COLLAGENEX
pharmaceuticals

July 14, 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 Mutual Pharmaceutical Company, Inc. ("Mutual") for doxycycline hyclate tablets in which bioequivalence of the Mutual product to CollaGenex' Periostat® (doxycycline hyclate tablets 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 "Mutual study." The Mutual study artificially and inappropriately excludes a significant source 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 Mutual product is bioequivalent to Periostat, the reference listed drug, and FDA must therefore refuse to approve Mutual's ANDA. § 505(j)(4)(F) and 21 C.F.R. § 314.127(a)(6)(i).[1]

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

1. FDA is also barred from approving Mutual's ANDA for the reasons stated in CollaGenex's July 10, 2002 Citizen Petition and Petition for Stay of Action, available at http://www.fda.gov/ohrms/dockets/dailys/02/Jul02/071102/02p-312_cp00001_vol1.pdf ("CollaGenex Citizen Petition"). 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 and the accompanying expert declaration.

2003P-0315 CP1

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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]

Mutual submitted ANDA 65-134 seeking approval to market doxycycline hyclate tablets with Periostat 20 mg tablets as the reference listed drug.[7] CollaGenex has obtained from the New Jersey Drug Utilization Review Council the Mutual study which purports to show bioequivalence of the Mutual doxycycline hyclate tablets to Periostat tablets.

As explained in the González Declaration, a fundamental precept observed by experts in the design and review of bioequivalence studies is that a study should not artificially exclude

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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, available at http://www.fda.gov/cder/news/cebackground.htm (May 5, 1997).

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

5. 21 CFR § 320.24(a).

6. Id. at (b).

7. Mutual's Unopposed Motion for Scheduling Order and Memorandum of Points and Authorities in Support Thereof, CollaGenex Pharmaceuticals, Inc. v. Tommy G. Thompson, Secretary of Health and Human Services, et al. and Mutual Pharmaceutical Company, Inc. (D.D.C. 2003) (No. 1:03-cv-01405-RMC).

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 Mutual study design systematically reduced the variability in observed pharmacokinetic responses by excluding female subjects, thus biasing the study toward a finding of bioequivalence. As a result, the methods employed by Mutual were not "capable of establishing bioequivalence" and therefore the study results cannot be relied upon to meet Mutual's burden of proving that its product is bioequivalent to Periostat.[9]

Because many drugs exhibit gender differences in phamacokinetics, 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 BE 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 Consideration" (the "BE Guidance"),[10] and thus reflected both FDA's current thinking about the proper conduct of BE studies and the accepted current practice among pharmaceutical research experts.[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, with women having a higher extent of absorption (Cmax) under both fasted and fed conditions.[12] The Mutual study therefore fails to take into account an important and known source of variability in pharmacokinetic responses, thus biasing the study in favor of incorrectly finding bioqeuivalence.

As explained by Dr. González, the likelihood that Mutual'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 tablets reported in the Mutual study with the corresponding CV for Periostat tablets in the CollaGenex BE study, which was appropriately conducted using a

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8. González Declaration ¶ 4.

9. Id. ¶ 5.

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

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

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

mixed-gender study population.[13] 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 tablets). The CV for C_{max} from Periostat tablets in the Mutual study was 26.65%. By contrast, the corresponding CV for C_{max} from Periostat tablets in the CollaGenex study was higher, i.e., more variable, at 28.0%. Similarly, for the parameter AUC_{inf}, the CV for the Mutual study was 25.56%, but in the CollaGenex study, the CV was 37.1%. These results strongly suggest that the variability in C_{max} and AUC_{inf} of Periostat in a study including women was artificially reduced in the male-only Mutual study. The resulting finding of bioequivalence is therefore suspect.[14]

Conclusion

In order to obtain an ANDA for its doxycycline hyclate 20 mg tablets, Mutual 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 § 320.24. For the reasons discussed above, the Mutual study design was not capable of showing bioequivalence due to its all-male study population, which would make it more likely to find bioequivalence when the products are not, in fact, bioequivalent. The results of that or any similarly designed study therefore cannot satisfy Mutual's evidentiary burden, and FDA must therefore refuse to approve Mutual'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.[15] 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 Mutual product. Although the risk that Mutual's product might result in antibiotic serum concentrations of doxycycline cannot be evaluated from the Mutual study data, it is known that the rate and extent of doxycycline absorption from Periostat are higher for women than for men. Because the Mutual 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.[16]

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13. Id. ¶ 9.

14. Id.

15. González Declaration ¶ 10 (citing Periostat Capsule and Tablet Package Inserts).

16. Id.

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 form 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.

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.

July 14, 2003
Date

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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 "A relative bioavailability study of 20 mg doxycycline hyclate tablets under fasting conditions," which was prepared by PRACS Institute, Ltd. for Mutual Pharmaceutical Company, Inc. (referred to in this declaration as the "Mutual study"). 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 Mutual study was to compare the single-dose relative bioavailability (i.e., bioequivalence) of Mutual and CollaGenex (Periostat) 20 mg doxycycline hyclate tablets. Based on statistical analysis of pharmacokinetic data from the Mutual study, the investigators concluded that the study results indicate bioequivalence between the test and reference products under fasting conditions. Mutual study at Statistics-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 $AUC_{0\text{-}t}$, 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. In my opinion, the Mutual study design systematically reduced the variability in observed pharmacokinetic responses by excluding female subjects, thus biasing the study toward a finding of bioequivalence. As a result, the results and conclusions of the Mutual study do not and could not show that Mutual's product is bioequivalent to Periostat. The basis for that opinion is set out in the paragraphs that follow.

6. Periostat was originally approved for marketing in a capsule dosage form containing 20 mg doxycycline hyclate. Periostat Capsule Package Insert. 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. Consistent with the population of adult periodontitis patients, the CollaGenex BE study was conducted in a population of both male and female healthy volunteers. CollaGenex BE study.

7. Because many drugs exhibit gender differences in pharmacokinetics, 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. http://www.fda.gov/cder/guidance/4964dft.pdf at 7. The guidance represents FDA's current thinking on this point as well as current practice by research experts.

8. 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 Mutual 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 Mutual study therefore fails to take into account an important and known source of variability in pharmacokinetic responses, thus biasing the study in favor of incorrectly finding bioequivalence.

9. The likelihood that Mutual'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 tablets reported in the Mutual study with the corresponding CV for Periostat tablets in the CollaGenex BE study, which was appropriately conducted using 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 tablets). The CV for C_{max} from Periostat tablets in the Mutual study was 26.65%. By contrast, the corresponding CV for C_{max} from Periostat tablets in the CollaGenex study was higher, i.e., more variable, at 27.9%. Similarly, for the parameter AUC_{inf}, the CV for the Mutual study was 25.56%, but in the CollaGenex study, the CV was 37.1%. These results strongly suggest that the variability in C_{max} and AUC_{inf} of Periostat in a study including women was artificially reduced in the male-only Mutual study. The resulting finding of bioequivalence is therefore suspect.

10. 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 Mutual product. Although the risk that Mutual's product might result in antibiotic serum concentrations of doxycycline cannot be evaluated from the Mutual study

data, it is known that the rate and extent of doxycycline absorption from Periostat are higher for women than for men. Because the Mutual study systematically excluded women from the BE analysis, 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.