnenfeld, MD

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Dr. Donnenfeld is a consultant for Allergan and has no financial interest in

Restasis.

Peter J. McDonnell, MD

E-mail: pjmcdonn@uci.edu

Dr. McDonnell has no proprietary interest in **Restasis**; he has received grant support and speaking honoraria from

Allergan.

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HEALTH

TUESDAY, JULY 1, 2003

MIDLIFE

Stefanie Weiss

How Dry Eye Am

would have cried a river if I had produced the tears, but that was the problem. Just before I turned 40, my eye doctor made the breaking diagnosis: dry eye syndrome.

Think about bad timing. I could have had the itchy, irritated eyes. It would have been harder to say goodbye to my contact lenses after a long run.

Well, come on. I was older than my mother. Did I need a doctor to tell me I was drying up? Twenty years have passed, and my eye melodrama has faded, but I still ask doctors about the dreaded dry eye. Here's what I've

definition You've got dry eye if, as Woody Allen might have said, your tears are lousy and there are few of them. To avoid dry eyes, you need quantity and quality. There are three tear layers—the mucous layer closest to the eye, the middle layer and the outer oily layer. You thought tears were just water and salt.

symptoms Like the name suggests, your eyes. Expect a gritty, itchy, your-eye feeling, scratching, stinging, redness, blurred vision, even excessive tearing (it's a defense mechanism). **risk scenario:** corneal damage.

diagnosis The tear break-up time test measures how quickly a drop in tears breaks up and starts to dry.

The normal tear break-up time is about 10 seconds; mine is 5. There are other tests that measure tear volume and examine the eye under the microscope, but patient complaints are a lot of common-sense clues.

prevalence Dry eye syndrome is widespread. It's been called "the common cold of the eye." As for me, I throw a dart. Estimates of the number of Americans affected range from 10 million to 60 million. **spoiler alert** If I were to accept an eye doctor's diagnosis of dry eye syndrome, I'd thank aging (we're all drying up) and menopause. Then I'd thank menopause.

Dryness: What to Do When the Eyes Have It

MIDLIFE, From F1

pregnancy, thyroid disease and autoimmune problems. I'd thank the environmental factors that can play a role: contact lens use, computer use, smoke, air pollution, wind, air conditioning, heaters and ceiling fans. And wait, wait, I need another minute to thank the medications: diuretics, birth control pills, beta blockers, blood pressure medications, antihistamines, decongestants, antidepressants and redness-reducing drops.

The treatments Terrence P. O'Brien, ophthalmology professor at the Wilmer Eye Institute at Johns Hopkins in Baltimore, suggests a variety of fixes, including:

Warm compresses Microwave a moistened washcloth until hot but not scalding (about 45 seconds), then apply it over your eyes for five minutes. O'Brien says

it "helps promote better flow of oil into tear film and increases blood flow into the oil glands of the eyelids." I say it feels good.

Diet and supplements O'Brien says there's an "evolving body of scientific evidence" that the omega-3 fatty acids found in flaxseed and fish oils may help. Although he acknowledges the need for more controlled trials of the supplement, O'Brien currently recommends TheraTears Nutrition for Dry Eyes, a capsule that includes flaxseed oil, fish oil and vitamin E.

Prescription drops In April, the Food and Drug Administration approved Restasis, an anti-inflammatory drop that O'Brien helped to test. He says it's the first prescription treatment that has been shown to help improve the quality and quantity of tears.

Punctal plugs O'Brien likened this to "stopping up the drain of the kitchen sink."

Doctors insert silicone or collagen plugs into the puncta, the tiny opening at the inside corner of your eye that drains tears. No drain, no dryness—at least that's the theory. It didn't work for me.

The end In my case, as long as I don't wear my contact lenses, I don't notice any significant symptoms. Yes, it's four-oh, four eyes. But don't cry for me. I just spent more on a new pair of glasses than I spent for my first car. How's that for dating myself?

The columns KidLife and MidLife, devoted to healthy handling of children and adulthood, appear in alternating weeks. Send comments, suggestions and questions to kidmid@washpost.com. For U.S. Mail, see address on page F2. No calls, please.

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Clinical Experience with Cyclosporine (Restasis™) for Dry Eye

Laurie Barber, MD

Restasis™, the first prescription pharmaceutical with an indication for the treatment of dry eye, works by attacking the underlying inflammatory pathophysiology of moderate to severe dry eye. In my experience with clinical trials of Restasis, it made a significant positive difference in patients' lives.

THE BOTTOM LINE

Restasis, the first prescription medication for dry eye, reduced signs and produced significant relief of patients' symptoms. Patients with Sjogrens and non-Sjogrens-associated aqueous tear deficient dry eye are candidates for the drug. Patients with meibomian gland deficiency can be tested on the drug, but may do as well with the vehicle (sold as Refresh Endura) alone. Restasis is typically used in conjunction with artificial tears; however, taking Restasis often brings a significant decrease in the quantity of tears patients take. In clinical study, Restasis proved safe and effective and made a positive difference in patients' lives.

Laurie Barber, MD, is an associate professor of ophthalmology at the University of Arkansas for Medical Sciences, Little Rock, AK



FIGURE 1 Lissamine green staining results in a LASIK patient with dry eye.



FIGURE 2 Rose bengal staining results in a dry eye patient.

PEARLS

- **Expect a Surge of New Patients**
I believe that once word of Restasis spreads in the patient community, we

will see a surge of patients. There is considerable pent-up demand among dry eye patients who have simply given up on the medical profession. When these patients hear about Restasis, many will decide to give their doctors another try

- **Use Restasis with Artificial Tears, but not with Refresh Endura™**

While artificial tears can be taken between doses of Restasis to improve comfort, especially in the first months, I would recommend against using Refresh Endura concomitantly. This product happens to be the vehicle used in Restasis and, while Refresh Endura is an excellent preparation, especially for people with meibomian gland dysfunction, using it in combination with Restasis can cause too much lipid build-up on the eye and may decrease rather than increase comfort.

- **With Restasis, We Can Prevent Disease**

Dry eye is a progressive disease. With Restasis we can break the destructive cycle that produces increasing damage to the ocular surface. In so doing, we can preserve both the quality of vision and the quality of life for our patients for years to come

- **Follow-up Schedule**

While follow-up intervals will depend on the severity of symptoms and other individual patient factors, a typical follow-up regimen for dry eye patients once they start on Restasis is to see them at:

- 1-3 months after they start the drug.
- 6 months after that, and then
- Annually.

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DRY EYE***The flap's important role in LASIK-induced dry eye***

by Michelle Stephenson Contributing Editor

When Restasis (Allergan, Irvine, Calif.) gained Food and Drug Administration approval last December, for the first time ophthalmologists found that they were able to get at the underlying cause of dry eye disease rather than simply offering patients palliative options. Restasis is currently in a category all its own, said Henry D. Perry, M.D., clinical associate professor of ophthalmology, the Weill School of Medicine, Cornell University, New York.

The drug works to sideline inflammation linked to dry eyes. "Restasis is in a 0.05% cyclosporine A emulsion that when applied twice daily to patients with moderate to severe dry eyes tends to decrease the inflammation that these patients have and restore the patients to more normal tear flow," Perry said.

Restasis at work

In patients with dry eye, there is an autoimmune signal given somewhere in the body that causes T cells to attack lacrimal gland tissues. These tissues in turn start secreting inflammatory mediators that bathe the ocular surface with these toxic substances.

"Cyclosporine, which is a very powerful T-cell modulator, inhibits these T lymphocytes from turning on and producing these toxic mediators," Perry said. "By preventing activation of the T-cells, it prevents the feeling of dryness in patients."

The treatment, however, takes several months to garner full effect. "Lymphocytes live in the body for approximately 110 days," Perry said. "It takes at least 110 days to get all the activated lymphocytes out of the lacrimal gland tissues, because those that are already there are going to keep secreting the inflammatory mediators." Restasis cannot turn off the lymphocytes once they have been activated, it can only prevent the new crop from becoming activated.

Patients do get some early relief as well from the active Restasis vehicle, believes Michael E. Stern, Ph.D., research investigator at Allergan. "It lasts

on the eye for a matter of hours rather than just seconds or minutes, and it totally gets rid of the irritative component of the disease,” Stern said.

Considering results

With Restasis, patients enjoy an improvement in both quantity and quality of tears, Stern said.

“Patients whose level of tear secretion has been decreased due to this inflammation get that back and show an increase in tears,” he said. “What the results also show is that we are allowing the secretion of more normal tears.”

The Phase III study results of Restasis showed significant improvement in symptoms of the disease as well as health of the eye. Patients claimed that their foreign body sensation had improved, they showed a decreased need for artificial tears, and the areas of staining of the conjunctiva and cornea, which showed the harmful effects of dry eye disease, were improved significantly, according to Perry. “In up to 15% of patients there was a tripling of their tear volume,” he said.

Also very telling were the laboratory examinations. Investigators performed CD3 counts to show the total number of lymphocytes present at baseline and at six months. “At baseline, patients with keratoconjunctivitis sicca without Sjogren’s syndrome had an average of approximately 2,300 cells per square millimeter, and after six months this decreased to approximately 762 cells per square millimeter,” Perry said. “More significantly, patients with Sjogren’s syndrome had an average of almost 4,000 cells per square millimeter and this decreased to 819 cells per square millimeter after six months.” Investigators also found that inflammatory mediators that were measured also decreased dramatically from baseline to six months, while the goblet cell count, which measures the relative health of the conjunctiva, increased 200%.

Educating patients

Because Restasis is the first medication of its kind, some patient education is usually needed. Patients should be reminded that this is a prescription medication, said Gary N. Foulks, M.D., professor of ophthalmology, University of Pittsburgh School of Medicine. “Restasis is not to be used as an artificial tear, which is on a PRN [as needed] basis,” Foulks said. “This is a prescription medication to be used twice daily.” With Restasis, patients can still use artificial tears with the exception of Refresh Endura (Allergan), which is the equivalent of the vehicle for the drug, Foulks said.

Patients need to understand that Restasis can take months to work. “They have to understand that they are getting benefit of the drug even though it is not like an antibiotic where the bacteria go away and everything is fine with 48 hours,” Stern said.

Overall, Stern sees Restasis as a very effective breakthrough treatment. "With Restasis, you get relief based upon resolution of the disease and not just based upon palliation of the ocular surface, which is a new paradigm" Stern said.

Editors' note: Perry has spoken on Allergan products and is an Allergan grant recipient.

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FDA (“Federal Defendants”), along with Intervenor Defendant Mutual Pharmaceutical Company, Inc. (“Mutual”), oppose. The Federal Defendants have also filed a Motion to Dismiss under FED. R. CIV. P. 12(b)(1) and 12(b)(6). Upon consideration of the briefs and oral argument of the parties, the Court finds that CollaGenex has made a strong showing of irreparable harm, that the balance of harms clearly favors CollaGenex, and that the public interest will be served by the issuance of a preliminary injunction. Because FDA is mute on the merits of the case and the Court does not have the administrative record, it cannot perform the normal evaluation of likelihood of success on the merits. Nonetheless, it appearing that CollaGenex has at least a colorable claim under § 321(jj), the Court finds that this is a sufficient showing of likelihood of success under these circumstances. CollaGenex’s Motion for a Preliminary Injunction will be granted in part and denied in part and the Federal Defendants’ Motion to Dismiss will be granted in part and denied in part pending receipt of the administrative record and its full review.

Background

I. Statutory Framework

New drugs are approved by FDA only after an extensive investigation into their safety and efficacy. An applicant files a new drug application (“NDA”) containing detailed data. *See* 21 U.S.C. § 355(j)(7). As described by the parties during oral argument, the process to achieve FDA approval of a new or “pioneer” drug¹ entails a form of negotiation between the applicant and FDA in which the government “gets whatever it wants.” It can take tens of millions of dollars and years to develop a new drug and obtain FDA approval.

¹ The term “pioneer” as applied to a drug means the first approved use of a chemical substance for a specific therapeutic purpose. *See* Donald O. Beers, *Generic and Innovator Drugs*, § 1.1 (4th ed. 1995).

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984), commonly known as Hatch Waxman. One purpose of Hatch Waxman was to make it easier for drug manufacturers to obtain FDA approval for generic drugs. The generic manufacturer does not have to repeat the expensive and extensive testing associated with obtaining initial approval of an NDA. The generic manufacturer instead may file an abbreviated new drug application (“ANDA”), relying on the testing conducted by the original manufacturer that showed safety and effectiveness. *See Am. Bioscience*, 243 F.3d at 580. The generic manufacturer need only establish that the generic drug is the “bioequivalent” of the brand name drug. 21 U.S.C. §§ 355(j)(2)(A), (j)(8).

In enacting Hatch Waxman, Congress also sought to encourage research and innovation by providing a period of market exclusivity and patent protection for certain pioneer drugs. *See Am. Bioscience*, 243 F.3d at 580. These protections allow recoupment of the costs of development and the approval process without competition from less expensive generic versions of a drug. *See* 59 FED. REG. 50,338 (Oct. 2, 1994). Under Hatch Waxman, certain pioneer drugs enjoy a five-year period of market exclusivity during which no ANDA for a generic copy of the drug may be approved. *See* 21 U.S.C. §§ 355(c)(3)(D), (j)(5)(D)(ii). With respect to patent protection, an NDA applicant must submit the patent number and expiration date of any patents that claim the drug. When a manufacturer files an ANDA to market a generic copy of a drug, the ANDA applicant must certify “(1) that no patent has been filed with the FDA; or (2) that the patent has expired; or (3) that the patent has not expired, but will expire on a particular date; or (4) that the patent is either invalid or the generic drug will not infringe it.” *Am. Bioscience*, 243 F.3d at 580. If the ANDA makes a certification under subsection four (commonly called a Paragraph IV certification), the applicant

must provide notice to the patent holder that it has filed the ANDA. *See id.* The patent holder then has a forty-five day period in which to file a patent infringement action. If suit is filed within this period, FDA may not approve the ANDA application until the patent dispute is resolved, or for 30 months, whichever is sooner. *See id.*

Congress enacted the Food and Drug Administration Modernization Act of 1997 (“FDAMA”) in November 1997. Prior to its enactment, NDA applications for antibiotic drugs were governed by 21 U.S.C. § 357, and NDA applications for all other drugs were governed by 21 U.S.C. § 355. FDAMA repealed § 357 and requires that NDA applications for antibiotic drugs be submitted under § 355. FDAMA also contains exemption provisions that make antibiotic drugs ineligible for the Hatch Waxman market exclusivity period and patent protections. *See* FDAMA § 125(d)(2). An “antibiotic drug” is defined by FDCA as

any drug (except drugs for use in animals other than humans) 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 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).

After an NDA is awarded, the holder may voluntarily withdraw the drug from sale. FDA then moves the drug to the Discontinued Drug List to provide notice that it has been withdrawn. When this happens, any petition for an ANDA that refers to the prior drug must be accompanied by a petition requesting FDA to determine that the drug was not withdrawn for reasons of safety or efficacy. *See* 21 C.F.R. § 314.122. FDA may not approve the ANDA until FDA makes this

determination. *See* 21 C.F.R. § 314.161(a)(1). If FDA determines the drug was withdrawn for safety or effectiveness reasons, the ANDA will not receive government approval. *See* 21 C.F.R. § 314.162.

II. Factual Background²

CollaGenex is a small pharmaceutical company that employs approximately 150 people. Its primary product is a prescription pharmaceutical, Periostat, that is used to treat adult periodontitis. Periostat works by reducing the levels of enzymes, known as collagenase, that destroy the connective tissues that support teeth. The active ingredient in Periostat consists of a 20 milligram (“mg”) dose of doxycycline hyclate.

CollaGenex states that it spent nearly twelve years and \$70 million dollars developing Periostat. In addition, since 1999, CollaGenex states that it has expended over \$87.5 million dollars in direct sales and marketing expenses related to Periostat. Without contradiction, CollaGenex asserts that its only significant revenue comes from sales of Periostat. During 1999, 2000, 2001, and 2002, Periostat accounted for 95%, 84%, 87%, and 82%, respectively, of the total revenues of CollaGenex, with total revenue during 2002 amounting to \$44.5 million. While CollaGenex yielded a net positive income in the last two quarters of 2002, it has experienced net losses each year.

In August 1996, CollaGenex submitted an NDA for 20 mg Periostat capsules under Section 505 of the FDCA, 21 U.S.C. § 355. Shortly thereafter, FDA requested that CollaGenex resubmit its NDA under Section 507 of the FDCA, 21 U.S.C. § 357, the section that governed the review and approval of antibiotic drugs at the time. CollaGenex protested, asserting that Periostat did not meet

² The facts are taken from the Complaint, the parties’ briefs and supporting affidavits, and representations made by counsel in open court.

the statutory definition of an antibiotic drug. FDA advised CollaGenex that it could pursue its claim and postpone approval of its application or submit the NDA as an antibiotic drug and contemporaneously attempt to get it re-classified. CollaGenex elected to submit the NDA as an antibiotic drug under § 357 and concurrently pursue its objections during the NDA review. On September 11, 1997, CollaGenex submitted a Request for Designation to the FDA Ombudsman asking that Periostat be designated a nonantibiotic drug under 21 U.S.C. § 355, rather than an antibiotic drug under 21 U.S.C. § 357. Two years after the application process began, FDA approved the NDA for Periostat in September 1998. The approval stated, without explanation, that Periostat is subject to the exemption provisions of FDAMA § 125(d)(2), and not eligible for market exclusivity and patent protections available to drugs approved under 21 U.S.C. § 355. In 2001, the FDA approved an NDA permitting CollaGenex to market Periostat tablets.

CollaGenex voluntarily stopped distributing and marketing Periostat capsules in August 2001. CollaGenex wrote to FDA in September 2001 to withdraw the NDA for Periostat capsules, and submitted the requisite paperwork under 21 C.F.R. § 314.81(b)(3)(iii). FDA neither published a notice in the Federal Register announcing this withdrawal nor moved the capsules to the “Discontinued Product List.”³ On July 10, 2002, CollaGenex submitted a Citizen Petition to FDA and a Petition for Stay of Action. The Citizen Petition requested that FDA not approve any ANDA for Periostat capsules until FDA determined that the capsules had not been withdrawn for safety and effectiveness reasons, that FDA refuse to receive or approve any ANDA for a generic version of Periostat capsules not accompanied by a petition seeking a determination regarding whether the

³ This list contains all the products that have been discontinued from marketing and is one of the places where a company would look to determine if it needed to attach a safety or effectiveness petition to its ANDA application.

capsules were withdrawn for safety or effectiveness reasons, that FDA immediately move the capsules to the Discontinued Product List, and that FDA publish a Federal Register notice announcing the withdrawal of the NDA for Periostat capsules. In the Stay Petition, CollaGenex requested that FDA not to take any action on any ANDA for a generic version of Periostat until it had decided the Citizen Petition. FDA has yet to issue a decision on these Petitions.

FDA's Chief Counsel, Daniel E. Troy, has encouraged companies that are considering filing suit against FDA to "lay [their] cards on the table" by meeting with him and discussing the potential suit. *See Unsupported Claims Should Be Brought to FDA by Industry*, F-D-C Rep. ("The Tan Sheet"), Oct. 14, 2002, at 11. Pursuant to this approach, counsel for CollaGenex met with him in January 2003 to discuss FDA's determination that Periostat is an antibiotic drug and CollaGenex's contemplated federal court litigation. Mr. Troy suggested that CollaGenex submit a letter following the meeting rather than file a citizen petition or a petition for stay of action, outlining its arguments concerning the classification of Periostat. CollaGenex complied with this request on January 21, 2003, submitting a lengthy letter explaining its arguments that Periostat is not an antibiotic drug. *See Federal Defendants' Memorandum in Support of its Motion to Dismiss and in Opposition to Plaintiff's Motion for Preliminary Injunction, Attachment A at 1* ("Federal Opposition"). In this letter, CollaGenex noted that it had delayed filing suit to enable the parties to resolve the matter short of litigation. It also requested ten business days notice if FDA were going to approve a pending ANDA, in order to allow CollaGenex time to initiate litigation. *See id.* at 12.

In the meantime, at least two companies, Intervenor Mutual and West-ward Pharmaceutical Corporation, have submitted an ANDA to market a generic version of Periostat.⁴ FDA has not acted on these applications yet, but has represented to the Court that action is imminent.

Analysis

I. Ripeness

FDA rests its case for dismissal almost entirely on the issue of ripeness. As to the question of whether Periostat is an “antibiotic drug,” FDA presents the argument as encompassing two separate points. First, FDA asserts that CollaGenex has not exhausted its administrative remedies because it submitted a January 2003 request for reconsideration of FDA’s 1998 determination that Periostat is an antibiotic drug, which is still under review. *See Stone v. INS*, 514 U.S. 386, 392 (1995) (Under the APA, “filing of a motion to reconsider renders the underlying order nonfinal for purposes of judicial review.”); 21 C.F.R. § 10.45(b). Second, FDA argues that CollaGenex has not been harmed by any Agency action inasmuch as FDA has not yet approved any ANDA. *See Pfizer Inc. v. Shalala, et al.*, 182 F.3d 975, 978 (1999) (FDA acceptance of ANDA for processing not a final agency action). These arguments on the initial counts of the Complaint are not persuasive.

However, Count V of the Complaint is premature and will be dismissed. That Count relates to a September 2001 letter to FDA from CollaGenex requesting that FDA withdraw the NDA for Periostat capsules and a July 2002 Citizen Petition and Stay Petition requesting that FDA not approve any ANDA for Periostat capsules until FDA has determined that the capsules were not withdrawn for safety and effectiveness reasons. FDA has not yet issued responses to these requests. Without final agency action, neither claim is ripe for review. *Reliable Automatic Sprinkler Co. v.*

⁴ CollaGenex is presently proceeding against West-ward in a patent infringement action.

CPSC, 324 F.3d 726, 731 (D.C. Cir. 2003) (dismissal under Fed. R. Civ. P. 12(b)(6) when there is no final agency action). Therefore, the Federal Defendants' Motion to Dismiss is granted with respect to Count V.

FDA's "failure to exhaust" argument categorizes a January 2003 letter from CollaGenex to Chief Counsel Troy as a request for reconsideration. CollaGenex describes its January 2003 letter as an effort, in response to speeches from the Chief Counsel of FDA, to approach the Agency prior to suit, lay out its theories of litigation, and potentially achieve a settlement.⁵ The Court agrees and finds that the January 2003 letter was not a request for reconsideration. It specifically stated that it was submitted "in letter form rather than as a citizen petition and related petition for stay of action." See Federal Opposition, Attachment A at 1. More significantly, despite the frequent use of the word "request" in the letter, it stated in the conclusion that

CollaGenex has delayed filing a lawsuit in Federal Court solely to provide a period of time to resolve these issues without resort to litigation. . . . [I]f FDA believes that it must approve the West-Ward ANDA imminently, [we ask for] at least ten business days notice so that CollaGenex will have the opportunity to initiate litigation on the issue

Id. at 12. These statements demonstrate that the January 2003 letter was intended to speak frankly with FDA in an effort to avoid litigation and was not intended to be a request for reconsideration.

The *Pfizer* argument presented by FDA appears at first blush to have greater significance. In *Pfizer*, the drug company sought to prevent FDA from approving an ANDA without Pfizer's extended release mechanism. Citing *Texas v. United States*, 523 U.S. 296, 300 (1998), for the

⁵ Memorandum of Points and Authorities in Reply to Federal Defendants' Opposition to Plaintiff's Motion for a Preliminary Injunction at 3 ("FDA's Chief Counsel has invited companies that are considering suing FDA to meet with him first to 'lay [the] cards on the table.'") (hereafter "CollaGenex's Reply"); see also, e.g., *Unsupported Claims Should Be Brought to FDA By Industry*, F-D-C Rep. ("The Tan Sheet"), Oct. 14, 2002, at 11.

proposition that “[a] claim is not ripe for adjudication if it rests upon contingent future events that may not occur as anticipated, or indeed may not occur at all,” the D.C. Circuit agreed that Pfizer’s claim was premature because FDA had not approved the ANDA and might not do so. FDA argues that this proposition applies and bars the CollaGenex suit as premature.

The difference here is that CollaGenex appeals a final agency decision of 1998 relating to FDA’s determination that Periostat is an antibiotic drug. If FDA erred in its 1998 determination, then CollaGenex would be entitled to the protections from generic drugs that are available under Hatch Waxman. Its effort to prevent approval of Mutual’s ANDA is therefore not an attack on the ANDA itself – which is not *quite* final but, according to government counsel, will be after Wednesday, July 23, 2003 – but rather an appeal from the 1998 final agency decision and its present-day consequences.

It is easy to agree with FDA and Mutual that CollaGenex could have filed this appeal at any time between 1998 and the present and that its timing has created an emergency that might have been avoided. The Court cannot reasonably object, however, to a litigant who did not run to the courthouse at the first opportunity and who hoped, perhaps naively, that such litigation would never be necessary. CollaGenex has filed suit over the 1998 final agency decision within the six years of the statute of limitations and has a right to have its case heard and decided. This lawsuit is not premature; rather, it is fully ripe for decision.

II. Preliminary Injunction

A preliminary injunction may only be granted when a party shows a substantial likelihood of success on the merits, a balance of harms that favors the movant, irreparable harm if no injunction is granted, and service in the public interest from an injunction. *See Katz v. Georgetown Univ.*, 246

F.3d 685, 687-88 (D.C. Cir. 2001); *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1066 (D.C. Cir. 1998). A court balances the four factors and a particularly strong showing on one or more can outbalance a weaker showing on another. *CityFed Fin. Corp. v. Office of Thrift Supervision*, 58 F.3d 738, 747 (D.C. Cir. 1995); *Wash. Metro. Area Transit Comm'n v. Holiday Tours*, 559 F.2d 841, 843-45 (D.C. Cir. 1977). Here, the Court concludes that CollaGenex has at least a legitimate claim on the merits and that the other three factors strongly support a preliminary injunction.

1. Likelihood of success on the merits

The analysis of CollaGenex's likelihood of success is influenced by FDA's present litigating posture. Since the Agency asserts that the January 2003 letter constituted a request for reconsideration, it has been able to argue that the case is not ripe and to avoid almost all comment on the substantive issue of whether Periostat is an antibiotic drug. In theory, as explained by FDA counsel, that issue is under active reconsideration. Only when FDA counsel told the Court, at the close of oral argument, that FDA's decisions on these matters would issue on Monday, July 21, 2003,⁶ did counsel also admit that it is unlikely that FDA would change its determination that Periostat is an antibiotic drug. Nonetheless, FDA argues that CollaGenex has little likelihood of success on the merits because FDA's future determination that Periostat is an antibiotic drug will be entitled to great deference so that the Court would have no reason to overturn it. *See* Federal

⁶ FDA counsel assured the Court, at the beginning of oral argument on Wednesday, July 16, 2003, that FDA would only issue its decisions "after Friday" in an effort to allow the Court to rule on this matter. At the end of the argument, when pressed by the Court as to when FDA really would act, FDA counsel conceded that FDA intended to act on Monday, July 21. The Court agrees that Monday, July 21, is "after Friday," July 18. However, the lack of a forthright statement on the planned schedule when specifically asked by the Court was little short of gamesmanship and hide-the-ball which is unbecoming to a federal official or an officer of the court. Only reluctantly did FDA, when its actual schedule was revealed, agree to withhold action until after Wednesday, July 23, 2003, so that this matter might be addressed here.

Opposition at 16 (“Once FDA makes its final decisions on whether Periostat should be designated an antibiotic . . . , CollaGenex would be unlikely to succeed in showing that FDA’s decisions are arbitrary and capricious.”); *see also* 5 U.S.C. § 706(2)(A) (standard of reversal under APA is “arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.”) FDA also argues that it is regularly “accorded particular deference when its decisions are based on evaluation of scientific information within its area of technical expertise.” Federal Opposition at 17; *see also Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (Courts “review scientific judgments of the agency ‘not as the chemist, biologist, or statistician that we are qualified neither by training nor experience to be, but as a reviewing court exercising our narrowly defined duty of holding agencies to certain minimal standards of rationality.”) (quoting *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976)).

Additionally, FDA and Mutual argue that the Court cannot rule on the motion for a preliminary injunction because there is no administrative record on which to base its decision. *American Bioscience* appears to support this argument. In *American Bioscience*, the plaintiff sought a preliminary injunction to prevent FDA from approving an ANDA. Without the formal administrative record before it, the district court had made findings of fact as to the bases for FDA action based on “the parties’ written or oral representations.” *Am Bioscience*, 243 F.3d at 582. The Court of Appeals reversed, holding that “the court, before assessing American Bioscience’s probability of success on the merits, should have required the FDA to file the administrative record and should have determined the grounds on which the FDA granted Baker Norton’s application.” *Id.* at 582. *American Bioscience* based its holding on *Citizens to Preserve Overton Park v. Volpe*,

Court means a “claim that is legitimate and that may reasonably be asserted given the facts presented and the current law.” BLACK’S LAW DICTIONARY 240 (7th Ed. 1999); *see also* *Cuomo v. United States Nuclear Regulatory Comm’n*, 772 F.2d 972, 974 (D.C. Cir. 1985) (“A stay may be granted with either a high probability of success and some injury, *or vice versa*.” (emphasis in original)) Without the administrative record from the 1998 decision, or even any input from the FDA, the Court is left to the use of the English language to determine if CollaGenex has made a colorable claim.

The place to start, as with any statutory question, is the language of the statute itself. The FDCA defines an antibiotic drug at 21 U.S.C. § 321(jj):

The term “antibiotic drug” means any drug (except drugs for use in animals other than humans) 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 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.

No one argues that Periostat is one of, or a derivative of one of, the antibiotic drugs specifically identified in § 321(jj). Nor is its intended use for humans under question. Therefore, as relevant here, the statute provides:

and, instead, sent it as an attachment to an email to the Clerk’s Office. The email was sent after 11 pm on Friday, July 11, 2003, when there was no one working in the Clerk’s Office to transfer the materials from email to ECF. That transfer occurred on Monday, July 14, 2003, when the Clerk’s Office opened. As a result, neither CollaGenex nor FDA was able to read or respond to the substantive arguments in Mutual’s brief and attachments prior to the oral argument on July 16, although CollaGenex disputed them before the Court. Because of this accident and because the Court cannot determine whether Periostat is or is not an antibiotic drug without a full administrative record, Mutual’s arguments on these points will be disregarded.

The term “antibiotic drug” means any drug . . . 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)

This language might appear daunting to non-scientists but it is simpler than it first appears. WEBSTER’S defines “antibiotic” as “a substance produced by a microorganism (as a bacterium or a fungus) and in dilute solution having the capacity to inhibit the growth of or kill another microorganism (as a disease germ).” WEBSTER’S THIRD NEW INT’L DICTIONARY UNABRIDGED 93 (2002). Asked by the Court, CollaGenex, FDA and Mutual all defined an antibiotic as having the two characteristics identified by WEBSTER’S: 1) produced by a microorganism and 2) having the capacity to inhibit or kill microorganisms. With this assistance from Mr. Webster and the parties, the Court can parse the statute to mean:

The term “antibiotic drug” means any drug . . . containing any quantity of [an antibiotic] (including a chemically synthesized equivalent of any [antibiotic])”

Thus, an “antibiotic drug” must contain an “antibiotic,” which, by definition, 1) is produced by a microorganism and 2) has the capacity to inhibit or kill microorganisms. The active ingredient in Periostat is doxycycline hyclate 20 mg. It is agreed by all that doxycycline hyclate at 50 mg or higher concentrations is an “antibiotic drug” because it contains an “antibiotic” that is produced by a microorganism and has the capacity to kill microorganisms. CollaGenex asserts that doxycycline hyclate 20 mg is produced by a microorganism but does not have the capacity to kill microorganisms because the concentration of doxycycline is too low to have that ability or to achieve that result. FDA seems to agree: The Dental Officer reviewing CollaGenex’s application for approval of Periostat concluded that the drug was “not antimicrobial at this [20 mg] dosage.” Robert A. Ashley

Decl. at ¶ 31 (hereafter “Ashley Decl.”); Memorandum of Points and Authorities in Support of Plaintiff’s Motion for a Preliminary Injunction (hereafter “CollaGenex’s Brief”), Att. 12 at 1. The Review and Evaluation of Pharmacology and Toxicology Data said that the proposed dosage for Periostat was “apparently below the threshold for antibacterial effects.” Ashley Decl. at ¶ 32; CollaGenex’s Brief, Att. 13 at 4. The package insert for Periostat, which was extensively negotiated between CollaGenex and FDA according to both parties, states that “[t]he dosage of doxycycline achieved with this product during administration is well below the concentration required to inhibit microorganisms commonly associated with adult periodontitis.” Ashley Decl. at ¶ 26; CollaGenex’s Brief, Att. 7 at 1.

Per § 321(jj), an antibiotic drug must contain an antibiotic. An antibiotic must have the *capacity* to kill (or inhibit) microorganisms. Doxycycline at 20 mg does not have the capacity to kill or inhibit microorganisms – it is too weak. Mutual argues that the statute provides that it takes only “any quantity” of an antibiotic to constitute an antibiotic drug and that, as long as doxycycline has antibiotic capacity at some concentrations, it is an antibiotic drug at all concentrations. FDA, having taken the position that this is all premature, offers no opinion. Mutual’s reading of the statute may align with the silent FDA but it is not the only reading. Thus, while it is true that “any quantity” of an antibiotic in a drug will make that drug an “antibiotic drug,” the drug still must contain some amount of an “antibiotic,” *i.e.*, a chemical substance 1) produced by microorganisms and 2) with the capacity to kill (or inhibit) microorganisms. At a 20 mg concentration, doxycycline does not have

the capacity to kill or inhibit microorganisms and, arguably, does not therefore meet the definition of an “antibiotic” or an “antibiotic drug.”⁸

The Court hastens to say that its conclusion arises only from a reading of the statutory language, without the benefit of the administrative record or even an articulated position from FDA. FDA experts apparently reached a different conclusion in 1998, which will be subject to review and deference as warranted when the administrative record is before the Court. *See Chevron U.S.A. v. Nat’l Res. Def. Council, Inc.*, 467 U.S. 837 (1984). Since FDA has not filed the record at this time, however, it is enough to say that CollaGenex has a colorable claim that Periostat is not an antibiotic drug and therefore has made a sufficient showing of likelihood of success.

2. Balance of Harms

To be sure, CollaGenex has shown that it could suffer devastating losses that would affect its viability. The harm that the defendants would suffer is minimal. FDA argues that its administrative process for regulating drugs would be disrupted, but that point of view is dependent on FDA’s belief that CollaGenex seeks review of the alleged motion for reconsideration, which the Court has rejected. CollaGenex seeks review of FDA’s final agency decision from 1998 and that review is customary, normal and not disruptive of the administrative process. Mutual, which has a pending ANDA, may suffer some harm from entry of an injunction because the injunction will delay its ability to bring a generic version of Periostat to market. Given Mutual’s large size, resources, and

⁸ Over time, patients who take antibiotics can develop resistance to them making their next disease more difficult to treat. Therefore, it would be reasonable for Congress to require that drug manufacturers advise patients of the presence of antibiotics in their medicine, regardless of whether the antibiotic (which is produced by microorganisms and has the capacity to kill or inhibit microorganisms) constitutes only a very small percentage of the total medication. CollaGenex asserts that the concentrations of doxycycline in Periostat are too low to contribute to antibiotic resistance.

essentially limited investment in its generic drug, in contrast to CollaGenex's small size, limited product line, and significant investment in Periostat, the potential harm to Mutual is comparatively minimal. The Court finds that the balance of harms clearly and substantially weighs in favor of an injunction so that the Court can receive the full administrative record and make a determination on it.

3. Irreparable Harm

CollaGenex depends on Periostat for over 80% of its revenue. Approval of one or more ANDAs is imminent; in fact, "Mutual believes [its ANDA] is ready for approval." Memorandum of Intervenor-Defendant Mutual Pharmaceutical Company, Inc. in Opposition to Plaintiff's Motion for Preliminary Injunction at 1. Mutual has already begun a web-based marketing effort for its generic version of Periostat, offering a discount for early orders which could otherwise go only to CollaGenex. It plans to "ship product to [purchasers] upon receipt of FDA approval." Gallagher Supp. Decl. at ¶ 1, Exh. 1 at 2. Thus, it appears that Mutual may already be eroding CollaGenex's market share.

FDA argues that no harm is "imminent" to CollaGenex. There are two problems with the argument. First, it is advanced, as are all FDA arguments, from the point of view that this lawsuit is premature. FDA suggests that CollaGenex could and should act only if and when FDA actually approves an ANDA. But if CollaGenex is correct that Periostat is not an antibiotic drug and that FDA's 1998 determination was incorrect, it should not be facing the competition from one or more ANDAs at this time. In fact, Mutual is already working to build its market share so that approval of its ANDA would not initiate the potential harm to CollaGenex; it is happening now. Second, the argument ignores the evidence proffered by CollaGenex that rapid erosion of branded drug sales can

occur when a generic enters the market. It cites industry publications to demonstrate that generic Prozac achieved 59% market penetration of total prescriptions for one dosage strength and 70% of new prescriptions for another dosage strength within one month of launch. Within two weeks of availability of a generic version of Astra's drug Zestril, Merck-Medco mail order pharmacy apparently achieved 91% generic conversion. Megestrol is said to have achieved 75% market share within six months. *See* CollaGenex's Reply at 11-12.

These figures are not surprising in the modern world where individual doctors and patients no longer make many prescription choice decisions. Those decisions are often dictated by insurers, who insist on cheaper, generic drugs as soon as they are available unless a physician can demonstrate a medical need for the pioneer drug. It is not at all difficult to foresee that CollaGenex's market position would collapse as soon as one or more generic drugs became available. CollaGenex would lose its head start in the market and its continued viability would be at issue. It could never recoup from FDA any losses that would occur. Its David-and-Goliath size comparison to Mutual could make competition between the two a very uneven match.⁹ These are the kinds of circumstances in which irreparable harm has been found. *See Mova Pharm Corp. v. Shalala*, 140 F.3d at 1066 n.6 (“[T]he district court found that Mova would be harmed by the loss of its ‘officially sanctioned head start’ and that Mova’s small size put it at a particular disadvantage. This suffices to show a severe economic impact to Mova.”); *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 29 (D.D.C. 1997) (“While the injury to plaintiffs is ‘admittedly economic,’ there is ‘no adequate compensatory

⁹ Mutual enjoyed over \$290 million in sales of generic drugs in one year alone. United Research Laboratories/Mutual Pharmaceutical Sales Top \$290 Million, Health and Medicine Week, at 16, March 10, 2003; *see also* CollaGenex Reply at 14. Counsel for Mutual informed the Court that Mutual manufactures only generic drugs and does no initial research or new-drug development.

or other corrective relief that can be provided at a later date, tipping the balance in favor of injunctive relief.”) (quoting *Hoffman Laroche Inc. v. Califano*, 453 F. Supp. 900, 903 (D.D.C. 1978)).

The Court finds that CollaGenex has shown substantial and convincing evidence that it would suffer irreparable harm without a preliminary injunction.

4. Public Interest

FDA and Mutual argue that the public interest is served by ready access to less-expensive generic drugs and that the Court should not prevent FDA approval of Mutual’s ANDA. CollaGenex argues that the public has an interest in its ability to continue research and development on new disease treatments.

Congress has determined that those companies that engage in research and new-drug development should have certain protections from competition when a drug is first introduced to the market place. These protections are built into the governing law to provide an inducement to the lengthy and expensive research and development process by assuring a legitimate profit before competitors can intrude. Without these inducements, there would be very little reason for a research company to invest millions of dollars only to have another company re-formulate the same drug, submit an ANDA, avoid the costs of development, charge less for its product, and assume dominance in the market. Thus, the barriers to competition that Congress has erected are in the public interest because they encourage the development of innovative drugs by ensuring a period of market exclusivity. As stated above, CollaGenex has made a sufficient showing of likelihood of success, given the awkward posture of this suit. For this reason, as well as the strength of the showing on balance of harms and irreparable harm, the countervailing public interest in the

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DEPUTY GENERAL COUNSEL



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April 24, 2000

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.

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, chloritracycline, 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 moiety 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 FDAMA² merely defines the types of drugs that are “antibiotic.” As described above, it does not and cannot define the scope

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, chloritracycline, 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 . . .

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:

“[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 moieties*.

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.

⁵ Section 125(d) of FDAMA (emphasis added).

⁶ H R. Rep No. 105-310 (1997) (emphasis added).

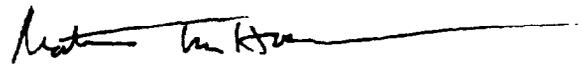
⁷ Letter from Rep. Tom Bliley, Chairman, House Commerce Committee, Rep. Michael Bilirakis, Chairman, House Commerce Subcommittee on Health and Environment, and Richard Burr, member of the House Commerce Committee to Michael A. Friedman, M.D., Lead Deputy Commissioner, United States Food and Drug Administration (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,

A handwritten signature in black ink, appearing to read "Matthew B. Van Hook", written over a horizontal line.

Matthew B. Van Hook

SB
SmithKline Beecham
Pharmaceuticals

2140 '00 APR 18 10:19

April 14, 2000

Dockets Management Branch (HFA-305)
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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).

99N-3088

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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

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

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.

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

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.

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."

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."

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 226 (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

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

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

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.

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Docket No. 99N-3088
Marketing Exclusivity and
Patent Provisions for Certain
Antibiotic Drugs

Merck & Co., Inc. is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than \$2 Billion annually on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness and safety of our products. It is in both of our interests to see that important therapeutic advances reach patients without unnecessary or unusual delays.

Among Merck's human health products is Primaxin, a leading wide-spectrum antibiotic. For this reason, we are very interested in and well qualified to comment on this Draft FDA guidance to provide Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs.

Merck strongly disagrees with FDA's proposed reliance on a comparison of "active moieties" to determine whether a drug that is the subject of a post-FDAMA NDA contains a pre-repeal antibiotic drug and is therefore to be exempted from the marketing exclusivity and patent provisions of section 505 of the Act. Merck's position on this issue is in agreement with that of PhRMA.

The FDA's Hatch-Waxman Act exclusivity regulations define "active moiety" to include non-covalent salts and covalent ester derivatives of the "active moiety". Merck is hereby requesting that the FDA in its final rule for marketing exclusivity and patent provisions for antibiotic drugs provide clarification that a covalent derivative of a pre-repeal antibiotic drug (other than an ester) that requires metabolic conversion to generate the pre-repeal "active moiety" will be considered a "New Chemical Entity" and thus be entitled to the marketing exclusivity provisions of sections 505(c)(3)(D)(ii) and 505(j)(5)(D)(ii) of the Act. The Hatch-Waxman exclusivity regulations for non-antibiotic

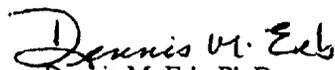
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drugs have considered such metabolically-converted compounds to be "new chemical entities" entitled to 5-years of exclusivity [see 59 Fed. Reg. 50338 (October 3, 1994)]. Merck is requesting a consistent interpretation by the FDA of the term "active moiety" for both antibiotic and non-antibiotic drugs such that a compound (other than an ester) that requires metabolic conversion to produce an already approved active moiety will be considered a "new chemical entity" entitled to 5 years of exclusivity under sections 505(c)(3)(ii) and 505(j)(5)(D)(ii) of the Act.

We appreciate the opportunity to provide comments which, from our perspective, will clarify some of the outstanding issues. We trust that these comments will be considered in further development of the proposed rule.

Sincerely,


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April 21, 2000

Via Hand Delivery
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Re: Comments To Proposed Rule, *Marketing Exclusivity And Patent Provisions For Certain Antibiotic Drugs*;
Docket Number 99N-3088

Dear Sir or Madam:

This letter provides the comments of Alcon Laboratories, Inc. ("Alcon") on the Food and Drug Administration's proposed rule entitled, *Marketing Exclusivity And Patent Provisions For Certain Antibiotic Drugs* ("Proposed Rule"). This Proposed Rule was published in the Federal Register on January 24, 2000 (65 Fed. Reg. 3623) and assigned Docket Number 99N-3088.

While Alcon is generally supportive of the Agency's efforts to implement Section 125 of the Food and Drug Administration Modernization Act ("FDAMA"), we believe the current proposal is incomplete. Although it exempts "pre-repeal antibiotics" from the marketing exclusivity and patent provisions in Section 505 of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"), it fails to recognize that pre-repeal antibiotics are now eligible for the enhanced patent protections afforded under 35 U.S.C. §271(e)(2). That section permits patent owners to file infringement lawsuits earlier than would otherwise be allowed, i.e., at the time an Abbreviated New Drug Application ("ANDA") or 505(b)(2) application is submitted rather than when the allegedly infringing drug product is first commercially marketed.

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FDA's proposed regulatory framework, however, would significantly impair the ability of pre-repeal antibiotic patent holders to take advantage of this new patent remedy created by Congress. This is because: (1) ANDA and 505(b)(2) applicants for pre-repeal antibiotics are not required under the current proposal to notify the New Drug Application ("NDA") holder (or patent owner) of their submissions, and (2) FDA will not disclose the existence of a pending submission under its existing Freedom of Information ("FOI") regulations. 21 C.F.R. §314.430(b) (1999). FDA's proposed regulatory framework thus would restrict access to the very information needed to utilize the new patent remedy for pre-repeal antibiotics, i.e., information about the filing of ANDAs and 505(b)(2) applications for potentially infringing products

We believe it is highly unlikely that Congress intended to grant a remedy that, as a practical matter, can never be used. Accordingly, in tandem with exempting pre-repeal antibiotics from the patent listing and certification provisions of Section 505, FDA should implement alternative regulatory procedures by which pioneer manufacturers and patent owners of pre-repeal antibiotic drug products can be advised of the filing of an ANDA or 505(b)(2) application and, if warranted, take advantage of the Section 271(e)(2) remedy provided by Congress.

A. **The Patent Remedy Set Forth At 35 U.S.C. §271(e)(2) Now Applies To Pre-Repeal Antibiotics**

Prior to the enactment of FDAMA in 1997, antibiotic drug products were required to be marketed in accordance with Section 507 of the FD&C Act, 21 U.S.C. §357. As a result, they were not eligible for the exclusivity and patent protections afforded to non-antibiotic drug products under Section 505 of the Act, including three- and five-year non-

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patent exclusivity and the patent listing, certification and 30-month stay procedures. 21 U.S.C. §§355(c)(3), (j)(5)(B), (D). Nor were antibiotic drug products eligible for the patent remedy set forth at 35 U.S.C. §271(e)(2), which applies only to human drug products that can be approved via an ANDA or 505(b)(2) application, both of which were unavailable to antibiotics prior to 1997.

In 1997, Congress repealed Section 507 and subjected antibiotic drug approvals to Section 505 of the FD&C Act. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, §125(b)(1), 111 Stat. 2296, 2325 (1997). This revision made antibiotics eligible for the first time for Section 505's patent and non-patent exclusivity provisions.

It also brought antibiotics within the scope of the patent remedy set forth at 35 U.S.C. §271(e)(2). That section makes it an act of infringement to submit an ANDA or 505(b)(2) application for a drug or drug use claimed in a patent if the purpose of such submission is to gain FDA approval to commercially manufacture, use or sell the potentially infringing drug prior to expiration of the patent. 35 U.S.C. §271(e)(2). This is a "technical infringement" which provides a basis for the patent holder to file an infringement suit earlier than would otherwise be possible, i.e., while the ANDA or 505(b)(2) application is being reviewed by FDA and before the drug product can be commercially marketed. Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1569 (Fed. Cir. 1997).¹ Since FDAMA for the first time subjected generic antibiotic products to approval

¹ This artificial act of infringement is necessary because most pre-approval uses of drugs and other medical products, including manufacture and clinical testing, are exempt from the infringement provisions under 35 U.S.C. §271(e)(1).

via ANDAs and 505(b)(2) applications, it concomitantly permitted owners of patents covering antibiotic drug products to take advantage of the patent remedy provided by 35 U.S.C. §271(e)(2).

The FDAMA provision affecting antibiotic drug products – Section 125 – also contains a transition provision affecting certain “old” antibiotics, i.e., antibiotics for which a marketing application had been submitted to FDA prior to the repeal of Section 507 (these are referred to as “pre-repeal antibiotics” in the Proposed Rule). The transition provision exempts pre-repeal antibiotics from the exclusivity and patent protections otherwise available under Section 505. Pub. L. No. 105-115, §125(d)(2), 111 Stat. 2296, 2325. In particular, Congress directed that the following statutory requirements would not apply to pre-repeal antibiotics:

1. Three- and five year non-patent exclusivity (21 U.S.C. §§355(c)(3), (j)(5)(D));
2. Patent listing (*Id.* §§355(b)(1), (c)(2));
3. Patent certification (*Id.* §§355(b)(2), (j)(2)(A)(vii), (j)(2)(A)(viii));
4. Notice to the NDA holder and patent owner of the filing of an ANDA or 505(b)(2) application containing a “Paragraph IV” certification (*Id.* §§355(b)(3), (j)(2)(B)); and
5. Thirty-month stay of approval of ANDAs and 505(b)(2) applications containing a Paragraph IV certification if a patent infringement suit is filed within 45 days of notice (*Id.* §§355(c)(3), (j)(5)(B)).

Pub. L. No. 105-115, §125(d)(2), 111 Stat. 2296, 2325.

Significantly, Congress did not exempt pre-repeal antibiotics from the enhanced

patent protections afforded under 35 U.S.C. §271(e)(2). Although the transition provision carefully lists the statutory provisions that do not apply to pre-repeal antibiotics, it is silent with respect to 35 U.S.C. §271(e)(2). *See* Pub. L. No. 105-115, §125(d)(2), 111 Stat. 2296, 2325. This silence should not be confused with ignorance of the issue. Congress was well aware of the interaction between the FD&C Act and the Patent Code and even amended portions of the Patent Code to reflect the repeal of Section 507. Pub. L. No. 105-115, §125(b)(2)(P), 111 Stat. 2296, 2325. Congress' refusal to exempt pre-repeal antibiotics from 35 U.S.C. §271(e)(2) thus must be considered deliberate.

Consequently, the patent remedy afforded by 35 U.S.C. §271(e)(2) now applies to all antibiotic drug products, both new antibiotics containing novel active moieties and pre-repeal antibiotics that are the subject of the Proposed Rule.

B. FDA's Proposed Rule Should Reflect The Fact That 35 U.S.C. §271(e)(2) Now Applies To Pre-Repeal Antibiotics

The Proposed Rule seeks to implement the transitional provision of Section 125 of FDAMA by exempting pre-repeal antibiotics from the regulatory requirements governing patent listing and certification and non-patent exclusivity, both of which affect the timing of approval of ANDAs and 505(b)(2) applications. Alcon is generally supportive of this aspect of the Proposed Rule and has no objection in that regard to the Agency's implementation of the transitional provision.

Alcon, however, believes that the Proposed Rule is incomplete and fails to reflect the fact that pre-repeal antibiotics are now covered by 35 U.S.C. §271(e)(2). If the regulation were to be finalized as proposed, it would operate – in conjunction with

existing FDA regulations – to essentially block pre-repeal antibiotic holders from taking advantage of the new patent remedy created by Congress by restricting access to the very information needed to use that remedy, i.e., information about the filing of ANDAs and 505(b)(2) applications for potentially infringing products.

Alcon does not believe it is reasonable to interpret Section 125 of FDAMA as granting a patent remedy that, for procedural reasons, cannot be used. Such an interpretation would effectively render a critical provision of Section 125 inoperative. *See Edison Elec. Inst. v. E.P.A.*, 996 F.2d 326, 335 (D.C. Cir. 1993) (a statute should not be interpreted so as to render one part inoperative). Yet this is precisely the interpretation that the Proposed Rule, in its current form, appears to adopt.

In order to remedy this situation, FDA should, in conjunction with exempting pre-repeal antibiotics from the patent listing and certification provisions of Section 505, implement alternative regulatory procedures by which pioneer manufacturers and patent owners of pre-repeal antibiotic drug products can be advised of the filing of an ANDA or 505(b)(2) application and, if necessary, take advantage of the Section 271(e)(2) remedy provided by Congress.

This can be accomplished in several ways. First, FDA could promulgate a regulation requiring that ANDA and 505(b)(2) applicants who intend to market a pre-repeal antibiotic prior to the expiration of an applicable patent provide notice to the NDA holder and patentee at the time the application is accepted for filing. Second, FDA could amend its existing FOI regulations at 21 C.F.R. §314.430(b) to permit public disclosure of the filing of an ANDA or 505(b)(2) application for a pre-repeal antibiotic. These alternatives are discussed further below.

1. **Required Notice By ANDA Or 505(b)(2) Applicant**

One regulatory option for fully implementing Section 125 of FDAMA is to require ANDA and 505(b)(2) applicants for pre-repeal antibiotics to notify the NDA holder and patentee of the filing of its application where the applicant intends to commercially market the drug product prior to expiration of any applicable patents. Although FDAMA exempts such ANDAs and 505(b)(2) applications from the patent certification and notification provisions of Section 505 of the FD&C Act, it does so only because those provisions have a significant effect upon the approval times of ANDAs and 505(b)(2) applications.

The legislative history indicates that Congress's sole purpose in enacting the transitional provision in Section 125 was to limit the availability of "market exclusivities," including patent certification exclusivity (e.g., 30-month stay), to "new" antibiotics. See H.R. Rep. No. 105-310, 105th Cong., 1st Sess., at 77 (granting of market exclusivities is limited to new antibiotic drugs). There is no indication that Congress intended to prohibit NDA holders and patentees from learning about the filing of an ANDA or 505(b)(2) application of a potentially infringing pre-repeal antibiotic in a manner that does not implicate any "market exclusivity." Accordingly, FDA is not precluded by Section 125 of FDAMA from implementing a "patent certification" and notice requirement provided such requirement has no effect upon the timing of FDA approval of the relevant ANDA and 505(b)(2) applications.

Since the purpose of the certification and notice requirement would be to implement the patent remedy set forth at 35 U.S.C. §271(e)(2) with respect to pre-repeal antibiotics, it should be limited to situations in which the ANDA or 505(b)(2) applicant

intends to commercially market its antibiotic prior to expiration of any applicable patent. In other words, it should be restricted to situations in which a "Paragraph IV" certification otherwise would be required. This limitation reflects the fact that, under 35 U.S.C. §271(e)(2), it is an act of infringement to submit an ANDA or 505(b)(2) application for a drug covered by a patent, but only if the purpose of the application is to obtain FDA approval to commercially market, use or sell the drug product before the expiration of the patent.

To discourage ANDA and 505(b)(2) applicants from manipulating the system by failing to give the required notice even though they intend to commercially market their drug product prior to expiration of an applicable patent, FDA should require ANDA and 505(b)(2) applicants for pre-repeal antibiotics to make one of two certifications:

1. that the applicant does not intend to market its antibiotic product until after a relevant patent or patents have expired; or
2. that the applicant intends to market its antibiotic product prior to expiration of a relevant patent or patents and that it will provide notice to the NDA holder and patentee of the reference listed drug when its application is accepted for filing.

If an ANDA or 505(b)(2) applicant provides a false certification (i.e., certifies that it does not intend to market until after a relevant patent has expired but, upon receiving FDA approval, immediately commences marketing the product), FDA should take all appropriate enforcement action, including withdrawing approval of the application and, in appropriate circumstances, criminal prosecution. *See* 18 U.S.C. §1001 (false statements); 21 U.S.C. §355(e)(5) (withdrawal).

The certification and notice requirement should apply to all patents that cover the pioneer product (i.e., drug substance, formulation, or and method of use)² which the ANDA or 505(b)(2) applicant is aware of or reasonably should be aware of. To facilitate the certification process, FDA should permit NDA holders of pre-repeal antibiotics to submit relevant patent information for inclusion in the Orange Book. Although FDAMA exempts such NDA holders from the *requirement* to submit patent information, FDAMA does not prohibit FDA from accepting patent information that is provided voluntarily. See Pub. L. No. 105-115, §125(d)(2), 111 Stat. 2296, 2325. Patent information that is published in the Orange Book, as well as patent information included in the labeling of a pioneer pre-repeal antibiotic, should presumptively be subject to the patent certification and notice requirement, since an ANDA or 505(b)(2) applicant should reasonably be aware of such patent information.

Alcon believes that a patent certification and notice process applicable to pre-repeal antibiotics can be implemented, consistent with the general principles discussed above, in several different ways. First, FDA could retain the existing patent certification and notice provisions set forth in its regulations (e.g., 21 C.F.R. §§314.50(i), 314.52, 314.94(a)(12), 314.95), but clarify that, for pre-repeal antibiotics, such certifications will not affect the timing of approval of the ANDA or 505(b)(2) application. This distinction should not create administrative difficulties since FDA has already decided to distinguish between pre-repeal antibiotics and other drugs through its application numbering system.

² Section 271(e)(2) of the Patent Code applies to patents which claim a "drug" or a drug "use." FDA previously has interpreted these terms to include drug substance (ingredient) patents, drug product (formulation and composition) patents, and method of use patents, but not process patents. 21 C.F.R. §314.53(b). Alcon sees no reason to depart from this interpretation.

See Guidance for Industry and Reviewers – Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act at 2-3 (May 1998). Accordingly, new applications assigned a pre-repeal antibiotic number (i.e., 50,000 or 60,000 series) would have to contain a certification like other applications, but this certification would not affect when they could be approved.

Second, FDA could create a separate certification and notification procedure specifically for pre-repeal antibiotics. These regulations could be added to the current proposal for 21 C.F.R. §314.109.

In sum, FDA clearly has broad discretion to fashion an appropriate patent certification and notification procedure that fully implements Section 125. Any such procedure that FDA adopts, however, should be consistent with the general principles discussed above.

2. Public Disclosure By FDA

As an alternative to requiring ANDA and 505(b)(2) applicants to provide notification to NDA holders and patentees, FDA could implement Section 125 of FDAMA by amending its FOI regulations to permit public disclosure of such information by FDA.

FDA's current regulations provide that "FDA will not publicly disclose the existence of an application or abbreviated application before an approvable letter is sent . . ." 21 C.F.R. §314.430(b). The purported basis for this regulation is that the mere existence of a pending ANDA or 505(b)(2) application constitutes "confidential commercial information" that is not required to be publicly disclosed by FDA under the Freedom of Information Act ("FOIA"). *See* 39 Fed. Reg. 44602, 44634 (Dec. 24, 1974);

see also 5 U.S.C. §552(b)(4) (FOIA exemption for trade secrets and confidential commercial information).

Even assuming that the existence of a pending ANDA or 505(b)(2) application constitutes confidential commercial information – a position FDA has seriously questioned in the past³ – FDA nevertheless retains authority to publicly disclose such information if, as here, there are strong policy reasons to do so. Indeed, the FOIA is not a prohibitive statute and does not enjoin federal agencies such as FDA from disclosing confidential commercial information. It merely provides that a federal agency may not be forced to disclose confidential commercial information under FOIA if it chooses not to. Chrysler Corp. v. Brown, 441 U.S. 281, 290-95 (1979). Accordingly, neither FOIA nor any other statute would restrict FDA from amending its existing regulations to permit the public disclosure of the existence of a pending ANDA or 505(b)(2) application for a

³ As originally proposed, FDA's regulations provided that a list of pending new drug applications would be available for public inspection. 37 Fed. Reg. 9128, 9131 (May 5, 1972). FDA reversed itself when it finalized the regulations in 1974. Four years later, FDA proposed to amend the regulations to permit public disclosure of the existence and status of applications on the basis that, upon reconsideration, FDA did not consider this information to be "confidential commercial information." 43 Fed. Reg. 12869, 12870 (March 28, 1978). This proposal was never acted on by FDA and was subsequently withdrawn in 1991. 56 Fed. Reg. 67446 (Dec. 30, 1991). Congress has recognized that public policy concerns sometimes outweigh a company's interest in confidential commercial information. For instance, in 1997 Congress required the Department of Health and Human Services to publicly release information about ongoing clinical trials for serious or life-threatening diseases. 42 U.S.C. 282(j) (added by Section 113 of FDAMA, Pub. L. No. 105-115, 111 Stat. 2310-12). This clinical trial information, like the existence of pending ANDAs and 505(b)(2) applications, traditionally has been considered to be confidential commercial information by FDA. See 21 C.F.R. 312.130(a).

pre-repeal antibiotic.⁴

In this case, there are strong public policy reasons to amend the existing regulations to permit such disclosure. First, such disclosure would promote the objectives of FDAMA, particularly Section 125, by providing NDA holders and patentees with the critical information they need to take advantage of the enhanced patent remedy provided by Congress. As discussed above, FDA's failure to make this information available to affected NDA holders and patentees would frustrate Congressional intent by making important provisions of Section 125 of FDAMA inoperative.

Second, public disclosure of the existence of ANDAs and 505(b)(2) applications for pre-repeal antibiotics would permit patent infringement cases to be filed – and resolved – earlier than otherwise possible, thereby facilitating the orderly market entry of generic antibiotics. It also would ease the burden on courts and litigants by providing several months advance notice of potentially infringing acts, thereby obviating the need for burdensome and potentially unnecessary interim injunctive relief (e.g., temporary restraining order). Both of these outcomes are in the public interest.

Moreover, all of these policy reasons, particularly the need to fully implement Section 125 in accordance with Congressional intent, outweigh any potential interest an ANDA or 505(b)(2) applicant for a pre-repeal antibiotic might have in maintaining the

⁴ The Trade Secrets Act, 18 U.S.C. §1905, would not be violated because the disclosure would be "authorized by law," i.e., by FDA's regulations. Chrysler Corp. v. Brown, 441 U.S. 281 (1979). Since the regulations permitting disclosure would be intended to implement Section 125 of FDAMA, if promulgated according to 5 U.S.C. §553, they should satisfy the necessary requirements for having the "force and effect of law." See Parkridge Hospital, Inc. v. Califano, 625 F.2d 719, 722-25 (6th Cir. 1980).

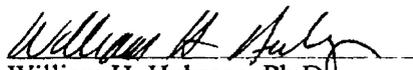
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Food and Drug Administration
April 21, 2000
Page 13

confidentiality of the existence of its submission.⁵ Although such an applicant for a pre-repeal antibiotic might be sued for patent infringement sooner than if the information about its pending ANDA or 505(b)(2) application were not publicly disclosed, this is exactly the outcome Congress intended when it enacted Section 125 of FDAMA and brought pre-repeal antibiotics within the scope of 35 U.S.C. §271(e)(2).

C. Conclusion

FDA's Proposed Rule is a good start in implementing Section 125 of FDAMA, but it does not go far enough. FDA should implement the specific exemptions that are applicable to pre-repeal antibiotics as a consequence of Section 125, but also should recognize that pre-repeal antibiotics were not exempted from the patent remedy set forth at 35 U.S.C. §271(e)(2) and implement procedures to facilitate use of that remedy by NDA holders and patentees of pre-repeal antibiotics.

Respectfully submitted,


William H. Hubregs, Ph.D.
Vice President
Corporate Regulatory Affairs

⁵ Alcon notes that it is not suggesting that the *content* of the submissions (as opposed to their existence) should be publicly disclosed. Nor is Alcon suggesting that the existence of pending marketing applications for products other than pre-repeal antibiotics should be publicly disclosed, since the same public policy concerns are not implicated.

AstraZeneca

COPY

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Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane
Rm 1061
Rockville, MD 20852

JAN 24 2001

2521 0 JAN 15 49 58

Re: **Docket No. 99N-3088**
RIN 0910-AB33
Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs

Dear Sir or Madam:

Reference is made to the FDA's proposed rule published in the Federal Register of January 24, 2000, to exempt marketing applications for certain antibiotic drug products from the regulatory provisions governing marketing exclusivity. The proposal would apply to marketing applications for drug products containing an antibiotic drug that was subject of a marketing application received by the FDA before November 21, 1997, the effective date of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to a January 22, 2001 telephone conversation between the FDA's Mr. Wayne Mitchell and the undersigned regarding a submission that AstraZeneca made to the FDA's Division of Anti-Infective Drug Products on January 22, 1999. In that submission, AstraZeneca Pharmaceuticals LP indicated that our drug product, MERREM® I.V. (meropenem for injection), NDA No. 50-706, should be classified as an "anti-infective" and not an antibiotic as defined previously by Section 507 [357](a) of the Federal Food, Drug and Cosmetic Act. Mr. Mitchell indicated that FDA is in the process of finalizing the proposed rule, and he requested that AstraZeneca submit a copy of our January 22, 1999 document to the above-referenced Docket for consideration as soon as possible.

Accordingly, attached is a copy of our January 22, 1999 submission to the FDA's Division of Anti-Infective Drug Products regarding the classification of MERREM® I.V. As noted in the document cover letter, microorganisms do not produce the structural component of the active ingredient of MERREM® I.V. that imparts the capacity to inhibit or destroy microorganisms. The synthesis of meropenem, and all intermediates in the synthetic pathway, cannot be manufactured by fermentation and is described in the MERREM® I.V., NDA No. 50-706 and in Sumitomo's DMF #10322. The January 22, 1999 submission also provided a review article by S. Coulton and E. Hunt (Progress in Medicinal Chemistry 1996; 33:99-145) that discusses the chemistry and biology of carbapenems. In this article, meropenem is characterized as a totally synthetic non-natural carbapenem, providing further evidence that MERREM® I.V. does not meet the strict definition of an antibiotic.

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 1985043355

A70010 (8/00)

99N-3088

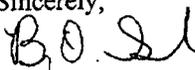
Docket No. 99N-3088

Page 2

The confidentiality of this submission, and all information contained herein, is claimed by AstraZeneca under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

I trust this information is helpful. If you have any questions or comments, please do not hesitate to contact me, or in my absence, Ms. Darci Bertelsen at (302) 886-7355.

Sincerely,



Barry D. Sickels
Director, Regulatory Affairs
(302) 886-5895
(302) 886-2822 (fax)

BDS/DLB/mrsc
Enclosure

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

SENT VIA UNITED PARCEL SERVICE

JAN 2 2 1999

Gary K. Chikami, M.D.
Director
Division of **Anti-Infective**
Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
HFD No. 520, Document Control Room
920 1 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Chikami:

Re: **MERREM**[®] I.V. (meropenem for injection)
NDA SO-706
Request for Drug Classification

Zeneca is writing in regards to an unresolved issue from 1993. At the request of Zeneca Pharmaceuticals (ZENECA), FDA pre-assigned an NDA number to the MERREM[®] I.V. (meropenem for injection) NDA on May 7, 1993. The MERREM I.V. NDA was inadvertently assigned a 50-series number (NDA 50-706). The original NDA for MERREM I.V. was submitted on October 28, 1993 by ZENECA under section 505(b) of the Federal Food, Drug and Cosmetic Act.

During a conversation initiated by Dr. Kathleen A. Creedon, (Microbiologist, Division of Anti-Infective Drug Products) on November 3, 1993, she noted that the NDA was submitted under section 505. Dr. Creedon commented that the NDA number was incorrectly cited since 50-series numbers are reserved for antibiotics, as defined by section 507.(357)(a) of the Act, and that drugs which are submitted under section 505 should be designated with 20-series NDA numbers. In the November 4, 1993 telephone conversation between Dr. Creedon and ZENECA, Dr. Creedon stated if MERREM I.V. was submitted under section 505 it should be referred to as an anti-infective, and that the NDA number for MERREM I.V. could be reassigned to the 20-series numbers upon the submission of documentation which proved that MERREM I.V. does not fit the definition of an antibiotic.

Section 507.[357](a) of the Federal Food, Drug and Cosmetic Act defined an antibiotic as: "*any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for use by man 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 the chemically synthesized equivalent of any such substance) or any derivative thereof.*" ZENECA is aware that section 507 has been repealed; however, the repeal of this section did not change the definition for antibiotic classification (see FDA Guidance for Industry and Reviewers: Repeal of section 507 of the Federal Food, Drug and Cosmetic Act [May 1998] referring to new section 201(j)(j) of the Act).

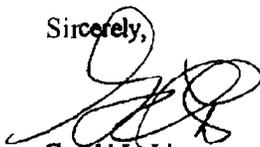
The structural component of the active ingredient of MERREM I.V. that imparts the capacity to inhibit or destroy micro-organisms is not produced by micro-organisms. The synthesis of meropenem, along with all intermediates in the synthetic pathway, cannot be manufactured by fermentation and is described in the MERREM I.V. NDA 50-706 and in the Sumitomo meropenem Drug Master File (DMF #10322). In addition, the attached review article written by S. Coulton discusses the chemistry and biology of carbapenems. In this article meropenem is characterized as a totally synthetic non-natural carbapenem. These documents provide evidence that MERREM I.V. does not meet the strict definition to be classified as an antibiotic.

3 Correspondence to FDA, dated December 3, 1993 requested that the MERREM I.V. NDA number be reassigned to a non 50-series NDA number, and the NDA be filed under section 505(b). Subsequently, the NDA was filed by FDA under section 507, and no further communication regarding this issue has been received.

By means of this correspondence, ZENECA again respectfully requests that the MERREM I.V. NDA be re-assigned a 20-series NDA number and be classified as an anti-infective drug.

We will be contacting the FDA Project Manager shortly to discuss this matter. If you have any questions or comments, please do not hesitate to contact me.

Sincerely,



Gerald L. Limp
Manager, Marketed Products Group
Drug Regulatory Affairs Department
(302) 886-8017
(302) 886-2822 (fax)

GLL/DLB/jr
Enclosure

Desk Copy: Ms. Maureen P. Dillon-Parker, HFD No. 520

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