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PETITION FOR STAY OF ACTION

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

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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.

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

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

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[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.

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-

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[4] As 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.").

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.

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[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.

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]

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[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

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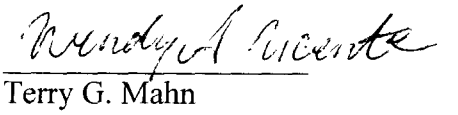
[11] *Id.*

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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