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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.

2003P-0315

CR 1

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.

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

Of Counsel:

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Jane E. Baluss
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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.

July 10, 2003
Date

Mario A. González, Ph.D.

EXHIBIT A

MARIO A. GONZÁLEZ, Ph.D.

Professional Title: President & CEO, GloboMax Américas, specializing in product development and pharmacokinetics research & a GloboMax Service Group company

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17140 Arvida Parkway, Suite 3
Weston, FL 33326

Telephone: (954) 349-9995
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Education:

B.S. Pharmacy with Honors,
University of Texas, Austin, 1964
M.S. Pharmacy,
University of Texas, Austin, 1967
Ph.D. Pharmacokinetics,
University of California, San Francisco, 1975

Positions Held:

Pharmacist-Tovar Pharmacy
Austin, Texas, 1965-1966
Pharmacist-Garcia Pharmacy
Alice, Texas, 1966-1967
Trainee on NIH Training Grant
University of California, San Francisco, 1968-1974
Assistant Professor of Biopharmaceutics
School of Pharmacy
University of Colorado, Boulder, 1974-1977
Affiliate Assistant Professor of Pharmacology
School of Veterinary Medicine
Colorado State University, Fort Collins, 1976-1977
Summer Visiting Professor, Abbott Laboratories
N. Chicago, Illinois, 5/77-8/77
Assistant Professor of Pharmaceutics
School of Pharmacy and Pharmacal Sciences
Purdue University
West Lafayette, Indiana 1977-1980
Manager, Clinical Pharmacology
Key Pharmaceuticals, Inc.
Miami, Florida, 1980-1983
Director, Biopharmaceutics and Pharmacokinetics
Key Pharmaceuticals, Inc.
Miami, Florida, 1983-1986
Director, Biopharmaceutics and Pharmacokinetics
Schering-Plough Research,
Miami, Florida, 7/86-4/91
President, P'Kinetics, Inc.
Pembroke Pines, Florida, 4/91-11/99
President, GloboMax Américas LLC
Pembroke Pines, Florida, 11/99-present

Membership in Scientific and Professional Societies:

American Association of Pharmaceutical Scientists
American Association of Colleges of Pharmacy
Controlled Release Society
Rho Chi
Sigma XI

Symposia and Invited Lectures:

1. Lecturer at 10th Annual Meeting of the American Society of Consultant Pharmacists in Dallas. Topic: Pharmacokinetic Considerations in Geriatrics, November, 1979.

2. Controlled-Release Delivery Systems for Theophylline: lecture at Industrial Pharmaceutical R & D Symposium, Oral Controlled Drug Administrations, Rutgers University, January, 1983.

3. Speaker at International Industrial Pharmacy Meeting (Lakeway Meeting), Topic: "Sustained-Release Theophylline Formulations" Austin, Texas, February, 1983.

4. Invited lecture entitled Pharmacokinetics and Its Utilization in a Pharmaceutical Dosage Regimen. Presented at the Miami Meeting of the Engineering in Medicine and Biology Society, June, 1983.

5. Speaker at 9th Annual Spring Meeting of AOAC (Association of Official Analytical Chemists). Topic: Problem Solving in Dosage from Design Using *In Vitro-In Vivo* Correlation, Philadelphia, April, 1984.

6. The Use of Pharmacokinetics in the Evaluation of Controlled-Release Delivery Systems: lecture at 12th International Symposium on Controlled Release of Bioactive Materials, Geneva, Switzerland, July, 1985.

7. Use of *In Vitro-In Vivo* Correlations in Dosage Form Design of Sustained-Release Theophylline: lecture at Symposium during Congress of the European Society of Pneumology, Milan, Italy, September, 1985.

8. Lecturer at Arden House Conference on Industrial Pharmacy. Topic of three-hour lecture: Evaluation of Oral Controlled-Release Dosage Forms, January, 1986.

9. Coordinator of Educational Session at National AphA Meeting in Atlanta, Title of Symposium: Transdermal Drug Delivery: Problems and Perspectives, March, 1988.

10. Seminar entitled Biopharmaceutic/Pharmacokinetic Considerations for Controlled-Release Dosage Forms. Presented at Nortec Oral Controlled-Release Dosage Forms Symposium, March, 1988.

11. Lecture entitled Controversies in the Interpretation of Transdermal Nitroglycerin Pharmacokinetics, presented at the Symposium on Transdermal Nitroglycerin Therapy in Ischemic Heart Disease, Newport Beach, June, 1988.

12. PDD Symposium Chairman-Physicochemical Means of Improving Skin Permeation, AAPS, Orlando Meeting, November, 1988.

13. Panel member at AAPS/FDA Workshop on *In Vitro* and *In Vivo* Testing and Correlation for Oral Controlled/Modified-Release Dosage Forms. Presentation entitled Bioequivalence Considerations: Fluid Content and Timing of Meals, Washington, D.C., December, 1988.

14. Lecture on Pharmacokinetic Evaluation of Transdermal Drug Delivery, Seminar at Bureau of Drug Research, Health Protection Branch, Ottawa, Ontario, March, 1989.

15. Seminar entitled Biopharmaceutic/Pharmacokinetic Considerations for Controlled-Release Dosage Forms. Presented at Nortec Oral Controlled-Release Dosage Forms Symposium, April, 1989.

16. Panel member at Bio International '89: Session title: Food Effects in Bioequivalency Evaluations, Toronto, Ontario, October, 1989.

17. PPDM Symposium Chairman: Trials and Tribulations with Pharmacokinetic Studies, AAPS, Atlanta Meeting, October, 1989.

18. Co-Chairman of Transdermal Focus Podium, AAPS, Las Vegas Meeting, November, 1990.

19. Speaker at 20th International Conference on Chronobiology; Satellite Conference on Chronopharmacology and Chronotherapy. Topic: Chronopharmacology of Theophylline, Jerusalem, Israel, June, 1991.

20. Update Lecturer, Pharmacy World Congress. Topic: Trends in Transdermal Drug Delivery, Washington, D.C., September, 1991.

21. PDD/PPDM Symposium Chairman: Pharmacokinetics and Pharmacodynamics of Transdermal Delivery Systems, AAPS, Washington, D.C. Meeting, November, 1991.

22. Speaker at "Nitrates for the Nineties". Topic: Pharmacokinetics of Transdermal Nitroglycerin, Gleneagles, Scotland, December, 1991.

23. Speaker at International Conference on Oral Controlled-Release Dosage Forms. Topic: Bioevaluation of Oral Sustained-Release Dosage Forms. Berlin, Germany, April, 1992.

24. Speaker at AAPS/FDA/USP Workshop on the Scale-Up of Oral Solid Extended Release Formulations. Topic: *In Vivo/In Vitro* Correlations: Mathematical Approach, Arlington, VA, September, 1992.

25. Speaker at Congreso Internacional Quimico Farmaceutico, Santiago, Chile, August, 1992.

Topics:
Transdermal Drug Delivery Systems. Design and Evaluation
Pharmacokinetic Evaluation of Transdermal Drug Delivery
Trends in Transdermal Drug Delivery

26. Speaker at 32nd Annual Eastern Pharmaceutical Technology Meeting (EPTM). Topic: Design of Controlled Release Formulations Through *In Vitro/In Vivo* Correlations. Princeton, New Jersey, October, 1992.

27. Co-Chair Drug/Polymer Interactions in Pharmaceutical Formulations, AIChE Annual Meeting, November, 1992.

28. Speaker at Technomic Conference: Oral Controlled-Release Dosage Forms- Research and Development, Evaluation, Scale-Up, Manufacture, Approval and Marketing. Topic: Bioevaluation of Oral Controlled-Release Formulations. Zurich, Switzerland, June, 1993.

29. Research seminars presented at Schools of Pharmacy:

a) University of California, San Francisco - 1979
b) University of Illinois Medical Center - 1979
c) University of Tennessee - 1982 and 1989
d) University of Geneva, Switzerland - 1984
e) University of West Virginia - 1985
f) University of Michigan - 1986 and 1990
g) Hebrew University, Jerusalem, Israel - 1991
h) University of Geneva, Switzerland - 1993
i) Nova Southeastern University, Miami - 1995

30. Lecturer at the International Course on Modern Pharmaceutical Dosage Forms, Pontifica Universidad Catolica de Chile, Santiago, Chile, November 30-December 3, 1993.

31. Speaker at FDA seminar on "Bioevaluation of Oral Controlled-Release Formulations and In *Vitro/In Vivo* Correlations ", Rockville, MD, December 7, 1993.

32. Speaker at TGA (Australian Therapeutic Goods Administration) Continuing Education Seminar on "Clinical Pharmacokinetics of Transdermal Nitroglycerin", Canberra, Australia, March 30, 1994.

33. 21st International Symposium on Controlled Release of Bioactive Materials: Chair & Speaker at Workshop on Scale-up & Manufacturing Site Change, topic "*In Vitro/In Vivo* Correlations", Nice, France, June 24-25, 1994.

34. Moderator and co-author of Consensus Report for the AAPS/FDA Workshop on Evaluation of Orally Administered Highly Variable Drugs and Drug Formulations, Arlington, VA, March 6-8, 1995.

35. Panel member at FIP BIO International '96: Session title: BA/BE of Extended and Controlled Release Products, Toyko, April 23, 1996.

36. Speaker & Co-Chair at AAPS/FDA/USP Workshop on Scale-Up of Adhesive Transdermal Drug Delivery Systems. Topics: Compositional Variables-Case Study 1: Adhesive Polymer Sources and Consensus Report: BE Studies vs *In Vitro,* Arlington, VA, April 29-May 1, 1996.

37. Speaker at the American College of Osteopathic Family Physicians Annual Meeting on "A Pharmacokinetic Review of Second Generation Antihistamines", Nashville, TN, April 3, 1998.

38. Speaker at the American Academy of Physician Assistants Annual Meeting on "Antihistamines: Pharmacokinetic Considerations in Their Selection", Salt Lake City, Utah, May 24, 1998.

39. Speaker at Respiratory 2000 on " Pharmacokinetics of Second-Generation Antihistamines", New York, NY, October 22, 1998.

40. Speaker at the American College of Allergy, Asthma & Immunology Annual Meeting on "Pharmacokinetic Considerations in Selecting an Antihistamine", Philadelphia, PA,
41. November 7, 1998.

42. Presented 1 day Workshop on "The Role of Pharmacokinetics in the Evaluation of Controlled-Release Formulations" at the Controlled Release Society/Argentine Chapter, 3rd International Symposium, Buenos Aires, Argentina, August 9, 1999

43. Speaker on "Transdermal Delivery Systems-BE and Analytical Concerns", at the 32nd annual Congreso Nacional de Ciencias Farmacéuticas: AAPS Symposium, Puerto Vallarta, Mexico, October 26, 1999.

44. Moderator of Symposium titled" New Approaches to BE: The Biopharmaceutics Classification System" at the Pan American Health Organization Conference: Trends in Regulatory Standards on Active Materials and Bioequivalence, Washington D.C., November 5, 1999.

45. Speaker at the VI Congreso de las Federación Farmacéutica Sudamericana (FEFAS): "*In Vitro/In Vivo* Correlation in the Evaluation of Extended-Release Dosage Forms", Montevideo, Uruguay, April 27, 2000.

46. Speaker at the Congreso Farmacéutico Argentino: "Transdermal Products - The Present & The Future", Buenos Aires, Argentina, April 29, 2000.

47. Co-Chair of CRS Workshop: In *Vitro/In Vivo* Correlations Applicable to Extended-Release Formulations, Paris, France, July 8-9, 2000.

48. Speaker at CRS Workshop: "Wagner-Nelson Analysis for *In Vitro/In Vivo* Correlations", Paris, France, July 8, 2000.

49. Speaker at Bioequivalence Evaluation of Oral Extended-Release Formulations Workshop: "Bioequivalence Requirements" & Scale-up & Post-Approval Changes (SUPAC) Biowavers", São Paulo, Brazil, August 10, 2000.

50. Speaker at X Congreso Nacional de Ciencias Farmacéuticas: "Correlaciones *In Vitro/In Vivo,*" Panama City, Panama; September 2, 2000.

51. Speaker at CRS Workshop: "Correlaciones *In Vitro/In Vivo*", Vitoria-Gasteiz, Spain; September 20, 2000.

52. Speaker at the XXXIV Congreso Nacional de Ciencias Farmacéuticas: "Requisitos Para Bioequivalencia," Ixtapa, México, October 23, 2000.

53. Speaker at the XVII Panamerican Congress of Pharmacy and the V World Congress of Pharmacists of Portuguese Language: "Biodisponibility and Bioequivalencia," Rio de Janeiro, Brazil; November 3, 2000.

54. Poster Presentation at the Congreso de Ciencias Farmacéuticas de las Américas (PCA): "*In Vitro/In Vivo* Correlation with a Liquid Extended-Release H_1 Antihistamine Formulation", Orlando, Florida; March 29, 2001.

55. Speaker at the College of Chemistry, Universidad Nacional Autónoma de México, (UNAM): "Correlaciones *In Vitro/In Vivo,*" May 29, 2001.

56. Moderator & Organizing Committee Chair for Asociación Farmacéutica Mexicana's (AFM) Seminario de Farmacología Clínica, Mexico City, Mexico; May 31-June 1, 2001.

57. Speaker at the III Congreso Regional de Químico Farmacéutico Biólogos: "El Uso de *In Vitro/In Vivo* en el Desarollo de Medicamentos", Monterrey, Mexico; August 31, 2001.

58. Workshop Speaker at the V Congreso del la Sociedad Española de Farmacia Industrial y Galéncia (SEFIG): "Biodisponibility and Bioequivalencia", Valencia, Spain; February 7, 2001.

59. Speaker at Symposium titled" "Can a Once-Daily Methylphenidate Patch Help Children with ADHD?" at the 48th Annual American Academy of Child & Adolescent Psychiatry:"Methylphenidate Pharmacokinetics After Dosing With A Once-Daily Transdermal System", Honolulu, Hawaii; October 27, 2001.

60. Poster presentation titled at the 48th Annual American Academy of Child & Adolescent Psychiatry: "Methylphenidate Bioavailability from an Extended-Release Capsule Administered Sprinkled or Intact " Honolulu, Hawaii; October 25, 2001.

61. Poster presentation titled at the 48th Annual American Academy of Child & Adolescent Psychiatry: "Methylphenidate Bioavailability Assessment From Two Modified Release Formulations", Honolulu, Hawaii; October 25, 2001.

62. Speaker at XXVII Congreso Centroamericano y del Caribe de Ciencias Farmacéuticas: "Conceptos de Bioequivalencia e Interpretaciones Equivocadas," Antigua, Guatemala; November 30, 2001.

63. Invited lecturer at 2-day seminar for Instituto Nacional de Higiene "Uso de la Farmacocinética en la Evaluación de Medicamentos," Caracas, Venezuela; January 22-23, 2002.

64. Speaker at ExpoFarma Congress & Exhibition: "Evolución de los Medicamentos Genéricos en las E.U.A.", México, D.F., March 14, 2002.

65. Workshop Speaker at Asociación Farmacéutica Mexicana's (AFM) Seminario Internacional de Medicamentos Genericos Intercambiables: "Sistema de Clasificación Biofarmacéutica", México, D.F.; April 4, 2002.

66. Workshop Speaker at AFM's Seminario Internacional de Medicamentos Genericos Intercambiables: "Aspectos Cientificos de los Estudios de Bioequivalencia y Requisitos del FDA", México, D.F.; April 5, 2002.

Volunteer Service:

American Association of Pharmaceutical Scientists (AAPS)

1. Chairman of PPDM Nominating Committee for 1987, 1988.

2. Chairman of Symposium for PDD Section at AAPS National Meeting, 1988.

3. PPDM Program Committee Member for Atlanta Meeting, 1988.

4. Candidate for Vice-Chair of PPDM , 1989.

5. Chairman of Symposium for PPDM Section at AAPS National Meeting, 1989.

6. Co-Chairman of PPDM Program Committee for Las Vegas Meeting, 1990.

7. Member of AAPS Task Force on Generic Drugs, 1990; AAPS spokesman at Blue Ribbon Committee on Generic Medicines Public Hearing, June 20, 1990 in Washington, DC.

8. Member of the AAPS Future Events Committee, 1990.

9. Vice-Chairman of Dermatopharmaceutics Focus Group, 1991.

10. Chairman of PPDM Publicity Committee, 1991.

11. Fund Raiser and Organizing Chairman for PPDM Open Forum I, 1991.

12. Chairman of Dermatopharmaceutics Focus Group, 1992.

13. Chairman Open Forum II Planning Committee, 1992.

14. Chairman of PPDM Publicity Committee, 1992, 1993.

15. Chairman of AAPS Publicity Committee, 1992, 1993.

16. Member of FDA/AAPS Workshop on Scale-Up of Oral Controlled-Release Dosage Forms, 1992.

17. Moderator for the AAPS/FDA Workshop on Evaluation of Orally Administered Highly Variable Drugs and Drug Formulations,
March 6-8, 1995.

18. Planning Committee Member for FDA/AAPS Workshop on Scale-Up on Heterogeneous Formulations, 1992-93.

19. Member of Annual Program Committee, 1993.

20. Vice-Chair of PPDM, 1993.

22. Chair-Elect of PPDM for 1994.

22. Chair of PPDM for 1995.

23. Moderator for the AAPS/FDA Workshop on Evaluation of Orally Administered Highly Variable Drugs and Drug Formulations,
March 6-8, 1995.

24. Co-Chair of Planning Committee for AAPS/FDA/USP Workshop IV: Scale-Up of Adhesive Transdermal Drug Delivery Systems, 1995-96.

25. Co-Chair of AAPS Pharmaceutical Congress of the Americas to be held March 23-29, 2001.

Controlled Release Society (CRS)

1. Member of CRS Programming Committee, 1992-93.

2. Chair of Workshop on Scale-up & Manufacturing Site Change at the 21st International Symposium on Controlled Release of Bioactive Materials: Nice, France, June 24-25, 1994.

3. Invited by the Argentina CRS Chapter to be sole presenter at a One-Day Workshop for the Regional CRS Meeting. Topic: "The Role of Pharmacokinetics In The Evaluation of Oral Extended-Release Formulations" to be presented in Buenos Aires, Argentina, August 9, 1999.

4. Co-Chair of Workshop on *In Vitro/in Vivo* Correlations Applicable to Extended-Release Formulations, Paris, France, July 8-9, 2000.

5. Co-Chair of "Emerging Fields of Oral Drug Delivery", The Eurand Award 2000, at the CRS Meeting, Paris, France, July 12, 2000.

European Journal of Pharmaceutics and Biopharmaceutics

1. International Editorial Board Member, 1992-present.

2. Author of nine "FDA Update" articles in EJPB in 1993 and 1994.

3. Editor (with Gordon Flynn, Ph.D. as Co-Editor) of the EJPB special issue on Transdermal Pharmacokinetics published in June, 1995, vol. 41, 3.

Publications:

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2. M.A. González, T.N. Tozer, and D.T.T. Chang: Nonlinear Tissue Disposition: Salicylic Acid in Rat Brain, J. Pharm. Sci., 64, 99-103, 1975.

3. L. Kisareck, P. Winston, and M.A. González: The Biological Half-Lives of Molybdenum as Based upon Biphasic Urinary Excretion in the Rat, Interface, 5, 45-46, 1976.

4. R.A. Landay and M.A. González: Effect of Phenobarbital on Theophylline Disposition, J. Allergy and Clinical Immunology, 62, 27-29, 1978.

5. G. Larsen, R. Barron, R. Landay, and M.A. González: The Effect of Intravenous Aminophylline on Pulmonary Function in Cystic Fibrosis, Amer. Review Resp. Dis., 117, 1978.

6. P. Goldberg, M.A. González, L. Gogenola, and F. Leffert: Comparison of Repeated Bolus Injection of Theophylline to Continuous Infusion in the Treatment of Asthma in Children, Ibid, 117, 1978.

7. R. Gurny, M.A. González, D. Kildsig, and G.S. Banker: The Determination of Entrapment Efficiency for a Molecular Dispersion System, Drug Development and Industrial Pharmacy, 5, 437-445, 1979.

8. J.W. Georgitis, H. Eigen, M. Glick, R. Warner and M.A. González: Theophylline Absorption in Cystic Fibrosis, Amer. Rev. Resp. Dis., 119, 276, 1979.

9. G.L. Larsen, R.J. Barron, R.A. Landay, and M.A. González: Intravenous Aminophylline in Patients with Cystic Fibrosis: Pharmacokinetics and Effect on Pulmonary Function Am. J. Dis. Child., 134, 1143-1148, 1980.

10. P.B. Goldberg, M.A. González, L. Gogenola, G. Zerbe, and F. Leffert: IV Aminophylline Therapy for Asthma: A Comparison of Two Methods of Administration in Children., Amer. J. Dis. Child., 134, 596-599, 1980.

11. J.L. Yaeger, R. Gurny, M.A. González, R. Sjoqvist, and G.S. Banker: Bioavailability Assessment of Polymer Interacted Dextropropoxyphene from Rectal Dosage Forms, Pharmazeutische Industry, 42, 1141-1143, 1980.

12. C. Williams, C.S. Huang, R. Erb, and M.A. González: High-Performance Liquid Chromatographic Assay for Plasma Dipyridamole Monitoring, J. Chrom. Biomed. Applications, 225, 225-230, 1981.

13. F.C. Robinson, R.N. Warner, and M.A. González: Predicting Individual Phenytoin Serum Levels of Patients Seen in a Private Office Practice, Neurology, 31, 761-763, 1981.

14. J.W. Georgitis, H. Eigen, M. Glick, R. Warner, and M.A. González: Oral Theophylline Disposition in Cystic Fibrosis, Annals of Allergy, 48, 175-177, 1982.

15. C. Williams, P.R. Mayer, and M.A. González: Comparative Bioavailability of Dipyridamole from Two Tablet Formulations, Current Therapeutic Research, 32, 236-242, 1982.

16. N. Patel, G.S. Banker, D. Kildsig, and M.A. González: Paired-Ion High-Performance Liquid Chromatographic Assay for Sulfinpyrazone in Plasma, J. Pharm. Sci., 71, 1413-1315, 1982.

17. M.A. González and A.L. Golub: Theo-Dur Sprinkle: Controlled-Release Delivery Systems for Theophylline, Drug Development and Industrial Pharmacy, 9, 1279-1396, 1983.

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19. A.B. Straughn, M. Meyer, A. Golub, and M.A. González: A Chronopharmacokinetic Model for Controlled-Release Formulations, In Annual Review of Chronopharmacology, A. Reinberg, M. Smolensky, and G. Labrecque (Eds.), Pergamon Press, New York, 1984.

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49. M.A. González and K. S. Estes: Pharmacokinetic Overview of Oral Second-Generation H_1 Antihistamines, International J. Clin. Pharmacol. Therap., Vol. 36, No. 5, 292-300, 1998.

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51. G. Hochhaus, M.A. González, R.J. Dockhorn, J. Shilstone, J. Karafilidis: A New Solution-Based Intranasal Triamcinolone Acetonide Formulation in Patients with Perennial Allergic Rhinitis: How Does the Pharmacokinetic/Pharmacodynamic Profile for Cortisol Suppression Compare with an Aqueous Suspension-Based Formulation?, J. Clin. Pharmacol., 42, 662-669, 2002.

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EXHIBIT B

Doxycycline Hyclate tablets, 20mg
Fasting Conditions
Protocol No. R02-253

Section I

Final Report

The documents in this section contain information regarding the objective, the study design, the number of subjects, inclusion/exclusion criteria, test and reference product descriptions, dose, sampling schedules, safety monitoring, fasting/meals, washout, results, discussion and conclusion.

Section II

Biodata Analysis Form

Section III

Pharmacokinetic Data to support the Application