COLLAGENEX
pharmaceuticals

August 15, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, MD 20852

CITIZEN PETITION

A. Action Requested

CollaGenex Pharmaceuticals, Inc. ("CollaGenex") submits this petition under Section 505(j) of the Food, Drug, and Cosmetic Act ("FDCA") and 21 C.F.R. §§ 10.30 and 314.127(a)(6)(i) to request that the Commissioner of Food and Drugs refuse to approve any ANDA submitted by West-ward Pharmaceutical Corporation ("West-ward") for doxycycline hyclate capsules in which bioequivalence of the West-ward product to CollaGenex's Periostat® (doxycycline hyclate capsules 20 mg) is purportedly demonstrated by the bioequivalence study that is appended hereto as Exhibit B to the attached Declaration of Mario A. González, Ph.D., and referred to in this petition as "the West-ward study." The West-ward study artificially and inappropriately excludes two significant sources of potential variability in pharmacokinetic responses, thus making it more likely to find bioequivalence when the two products are not, in fact, bioequivalent. For that reason, the study is insufficient to show that the West-ward product is bioequivalent to Periostat, the reference listed drug, and FDA must therefore refuse to approve West-ward's ANDA. § 505(j)(4)(F) and 21 C.F.R. § 314.127(a)(6)(i).[1]

1. FDA is also barred from approving West-ward's ANDA for the reasons stated in CollaGenex's July 10, 2002 Citizen Petition and Petition for Stay of Action (CollaGenex Citizen Petition"), available at http://www.fda.gov/ohrms/dockets/dailys/02/Jul02/071102/02p-312_cp00001_vol1.pdf. Pursuant to 21 C.F.R. § 10.20(c), cited materials that are routinely available on FDA's website (www.fda.gov) or elsewhere are not attached to this petition.

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CollaGenex Pharmaceuticals, Inc., 41 University Drive, Suite 200, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

B. Statement of Grounds

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.[2] As FDA has explained,

> "[By] showing that the generic drug [has the same active ingredient as and] 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."[3]

The burden of showing bioequivalence rests with the ANDA applicant,[4] and to meet its burden the applicant must conduct testing using a method that is "capable of establishing bioequivalence. . . for the product being tested."[5] For an orally administered drug such as Periostat, this means an appropriately designed in vivo study.[6]

West-ward submitted an ANDA for doxycycline hyclate capsules 20 mg on August 30, 2001, with Periostat doxcycline hyclate capsules 20 mg as the reference listed drug.[7] CollaGenex has obtained from the New Jersey Drug Utilization Review Council the West-ward

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2. 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).

3. FDA Backgrounder on Conjugated Estrogens, http://www.fda.gov/cder/news/cebackground.htm. (May 5, 1997).

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

5. 21 CFR § 320.24(a).

6. Id. at (b).

7. Comment of West-ward Pharmaceutical Corp. on CollaGenex Pharmaceuticals Citizen Petition and Petition for Stay of Action re: Periostat® capsules, available at http://www.fda.gov/ohrms/dockets/dailys/02/sep02/090502/80024aa6.pdf.

study which purports to show bioequivalence of the West-ward doxycycline hyclate capsules to Periostat capsules.

As explained in the attached Declaration of Dr. González ("González Declaration"), 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 phamacokenetic data can bias a study in favor of incorrectly showing bioequivalence when it does not in fact exist.[8]

The West-ward study design systematically excluded at least two important sources of variability in the pharmacokinetic data. First, the study inappropriately compared the West-ward product and Periostat using a two-capsule (40 mg) dose rather than a single 20 mg capsule. Second, the study population failed to include any female subjects. Either or both of those factors would artificially reduce the variability in observed pharmacokinetic responses and thus bias the study toward a finding of bioequivalence. As a result, the methods employed by West-ward were not "capable of estabishing bioequivalence" and therefore the study results cannot be relied upon to meet West-ward's burden of proving that its product is bioequivalent to Periostat.[9]

The West-ward Study used an inappropriate dose of doxycycline hyclate.

As stated above, Periostat capsules were approved for marketing in a single, 20 mg unit strength, to be taken twice daily at 12-hour intervals. The reference strength shown in FDA's Orange Book for purposes of establishing bioequivalence for would-be generics likewise is 20 mg.[10] When CollaGenex decided to market Periostat as a 20 mg tablet instead of a 20 mg capsule, it was required to conduct a BE study, the design and results of which were reviewed by FDA experts and found to be appropriate for showing bioequivalence. The dosage used in that study was a single 20-mg capsule or tablet dose.[11]

As Dr. González's declaration explains, the single-unit dosage used by CollaGenex was consistent with FDA's "Guidance for Industry [on] Bioavailability and Bioequivalence

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8. González Declaration ¶ 4.

9. Id. ¶ 5.

10. FDA, Approved Drug Products with Therapuetic Equivalence Evaluation ("Orange Book"), 23d Annual Edition, http://www.fda.gov/cder/ob/default.htm.

11. González Declaration ¶ 7.

Studies for Orally Administered Drug Products – General Considerations" (the "BE Guidance"),[12] and thus reflected both FDA's current thinking about the proper conduct of BE studies and the accepted current practice among pharmaceutical research experts.[13] With respect to choice of dosage, the guidance recommends that a BE study be conducted using the strength(s) specified in the Orange Book,[14] with the highest marketed strength administered as a single unit dose unless a multiple-unit dose is necessary for some reason.[15]

As Dr. González further explains, it is scientifically appropriate to avoid multiple-unit dosing whenever feasible in bioequivalence studies because both inter- and intra-subject variability are diminished when two or more units are administered instead of one, making it easier to show bioequivalence. Although multiple-unit doses are sometimes necessary (e.g., when it is technically infeasible to analyze the serum concentration produced by a single-unit dose, or when the recommended dose is a multiple of the highest available strength), CollaGenex is not aware of any scientific or technical reason that would either compel or justify the two-tablet dose used in the West-ward study. As a result, the appropriate dosage for a BE study using Periostat as the reference product would be a single-capsule, 20 mg dose and not the double-capsule dose used in the West-ward study.[16]

The West-ward study population inappropriately excluded female subjects.

A second major weakness in the West-ward study design was that the study population consisted exclusively of male volunteers. Because many drugs exhibit gender differences in phamacokinetics, it has long been standard practice to include both women and men in clinical trials, and FDA guidance specifically recommends including similar proportions of both male and female subjects in BE studies of drugs, such as Periostat, that are intended for use in both sexes.[17] Accordingly, CollaGenex's BE study included both male and female subjects.

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12. Available at http://www.fda.gov/cder/guidance/4964dft.pdf. (July 10, 2002).

13. González Declaration ¶ 8.

14. Id. (citing BE Guidance at 13).

15. Id. (citing BE Guidance at 21).

16. Id. ¶ 9.

17. Id. ¶ 10 (citing BE Guidance at 7): see also, e.g., Notice, Guideline for the Study and Evaluation of Gender Differences in the Evaluation of Drugs, 58 Fed. Reg. 394047 (July 23, 1993).

It is particularly important to include both males and females in BE 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.[18] The West-ward study reference therefore fails to take into account an important and known source of variability in pharmacokinetic responses, further biasing the study in favor of incorrectly finding bioqeuivalence.[19]

As explained by Dr. González, the likelihood that West-ward's study was biased in favor of showing bioequivalence is shown by a comparison of the coefficient of variance (CV) in Cmax values for Periostat capsules reported in the West-ward study with the corresponding CV for Periostat capsules in CollaGenex's BE study, which was appropriately conducted using both a single-capsule dosage and a mixed-gender study population.[20] The CV is a quantitative measure of the variability in a set of individual pharmacokinetic measures, based on the relationship of the standard deviation to the mean of a pharmacokinetic parameter. It is particularly useful for cross-study comparisons where, as here, the studies being compared were performed on the same drug product (i.e., Periostat capsules). The CV for Cmax from Periostat capsules in the West-ward study was 19.8%. By contrast, the corresponding CV for Cmax from Periostat capsules in the CollaGenex study was dramatically higher, i.e., more variable, at 31%. These results strongly suggest that the previously-demonstrated variability in Cmax from Periostat was artificially reduced in the West-ward study, and that the resulting finding of bioequivalence is therefore highly suspect.[21]

Conclusion

In order to obtain an ANDA for its doxycycline hyclate 20 mg capsules, West-ward has the burden of showing that the product is bioequivalent to Periostat, using methods that are "capable of establishing bioequivalence . . . for the product being tested" as required by 21 CFR § 320. For the reasons discussed above, the West-ward study design was not capable of showing bioequivalence due to its two-capsule dose and all-male study population, either or both of which would make it more likely to find bioequivalence when the products are not, in

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18. González Declaration ¶ 11 (citing approved package inserts for Periostat capsules and tablets).

19. Id.

20. Id. ¶ 12.

21. Id.

fact, bioequivalent. The results of that or any similarly designed study therefore cannot satisfy West-ward's evidentiary burden, and FDA must therefore refuse to approve West-ward's ANDA.

Finally, the potential consequences of falsely concluding that two drug products are bioequivalent are especially troubling when the drug at issue has a narrow therapeutic range, i.e., when even a small deviation from the target blood concentration can result in reduced effectiveness, increased risk, or both. Periostat is not an antibiotic, and has been shown to maintain blood concentrations of doxycycline that do not reach the serum concentration associated with antibiotic action.[22] As a result, patients who use Periostat are not subjected to antibiotic exposure and the attendant risk of increased antibacterial resistance. The same cannot be said of the West-ward product. Although the risk that West-ward's product might result in antibiotic serum concentrations of doxycycline cannot be evaluated from the West-ward study data, it is known that the rate and extent of doxycycline absorption from Periostat are higher for women than for men. Because the West-ward study systematically excluded women from the BE analysis, and compared two capsules instead of one, the possibility that the study failed to reveal inequivalence of serum concentrations at the high end cannot be discounted.

C. Enviromental Impact

The action requested qualifies for categorical exclusion from the requirement of issuance of an environmental assessment under 21 C.F.R. § 25.31(a). CollaGenex does not believe that any environmental impact will result from the granting of this petition.

D. Economic Impact

In accordance with 21 C.F.R. § 10.30(b), CollaGenex will provide data concerning the economic impact of the action sought if requested by the Commissioner.

22. González Declaration ¶ 13 (citing approved package inserts for Periostat capsules and tablets).

E. Certification

CollaGenex certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to CollaGenex that are unfavorable to the petition.

Aug. 15 2003
Date

Christopher V. Powala / jeb
Christopher V. Powala
Senior Director, Drug Development
and Regulatory Affairs
CollaGenex Pharmaceuticals, Inc.
41 University Drive
Newtown, PA 18940
(215) 579-7388

Of Counsel:

Nancy L. Buc
Jane E. Baluss
Buc & Beardsley
919 Eighteenth Street, N.W.
Suite 600
Washington, DC 20006
(202) 736-3600

DECLARATION OF MARIO A. GONZÁLEZ, PH.D.

1. I am President and C.E.O. of GloboMax Américas LLC, a consulting firm that provides expert advice to the pharmaceutical industry on pharmacokinetics research and pharmaceutical product development. I hold a Ph.D. in Pharmacokinetics from the University of California, San Francisco, and M.S. and B.S. degrees in Pharmacy from the University of Texas, Austin. I have more than 28 years' experience in academic and industrial pharmacokinetic research, including extensive experience in the design, interpretation, and review of studies designed to evaluate the bioequivalence of drug products. My qualifications and experience are detailed in my curriculum vita, attached as Exhibit A.

2. I have been retained by CollaGenex Pharmaceuticals ("CollaGenex") to review a study report entitled "Comparative, Randomized, Single-Dose, 2-Way Crossover Relative Bioavailability Study of West-ward and CollaGenex (Periostat) 20 Mg Doxycycline Hyclate Capsules in Healthy Adult Males Under Fasting Conditions Following Administration of a 40-Mg Dose" (Report No. 010787, July 18, 2001) (referred to in this declaration as the "West-ward study"), which was prepared for West-ward Pharmaceutical Corp. by MDS Pharma Services. A copy of the study report is attached as Exhibit B. I also have reviewed approved package inserts and portions of FDA's new drug application ("NDA") approval packages for Periostat® 20 mg capsules and tablets relating to FDA's review of pharmacokinetic and microbiological data, including an in vivo bioequivalence study conducted by CollaGenex. Those materials can be viewed on FDA's website at the following locations, and are referred to in this declaration using the description shown in parentheses following each citation: http://www.fda.gov/cder/foi/label/1998/50744lbl.pdf ("Periostat Capsule Package Insert"); http://www.fda.gov/cder/foi/nda/98/50744.htm ("Periostat Capsule Approval Package"); http://www.fda.gov/cder/foi/nda/2001/50-783_Periostat_prntlbl.pdf ("Periostat Tablet Package Insert"); http://www.fda.gov/cder/foi/nda/2001/50-

783_periostat.htm ("Periostat Tablet Approval Package");
http://www.fda.gov/cder/foi/nda/2001/50-783_Periostat_biopharmr.pdf ("CollaGenex BE study").

3. The objective of the West-ward study was to compare the single-dose relative bioavailability (i.e., bioequivalence) of West-ward and CollaGenex (Periostat) 20 mg doxycylate hyclate capsules. Based on statistical analysis of pharmacokinetic data from the West-ward study, the investigators concluded that "the West-ward and CollaGenex (Periostat) 20 mg doxycycline hyclate capsules are bioequivalent under fasting conditions following administration of a 40 mg dose." West-ward Study at 5. This determination was stated to be based on the statistical criterion for demonstrating bioequivalence that is routinely applied to orally-administered, immediate-release products by the FDA, which requires that the ratios of least-squares means and 90% confidence intervals derived from the log-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{inf}, and C_{max} for the test product be within 80-125% of the corresponding reference product values.

4. 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 the study in favor of incorrectly finding bioequivalence where it does not in fact exist.

5. The West-ward study design systematically excluded at least two important sources of variability in the pharmacokinetic data. First, the study inappropriately compared two West-ward doxycycline hyclate capsules to two Periostat capsules, rather than comparing a single 20 mg West-ward capsule to a single Periostat 20 mg capsule. Second, the study population failed to include any female subjects. In my opinion, each of those

factors would tend to artificially reduce the variability in observed pharmacokinetic responses and thus bias the study toward a finding of bioequivalence. Together, they would reduce the variability even more. As a result, the results and conclusions of the West-ward study do not and could not show that West-ward's product is bioequivalent to Periostat. The basis for that opinion is set out in the paragraphs that follow.

6. Periostat capsules were approved for marketing in a single, 20-mg unit strength, to be taken twice daily at 12-hour intervals. Periostat Capsule Package Insert. The FDA-designated reference strength for purposes of bioequivalence testing of would-be generic versions of Periostat is also 20 mg. FDA, Approved Drug Products with Therapeutic Equivalence Evaluation ("Orange Book"), 23rd Annual Edition, http://www.fda.gov/cder/ob/default.htm.

7. When CollaGenex decided to market Periostat as a 20 mg tablet instead of a 20 mg capsule, it was required to conduct a bioequivalence study comparing Periostat 20 mg capsules and tablets in order to obtain FDA marketing approval for its 20 mg tablet dosage form. The study design was specifically reviewed by FDA experts and found to be appropriate to evaluate bioequivalence between the 20 mg capsules and tablets. The dosage used in the CollaGenexs BE study was a single 20 mg unit (capsule or tablet). CollaGenex BE study.

8. The single-unit dosage used in CollaGenex's BE study was consistent with FDA's "Guidance for Industry [on] Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations" (referred to in this declaration as the "BE Guidance"), http://www.fda.gov/cder/guidance/4964dft.pdf. The BE Guidance represents FDA's current thinking about the topics it addresses as well as the accepted current practice among pharmaceutical research experts. The guidance recommends that a BE study be conducted using the strength(s) specified in the Orange Book, with the highest

marketed strength administered as a single unit dose, unless a multiple-unit dose is necessary for some reason. See BE Guidance at pages 13 and 22.

9. It is scientifically appropriate to avoid multiple-unit dosing whenever feasible in bioequivalence studies because both inter- and intra-subject variability is diminished when two or more units are administered instead of one, making it easier to show bioequivalence. Although multiple-unit doses are sometimes necessary (e.g., when it is technically infeasible to analyze the serum concentration produced by a single-unit dose, or when the dose recommended for testing is a multiple of the highest approved strength), I am aware of no scientific or technical reason that would either compel or justify the two-capsule dose used in the West-ward study. In my opinion, the appropriate dosage for a BE study using Periostat as the reference product would be a single-capsule, 20 mg dose and not the double-capsule dose used in the West-ward study.

10. A second major weakness in the West-ward BE study design was that the study population consisted exclusively of male volunteers. Because many drugs exhibit gender differences in pharmacokinetics, it has become standard practice to include both women and men in bioequivalence studies as well as other kinds of clinical trials. FDA guidance specifically recommends including similar proportions of both male and female subjects in BE studies of drugs such as Periostat that are intended for use in both sexes. BE Guidance at 8. The CollaGenex BE study appropriately included both male and female subjects.

11. It is particularly important to include both males and females in BE studies involving Periostat because doxycycline hyclate is known to exhibit different pharmacokinetics in women than in men. Data submitted for approval of Periostat capsules indicated that C_{max} was approximately 1.7-fold higher in women than in men when studied under fasting conditions (as used in the West-ward study). Periostat Capsule Package Insert, "Clinical Pharmacology . . . Special Populations . . Gender." In a subsequent study

comparing Periostat capsules and tablets, women again were found to have a higher rate (and also extent) of absorption under both fasting and fed conditions. Periostat Tablet Package Insert, "Clinical Pharmacology . . . Special Populations . . . Gender." (Note that although the approved tablet labeling goes on to state that the gender difference is thought to be due to weight differences, that observation has no relevance for purposes of this discussion). The West-ward study therefore fails to take into account an important and known source of variability in pharmacokinetic responses, further biasing the study in favor of incorrectly finding bioequivalence.

12. The likelihood that West-ward's study was biased in favor of showing bioequivalence is shown by a comparison of the coefficient of variance (CV) in C_{max} values for Periostat capsules reported in the West-ward study with the corresponding CV for Periostat capsules in the CollaGenex BE study, which was appropriately conducted using both a single capsule or tablet and a mixed-gender study population. The CV is a quantitative measure of the variability in a set of individual pharmacokinetic measures, based on the relationship of the standard deviation to the mean of a pharmacokinetic parameter. It is particularly useful for cross-study comparisons where, as here, the studies being compared were performed on the same drug product (i.e., Periostat capsules). The CV for C_{max} from Periostat capsules in the West-ward study was 19.8%. By contrast, the corresponding CV for C_{max} from Periostat capsules in the CollaGenex study was meaningfully higher, i.e., more variable, at 32.6%. Similarly, for the parameter AUC_{inf}, the CV for the West-ward study was 20.2% for the Periostat capsule, but in the CollaGenex study, the CV was 32.3%. These results strongly suggest that the variability in C_{max} and AUC_{inf} of Periostat in a study including women and administering the drug as a single dose 20 mg capsule was artificially reduced in the West-ward study, where there were no women and the drug was administered as two 20 mg capsules. The resulting finding of bioequivalence is therefore highly suspect.

13. The potential consequences of falsely concluding that two drug products are bioequivalent are especially troubling when the drug at issue has a narrow therapeutic range, i.e., when even a small deviation from the target blood concentration can result in reduced effectiveness, increased risk, or both. Periostat is not an antibiotic, and has been shown to maintain blood concentrations of doxycycline that do not reach the serum concentration associated with antibiotic action. Periostat Tablet and Capsule Package Inserts, "Clinical Pharmacology . . . Microbiology." As a result, patients who use Periostat are not subjected to antibiotic exposure and the attendant risk of increased antibacterial resistance. The same cannot be said of the West-ward product. Although the risk that West-ward's product might result in antibiotic serum concentrations of doxycycline cannot be evaluated from the West-ward study data, it is known that the rate and extent of doxycycline absorption from Periostat are higher for women than for men. Because the West-ward study systematically excluded women from the BE analysis, and compared two capsules instead of one, the possibility that the study failed to reveal inequivalence of serum concentrations at the high end cannot be discounted.

July 10, 2003
Date

Mario A. González, Ph.D.