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PETITION FOR STAY OF ACTION

CollaGenex Pharmaceuticals, Inc. ("CollaGenex") submits this stay petition under Section 505(j) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. §§ 10.35 and 314.127(a)(6)(i) to request that the Commissioner of Food and Drugs stay approval of any ANDAs submitted by Ivax Pharmaceuticals, Inc. ("Ivax"), CorePharma LLC ("CorePharma"), or any other party for which CollaGenex's Periostat® (doxycycline hyclate 20 mg) is the reference listed drug unless that ANDA's bioequivalence study or studies include female subjects.

A. Decision Involved

FDA has received several abbreviated new drug applications ("ANDA") for generic versions of CollaGenex's Periostat® (doxycycline hyclate 20 mg) tablets or capsules, including ANDAs submitted by Ivax (ANDA No. 65-163) and CorePharma (ANDA 65-182), at least two of which are pending approval.¹

1. Memorandum of IVAX Pharmaceuticals, Inc. in Support of Expedited Motion to Intervene as Defendant, CollaGenex Pharms., Inc. v. Thompson, No. 03-1405 (D.D.C. Aug. 19, 2004) at 3; Memorandum of Points and Authorities in Support of Expedited Motion by CorePharma LLC to Intervene, CollaGenex Pharms., Inc. v. Thompson, No. 03-1405 (D.D.C. Sept. 10, 2004) at 3. FDA has also received ANDAs submitted by Mutual Pharmaceutical Company (ANDA No. 65-134), and West-ward Pharmaceutical Corporation (ANDA No 65-103). Memorandum in Support of Unopposed Motion of Mutual Pharmaceutical Company, Inc. to Intervene as Defendant, CollaGenex Pharms., Inc. v. Thompson, No. 03-1405 (D.D.C. June 30, 2003) at 2; Citizen Petition filed by West-ward Pharmaceutical Corporation in opposition to CollaGenex's July 10, 2002 Citizen Petition re: Periostat® capsules (Aug. 13, 2002) at 1, available at <http://www.fda.gov/ohrms/dockets/dailys/02/Aug02/082802/8001fdbd.pdf>.

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The bioequivalence studies on which two previous ANDAs referencing Periostat relied excluded women.² CollaGenex does not know whether women were likewise excluded from the bioequivalence studies relied on by IVAX, CorePharma, or any other ANDAs for which Periostat is the reference listed drug. This Petition for Stay of Action applies to any ANDA referencing Periostat that rests on bioequivalence studies from which women were excluded.

FDA may not approve an ANDA unless the application contains information showing that the would-be generic drug is bioequivalent to a reference listed drug that has been shown to be safe and effective in an approved new drug application.³ As FDA has explained,

[By] showing that the generic drug is absorbed and used by the body in the same way as the brand name drug," the generic applicant "provides assurance that the generic copy will be as safe and effective as the reference listed drug, whose safety and effectiveness have been demonstrated through clinical trials. Because generic drug manufacturers do not have to repeat the clinical studies used to develop the original drug, . . . [this] assurance . . . is a crucial aspect of the scientific basis for their approval for marketing.⁴

The burden of showing bioequivalence rests with the ANDA applicant,⁵ and to meet its burden the applicant must conduct testing using a method that is "capable of . . . establishing

2. Citizen Petition filed by CollaGenex re: Mutual Pharmaceutical Company, Inc.'s ANDA for doxycycline hyclate tablets (July 14, 2003) at 1 ("CollaGenex BE Petition") at 1; Citizen Petition filed by CollaGenex Pharmaceuticals, Inc. re: West-ward Pharmaceutical Corporation's ANDA for doxycycline hyclate capsules (August 15, 2003) at 1. See also Petition for Stay of Action filed by CollaGenex Pharmaceuticals, Inc. re: Mutual Pharmaceutical Company's ANDA for doxycycline hyclate tablets (July 18, 2003) at 1. With the exception of the CollaGenex BE Petition, a copy of which is attached hereto and incorporated herein by reference, pursuant to 21 CFR § 10.20(c), documents that are routinely publicly available on FDA's website are cited in but not attached to this petition.

3. Federal Food, Drug, and Cosmetic Act § 505(j)(2)(A)(iv), 21 U.S.C. § 355; *id.* § 505(j)(4) (FDA may not approve an ANDA if information submitted is insufficient to show bioequivalence with the reference listed drug); 21 C.F.R. § 314.94(a)(7) (ANDA must contain information to show bioequivalence); *id.* § 314.125(b)(9) (FDA may refuse ANDA lacking required bioequivalence data); *id.* § 320.21(b)(i) (ANDA must include proof of bioequivalence).

4. FDA Backgrounder on Conjugated Estrogens, available at <http://www.fda.gov/cder/news/cebackground.htm> (May 5, 1997).

5. Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17976 (April 28, 1992).

bioequivalence . . . for the product being tested.”⁶ For an orally administered drug such as Periostat, this means an appropriately designed *in vivo* study.⁷

As explained in the González Declaration attached to the CollaGenex BE Petition, a fundamental precept observed by experts in the design and review of bioequivalence studies is that a study should not artificially exclude potential sources of variability that could make a showing of bioequivalence less likely if they were included in the analysis. Put another way, any aspect of study design that systematically reduces variability in the observed pharmacokinetic data can bias a study in favor of incorrectly showing bioequivalence when it does not in fact exist.⁸

A study design excluding female subjects would systematically reduce the variability in observed pharmacokinetic responses, thus biasing the study toward a finding of bioequivalence. As a result, it would not be “capable of establishing bioequivalence” and therefore the study results could not be relied upon to meet the burden of proving that the product is bioequivalent to Periostat.⁹

Because many drugs exhibit gender differences in pharmacokinetics, it has long been standard practice to include both women and men in clinical trials. Consistent with the population of adult periodontitis patients, CollaGenex’s bioequivalence study included both male and female subjects. As Dr. González’s declaration explains, the mixed-gender study population used by CollaGenex was consistent with FDA’s “Guidance for Industry [on] Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations” (July

6. 21 CFR § 320.24(a).

7. *Id.* at (b).

8. González Declaration ¶ 4.

9. *Id.* ¶ 5.

2002) (the “BE Guidance”),¹⁰ and thus reflected both FDA’s current thinking about the proper conduct of bioequivalence studies and the accepted current practice among pharmaceutical research experts.¹¹

It is particularly important to include both males and females in bioequivalence studies involving Periostat because doxycycline hyclate is known to exhibit different pharmacokinetics in women than in men, with women having a higher extent of absorption (Cmax) under both fasted and fed conditions.¹² A study which excludes women would therefore fail to take into account an important and known source of variability in pharmacokinetic responses, thus biasing the study in favor of incorrectly finding bioequivalence.

B. Action Requested

CollaGenex requests that the Commissioner stay action on any ANDA for a generic version of Periostat unless and until such ANDA is supported by a bioequivalence study or studies conducted on both male and female subjects.

C. Statement of Grounds

Mandatory Stay

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

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

10. The BE Guidance is available at <http://www.fda.gov/cder/guidance/4964dft.pdf>.

11. González Declaration ¶ 7 (citing BE Guidance at 7).

12. Id. ¶ 8 (citing Periostat Capsule and Tablet Package Inserts).

As demonstrated below, all these criteria are met here.

Without a stay, CollaGenex will suffer irreparable injury. FDA is preliminary enjoined by the U.S. District Court for the District of Columbia from approving any ANDAs for which Periostat is the reference listed drug.¹³ However, Ivax and CorePharma have filed motions to dissolve the injunction¹⁴; if either motion is granted, approval of one or more of these ANDAs could be imminent. In her memorandum opinion granting CollaGenex's motion for a preliminary injunction against FDA's approval of any ANDA for generic versions of Periostat, Judge Collyer held that the injury to CollaGenex resulting from FDA's approval of such an ANDA would be irreparable and immediate. Specifically, the court stated:

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 These are the kinds of circumstances in which irreparable harm has been found.¹⁵

CollaGenex's case is not frivolous and is being pursued in good faith. As discussed earlier in this Stay Petition, the case presented in CollaGenex's Stay Petition is far from frivolous; it is very strong. A bioequivalence study using Periostat as a reference list drug that tests only male subjects does not satisfy the statutory and regulatory requirements for proving bioequivalence, especially with respect to doxycycline hyclate, a drug which exhibits different pharmacokinetics in women than in men.

13. Memorandum Opinion, CollaGenex Pharms., Inc. v. Thompson, No. 03-1405 (D.D.C. July 22, 2003) ("Memorandum Opinion") at 21 (attached).

14. Expedited Motion of Ivax Pharmaceuticals, Inc. to Dissolve the Preliminary Injunction as to Ivax's ANDA at 1; Expedited Motion of CorePharma LLC to Dissolve the Preliminary Injunction as to CorePharma's ANDA at 1.

15. Memorandum Opinion at 19. See also Declarations of Brian W. Gallagher and Colin M. Stewart, CollaGenex's former and current Presidents and Chief Executive Officers, respectively, which stated that the potential harm to CollaGenex would be certain, devastating, and irreparable. Declaration of Brian W. Gallagher, Ph.D. (June 30, 2003) ¶¶ 49-61; Declaration of Colin W. Stewart (Sept. 13, 2004) ¶¶ 18-24. Copies of both declarations are attached.

CollaGenex's case also is being pursued in good faith. Pending ANDA applications and their contents are held confidential by FDA. It was only in August when IVAX moved to dissolve the preliminary injunction, that CollaGenex learned that IVAX's ANDA had been tentatively approved, and in CorePharma's September 2004 court filing, that CollaGenex learned that CorePharma's ANDA had also received tentative approval.¹⁶

Sound public policy grounds support the stay. The NDA and ANDA processes are intended simultaneously to encourage the costly research and development efforts that lead to the discovery of therapeutically important new drugs and to expedite the availability of safe, effective, and less expensive versions of approved drugs. The requirement for scientifically competent proof of bioequivalence is absolutely critical to the regulatory scheme because it alone provides the necessary assurance that a generic copy will be as safe and effective as the pioneer drug for which safety and effectiveness have been demonstrated by full investigations. For FDA to approve an ANDA based on data from an inherently biased study would be doubly detrimental to public policy because it would expose the public to unacceptable health risks while unlawfully relieving the ANDA applicant of its evidentiary burden.

The delay will not harm the public interest. This Stay Petition asks FDA to subject the design and results of any bioequivalence study submitted in support of any ANDA relying on Periostat as the reference listed drug to the same standard of review that the statute and FDA regulations require in any case. Any delay in approval resulting from that level of scrutiny properly should be attributed to the application itself, and not to CollaGenex's intervention. Moreover, the public interest would be significantly harmed if FDA were to approve an ANDA based on the results of an inadequate bioequivalence study. The strong public health interest in

16. Expedited Motion of Ivax Pharmaceuticals, Inc. to Dissolve the Preliminary Injunction as to Ivax's ANDA (Aug. 19, 2004) at 2; Expedited Motion of CorePharma LLC to Dissolve the Preliminary Injunction as to CorePharma's ANDA (Sept. 10, 2004) at 2.

assuring that generic drugs are safe and effective despite the lack of full safety and efficacy investigations must far outweigh any attendant delay in approval of any ANDA.

Discretionary Stay

FDA regulations also authorize the agency to grant a stay if it "is in the public interest and in the interest of justice." 21 C.F.R. § 10.35(e). For the reasons already explained, both the threat to public health and safety from erroneously approving any generic drug product as bioequivalent to Periostat and the resulting irreparable injury to CollaGenex demand that FDA not approve any ANDA relying on Periostat as the reference listed drug unless its studies establish bioequivalence in both male and female subjects. Accordingly, if FDA will not grant a mandatory stay, it should grant a discretionary stay.

D. Conclusion

CollaGenex's Stay Petition demonstrates that male-only bioequivalence studies are not capable of establishing bioequivalence with Periostat and that the grounds for both mandatory and discretionary stays are met. FDA therefore should grant the requested stay.

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