COLLAGENEX
pharmaceuticals

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July 18, 2003

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

PETITION FOR STAY OF ACTION

CollaGenex Pharmacetucials, Inc. ("CollaGenex") submits this petition under 21 C.F.R. §10.35 to request that the Commissioner of Food and Drugs stay administrative action on the following matter.

A. Decision Involved

FDA has before it an abbreviated new drug application (ANDA No. 65-134) submitted by Mutual Pharmaceutical Company ("Mutual") for a generic version of CollaGenex's Periostat® (doxycycline hyclate 20 mg) tablets.[1] In a Citizen Petition filed on July 14, 2003, CollaGenex asked the Commissioner to refuse to approve any such ANDA in which the bioequivalence of the Mutual product to Periostat is purportedly demonstrated by the bioequivalence study that is attached to that petition ("the Mutual study"), on grounds that the study design is incapable of establishing bioequivalence as required by section 505(j) of the Food, Drug, and Cosmetic Act and FDA's ANDA regulations. A copy of the July 14, 2003 Citizen Petition (referred to herein as the "BE Petition") is attached and incorporated by reference in this stay petition.[2]

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1. 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).

2. The BE Petition as submitted contained errors which were corrected by submission of substitute pages by telefax on July 15, 2003, followed by redelivery of the entire petition with corrected pages on July 16, 2003. The attached copy of the petition incorporates those corrections. With the exception of the attached materials, all documents relied on in this petition are routinely available on FDA's website (www.fda.gov) and accordingly are cited, but not attached, pursuant to 21 CFR § 10.20(c).

2003P-0315

PSA 1

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B. Action Requested

By this petition, CollaGenex requests that the Commissioner stay action on any ANDA addressed by the attached BE Petition until the agency has responded to the BE Petition.

C. Statement of Grounds

Mandatory Stay

Under 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.

As demonstrated below, all these criteria are met here.

Without a stay, CollaGenex will suffer irreparable injury. As detailed in the attached Declaration of Brian W. Gallagher, Ph.D., CollaGenex's President and Chief Executive Officer (the "Gallagher Declaration"), CollaGenex is a small company whose only significant revenues come from sales of Periostat.[3] If FDA were to approve an ANDA for Mutual's product, CollaGenex would face a precipitous and unjustified decline in market share and revenues that could significantly undermine the company's future viability as well as its immediate financial position. CollaGenex has invested approximately $70,000,000 to develop and introduce Periostat to the marketplace, which it has yet to recoup from sales of Periostat.[4] CollaGenex is at a critical point in its development; it is still building the market for Periostat, and it cannot yet finance its research and development program from sources other than Periostat's revenues.[5] In addition to causing substantial losses to current shareholders, severely diminished revenues from Periostat could require CollaGenex to substantially reduce its skilled staff and abandon ongoing research and development efforts, which in turn would cripple the company's ability to attract investors and talented staff in the future.[6] The impact

3. Gallagher Declaration ¶ 3; id. ¶ 8.

4. See id. ¶¶ 4, 5, and 11.

5. Id. ¶ 9.

6. Id. ¶¶ 11-13.

of a loss of revenues on CollaGenex will be worse than for most pharmaceutical companies because CollaGenex is small compared to other companies in the industry, and has fewer products.[7]

There is no mechanism by which sales and market share lost to generic products can be recovered. Even if they could, CollaGenex would have no way to recoup its losses from the government, which has no financial liability for erroneous decisions in these circumstances. Like the loss to plaintiffs in Bracco Diagnostics, Inc v. Shalala, 963 F. Supp. 20, 29 (D.D.C. 1997), the loss to CollaGenex in the absence of a stay, "[w]hile...'admittedly economic,'" would be without "'adequate compensatory or other corrective relief' that can be provided at a later date, tipping the balance in favor of [the]...relief."

CollaGenex's case is not frivolous and is being pursued in good faith. The case presented in CollaGenex's BE petition is far from frivolous; it is very strong. 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 (NDA). The burden of showing bioequivalence rests with the applicant, and to meet its burden the applicant must conduct testing using a method that is scientifically "capable of establishing bioequivalence . . . for the product being tested." 21 CFR § 320.24(a). As shown in the BE Petition, the study design was systematically biased and therefore scientifically incapable of establishing bioequivalence.

Collagenex's case also is being pursued in good faith. Because pending ANDA applications and their contents are held confidential by FDA, CollaGenex learned of Mutual's ANDA only when it learned that Mutual had submitted an application for its product to be listed as a substitute for Periostat in the New Jersey generic drug formulary.[8] CollaGenex became aware of the New Jersey application in mid-May, 2003, whereupon it promptly obtained the Mutual study, conducted its own expert evaluation, and prepared and filed the BE Petition.

Sound public policy grounds support the stay. The NDA and ANDA processes are intended to simultaneously encourage the costly research and development efforts that lead to the discovery of therapeutically important new drugs and 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

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7. Id. ¶ 15. Mutual, by contrast, is a large national supplier of generic pharmaceuticals that holds approvals for over 45 prescription drugs and distributes one of the most extensive product lines in the generic industry. Id.

8. New Jersey Drug Utilization Review Council, Drug Product Registration Application, filed March 21, 2003 by Mutual Pharmaceutical Company, Inc.

alone provides the necessary assurance that a generic copy will be as safe and effective as the pioneer drug whose 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. In effect, the BE Petition asks FDA to subject the design and results of Mutual's bioequivalence study 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 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 Mutual's 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 Mutual's product as bioequivalent to Periostat and the resulting irreparable injury to CollaGenex demand that FDA not approve Mutual's ANDA without carefully considering and responding to the BE Petition. Accordingly, if FDA will not grant a mandatory stay, it should grant a discretionary stay.

Declaration of Brian M. Gallagher, Ph.D.

1. I am the Chairman, President and Chief Executive Officer of CollaGenex Pharmaceuticals, Inc. ("CollaGenex"). As Chairman, President and Chief Executive Officer, I oversee the activities of CollaGenex including the commercial and scientific development of its products. I am familiar with the marketing of drug products in general, with the marketing and prospects for CollaGenex's product Periostat® (doxycycline hyclate 20 mg), and with the FDA regulatory process. This declaration is based upon my personal knowledge and the records maintained by CollaGenex in the course of its regular business activity.

2. I have a Bachelor of Science degree from St. Louis University and a Doctor of Philosophy from St. Johns University. I joined CollaGenex in April 1994 as President and Chief Executive Officer and was elected to the Board of Directors in November 1994. From 1988 until I joined CollaGenex, I was employed by Bristol-Myers Squibb Company and its predecessor, Squibb Corporation, in various executive positions, including strategic planning, worldwide product and business development and marketing. I was President of Squibb Diagnostics, the in vivo imaging pharmaceutical division where I was responsible for drug development, including submitting New Drug Applications to the Food and Drug Administration ("FDA") and other regulatory authorities worldwide. Prior to that, I served for ten years with E.I. DuPont de Nemours & Co. in a variety of pharmaceutical research, development, marketing, and business management positions.

3. CollaGenex is a corporation organized under the laws of the state of Delaware and having its principal place of business and corporate offices at 41 University Drive, Newtown, Pennsylvania. CollaGenex is a small pharmaceutical company that employs approximately 150 people. The company focuses on providing innovative therapies to treat unmet medical needs, primarily in the dental and dermatological markets. Its flagship and primary product is Periostat, a systemic, orally administered, prescription drug consisting of a 20 mg dose of doxycycline hyclate that helps treat adult periodontitis by inhibiting collagenase and other enzymes that directly cause periodontal breakdown. CollaGenex is conducting clinical studies to evaluate whether Periostat also is effective in treating other inflammatory diseases, notably acne and rosacea.

4. CollaGenex invested approximately $22 million and the time and effort of numerous scientists, clinicians, manufacturing experts, regulatory affairs experts, lawyers, and others in the risky but ultimately successful effort to obtain FDA approval for Periostat.

5. Because CollaGenex, Periostat, and the concept of a systemic anti-collagenase pharmaceutical product to treat periodontitis were all new to dentists, periodontists and other dental professionals, no market existed for Periostat. CollaGenex has conducted extensive market research and used a variety of techniques to develop such a market, at a cost of more than $87.5 million in direct sales and marketing expenses through 2002. CollaGenex has yet to recoup those costs.

6. Mutual Pharmaceutical Company ("Mutual"), based in Philadelphia, Pennsylvania, is a national supplier of generic pharmaceuticals and distributes one of the most extensive product lines in the generic industry. See http://urlmutual.com (last visited July 14, 2003).

Mutual submitted ANDA 65-134 to FDA seeking approval to market doxycycline hyclate tablets with Periostat 20 mg tablets as the reference listed drug. 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).

7. In mid-May, 2003, CollaGenex learned that Mutual has requested that its generic copy of Periostat be added to the New Jersey generic drug formulary. CollaGenex promptly requested a copy of the publicly-available application materials, including a copy of a bioequivalence study performed by Mutual (the "Mutual BE study"). Following expert review of the Mutual study, CollaGenex filed a citizen petition on July 14, 2003 (referred to in this declaration as the "BE petition") asking FDA not to approve an ANDA in which the bioequivalence of the Mutual product to Periostat is purportedly demonstrated by the Mutual study. The BE petition requests that FDA not approve such an ANDA because the study design is biased and therefore scientifically incapable of demonstrating bioequivalence as required by the Food, Drug, and Cosmetic Act and FDA regulations.

8. For FDA to approve an ANDA would cause immediate and irreparable injury to CollaGenex. CollaGenex is a small company that can ill afford to withstand a loss of revenue. CollaGenex's only significant revenue comes from sales of Periostat. During 1999, 2000, 2001, and 2002, Periostat accounted for approximately 95%, 84%, 87%, and 82%, respectively, of the total revenues of CollaGenex. Since the founding of CollaGenex in 1992,

only the last two quarters of 2002 yielded a net positive income for CollaGenex, although CollaGenex still experienced a net loss for 2002.

9. CollaGenex depends on the revenues from Periostat for its continued viability. CollaGenex is at a critical point in its development; it is still building the market for Periostat, and it cannot yet finance its research and development program from sources other than Periostat's revenues. CollaGenex needs to be allowed to recoup its investment in Periostat. At this point, every penny of revenue is required to make the company secure, and losing it would irreparably injure CollaGenex.

10. Once a generic drug is introduced in commerce, it quickly gains a large share of the market due to substantially lower retail costs that reflect lower research and development costs and lower costs for FDA approval. I recently commissioned a study of how quickly generic drugs erode the market share of the pioneer drug. My staff asked IMS Health to select pioneer drugs that experienced their first generic competition in the relatively recent past. IMS Health is a leading supplier of information to the pharmaceutical industry, government, and others about sales of pharmaceuticals. See http://www.imshealth.com/ims/portal/front. The data it provides are generally relied upon by persons in the pharmaceutical industry. IMS Health provided tabulations of market information on generic penetration of 17 drugs. My staff took the tabulations provided by IMS Health and aggregated them to calculate average rates of generic penetration at particular time points following introduction of these generic drugs. The data showed that, three months post-launch, average market penetration for the generic was 43%, 61% after 6 months, 69% after 9 months and 73% after 12 months. A loss

of market share anywhere in the range of this magnitude would erode CollaGenex/s financial base, cause extreme hardship, and threaten the company's viability.

11. Approval by FDA of Mutual's ANDA and the resulting market introduction of Mutual's product would damage CollaGenex beyond a simple diminution in revenue. CollaGenex has been able to enter and grow in this competitive pharmaceutical market because of its successful development of an innovative product, Periostat, and its ability to develop a market for that drug product. CollaGenex has invested approximately $70,000,000 to develop and introduce Periostat to the marketplace, which it has yet to recoup from sales of Periostat. CollaGenex will continue to incur significant expenses with respect to the sale and marketing of Periostat (or risk even greater loss of revenue if it does not). Severely diminishing the revenues from the sales of Periostat would force CollaGenex to dramatically reduce its staff and its marketing efforts. Highly skilled employees, having gained expertise by their work in the technology, would be laid off. CollaGenex employs over 150 people in marketing, manufacturing and research and development, all of whom are responsible for, and reliant on the continued success of Periostat for their employment.

12. Severely diminishing revenues also would force CollaGenex to abandon development work underway to identify new and clinically valuable applications for the Periostat technology, including current work on treating acne and rosacea, and plans to explore the technology's applications in other uses. Drug companies are evaluated as much on their "pipeline" of new products as on their marketed products. Without a "pipeline," the company would have difficulty recruiting talented staff and convincing investors that CollaGenex has a future.

13. CollaGenex would also become a less attractive candidate for investors as its revenue and product development activities were scaled back. CollaGenex's stock price would drop precipitously and immediately, as the market factored in the anticipated reduction in revenues and reduced potential for new product development. Current shareholders would suffer losses of many tens of millions of dollars in market value and the company would suffer irreparable damages.

14. CollaGenex currently enjoys a reputation as an up-and-coming company – a reputation earned by many years of hard work, millions of dollars of investment, and the goodwill and recognition acquired as the sole marketer of a breakthrough drug like Periostat. Losing that reputation and recognition as the sole developer and marketer of an innovative drug product based on an innovative technology would severely harm CollaGenex.

15. The impact of a loss of revenues on CollaGenex will be worse than for most other pharmaceutical companies because CollaGenex is small compared to other companies in the industry, and has fewer products. Mutual, by contrast, is a large national supplier of generic pharmaceuticals that holds approvals for over 45 prescription drugs and distributes one of the most extensive product lines in the generic industry.

16. The kind of injury that CollaGenex would suffer – the loss of its prospects for years if not forever – cannot be compensated financially. Even if it could, CollaGenex would have no way to recoup its losses from the government, which has no financial liability for erroneous decisions in these circumstances.

7/16/03
Date

Brian M. Gallagher, Ph.D.

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July 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

Re: Citizen Petition Filed By CollaGenex Pharmaceuticals, Inc. on July 14, 2003

The above-referenced Citizen Petition filed on July 14, 2003 contained errors on pages 1 and 4. I am attaching corrected pages and would appreciate your substituting them for the original pages in the copies of the Citizen Petition in the docket and on the agency's website. I will also deliver tomorrow four copies of the Citizen Petition with the corrected pages.

Thank you.

Sincerely,

Nancy L. Buc
Counsel to CollaGenex
Pharmaceuticals, Inc.

COLLAGENEX
pharmaceuticals

July 14, 2003

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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. 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.

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, 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

Christopher V. Powala /gb
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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-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.

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Date

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