DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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41 University Drive
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Docket Nos. 2003P-0315/CP1 and PSA1,
2003P-0372/CP1, and 2004P-0517/PSA1

Dear Mr. Powala:

This is a consolidated response to the petitions referenced above submitted by CollaGenex Pharmaceuticals, Inc. (CollaGenex), regarding bioequivalence requirements for doxycycline hyclate tablets and capsules, 20 milligrams (mg). In the petitions, CollaGenex requests that the Food and Drug Administration (FDA) stay or refuse to approve any abbreviated new drug application (ANDA) submitted by Mutual Pharmaceutical Company, Inc. (Mutual), West-ward Pharmaceutical Corporation (West-ward), Ivax Pharmaceuticals, Inc. (Ivax), CorePharma LLC (CorePharma), or any other party for which CollaGenex' Periostat (doxycycline hyclate) 20-mg tablet or capsule is the reference listed drug, unless and until such ANDAs are supported by a bioequivalence study or studies conducted on both male and female subjects. In its petition concerning West-ward, CollaGenex also requests that FDA refuse to approve West-ward's ANDA for doxycycline hyclate 20-mg capsules in which West-ward relies on a bioequivalence study using a two-capsule dose of doxycycline hyclate (40 mg) to demonstrate bioequivalence.

In reaching its decision, the FDA has considered information in the petitions, comments submitted to the FDA regarding the petitions, and other information available to the Agency. For the reasons set forth below, the petitions are denied.

I. Background

A. Periostat

Periostat (doxycycline hyclate) is used as an adjunctive therapy to treat adult periodontal disease. CollaGenex is the holder of new drug application (NDA) 50-783 for Periostat 20-mg tablets, approved on February 2, 2001. CollaGenex previously marketed a 20-mg capsule version of Periostat under NDA 50-744, also approved on February 2, 2001. In September 2001, CollaGenex requested that FDA withdraw approval of NDA 50-744 for Periostat 20-mg capsules.[1] FDA approved both the Periostat capsule and tablet, to be administered twice daily, for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

[1] We are separately addressing the citizen petitions for Docket Nos. 02P-0312/CP1 and 02P-0367/CP1, that request FDA determine whether Periostat capsules were withdrawn for reasons of safety or efficacy, and a related request for stay in Docket No. 02P-0312/PSA1.

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B. Statutory and Regulatory Basis for Approval of ANDAs

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. No. 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) (the Act), which established the current ANDA approval process. To gain approval, the ANDA must show, among other things, that with respect to a listed drug (i.e., a drug product previously approved for safety and effectiveness), the generic drug product has the same active ingredient or ingredients, the same dosage form, route of administration, and the same strength, and has essentially identical labeling, and is bioequivalent. The specific approved drug product to which an ANDA refers is known as the reference listed drug (RLD). The scientific premise underlying the Hatch-Waxman Amendments is that a drug product that meets the approval requirements of section 505(j) is as safe and effective as the RLD. In most cases, drug products approved under section 505(j) may be substituted for the RLD as therapeutic equivalents. Therapeutic equivalence requires a showing that the products are pharmaceutical equivalents (see 21 CFR 320.1(c)) and are bioequivalent.

Under the Act, a generic drug product is bioequivalent to the RLD "if the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient. . ." (21 U.S.C. 355(j)(8)(B)(i)).

FDA regulations specify that two drug products are bioequivalent if there is an:

> . . . absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (21 CFR 320.1(e); see also 21 CFR 320.23(b)).

FDA regulations at § 320.24 discuss the types of evidence required to establish bioequivalence. It is well-accepted that FDA has considerable discretion in determining how the bioequivalence requirement is met. FDA's discretion need only be based on a "'reasonable and scientifically supported criterion, whether [the Agency] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs. . .'" (*Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 218 (D.D.C. 1996) (quoting *Schering v. Sullivan Corp.*, 782 F. Supp. 645, 651 (D.D.C. 1992), *vacated as moot sub nom, Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993))).

II. Discussion

A. Mutual's and West-ward's Study Population Did Not Inappropriately Exclude Female Subjects.

1. Legal Status of FDA's Guidance

Your petitions argue that FDA must not approve any ANDAs that rely on bioequivalence studies that do not include female subjects. You state in your petitions that Mutual and West-ward were required to include both males and females in their bioequivalence studies as recommended by the guidance for industry in *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (the BA/BE guidance)[2] (Docket Nos. 2003P-0315 at 2, 2003P-0372 at 3 to 4, 2004P-0517 at 4). Your assertion is incorrect. FDA's guidance documents do not impose requirements on regulated entities. Instead, they offer recommendations on technical approaches that FDA considers appropriate. The BA/BE guidance gives recommendations on standards and procedures for establishing bioavailability and bioequivalence, representing the Agency's current thinking on the topic. As stated in the preamble, the BA/BE guidance ". . . does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations." Although the BA/BE guidance recommends that sponsors attempt to include similar proportions of males and females in their in vivo bioequivalence studies if the drug product is intended for use in both sexes, the inclusion of both sexes, as discussed below, is not a requirement for completion of an acceptable bioequivalence study. In addition, we note that both Mutual and West-ward submitted their ANDAs before the issuance of the BA/BE guidance recommending the inclusion of both sexes in bioequivalence studies.

2. Standard Bioequivalence Testing in Male Subjects Is Sufficient To Establish the Bioequivalence of Doxycycline Hyclate Drug Products.

You claim that a study design of a generic drug product that excludes females is inadequate to establish bioequivalence. You state that the absence of female subjects from a study design would systematically reduce the variability in observed pharmacokinetic responses, thus biasing the study toward a finding of bioequivalence (Docket Nos. 2003P-0315/CP1 at 3 and 2003P-0372CP1 at 3). We agree that a bioequivalence study should be designed to minimize variability that is not attributed to the drug itself and should seek to eliminate bias. We do not agree, however, with your claim that the absence of females from a bioequivalence study necessarily biases the study toward a finding of bioequivalence.

[2] Available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

As stated in subsection I.B of this letter, approval of an ANDA requires a showing that the proposed product is bioequivalent to the RLD. The FDA does not specify the design of studies that a generic applicant must conduct to establish bioequivalence. To establish bioequivalence, FDA may require that applicants conduct in vivo or in vitro testing, or both, and applicants must conduct bioequivalence testing to meet in vivo or in vitro requirements using the most accurate, sensitive, and reproducible approach to bioequivalence available (See 21 CFR 320.24(a) and (b)). For drug products that are absorbed into the bloodstream, such as doxycycline hyclate tablets and capsules, the standard bioequivalence study is conducted in a crossover fashion in which single doses of the test and reference drug are administered to a limited number of volunteers, usually 24 to 36 healthy normal adults. The concentration of the drug in blood or plasma is measured over time and then plotted on a graph. Characteristics of the resulting concentration-time curves, such as area under the curve (AUC) and the maximum or peak blood or plasma concentration (Cmax), are examined by statistical procedures. AUC represents the extent of absorption of the drug and Cmax represents the rate of absorption of the drug.

To be considered bioequivalent, a generic applicant must show that a 90 percent confidence interval for the ratios of the geometric means for AUC and Cmax of its product to that of the reference product are within the limits of an 80 percent to 125 percent acceptance interval, using two one-sided test procedures. The use of the 80 percent to 125 percent limits is based on a medical decision of the FDA that, for most drugs, the ratios of the geometric means within the 80 percent to 125 percent limits in the concentration of the active ingredient in blood will not produce a clinically significant difference.

The primary objective of a bioequivalence study is to compare the bioavailabilities of two formulations containing the same active ingredient in the same strength. The primary variable tested is the effect of the formulations on the rate and extent of absorption of the active ingredient. As noted in subsection II.A.2 of this letter, these formulations are administered to the study subjects in a crossover fashion for a standard in vivo bioequivalence study. Each subject receives the two different formulations (the test and reference products) during different time periods, serving as his or her own control. Thus, the main focus of a bioequivalence study is the difference in the two formulations within a particular subject, or in other words, whether the two formulations are behaving in a sufficiently similar way in the same subject, whether that subject is male or female.

FDA recognizes that some drugs exhibit gender differences in pharmacokinetics; however, the differences do not necessarily preclude a finding of bioequivalence. From a statistical perspective, different variability in female subject populations compared to male subject populations is not a primary concern in demonstrating bioequivalence of two drug products. If inclusion of female subject populations increases only the pharmacokinetic variability, the investigator needs only to increase the sample size to achieve adequate statistical power for the study. Thus, if either males or females are not included in a bioequivalence study, the study

results can still be deemed acceptable, unless there is evidence to suggest that a gender-by-treatment interaction exists, or the study fails to show that the two one-sided 90 percent confidence intervals are within the bioequivalence criteria of 80 to 125 percent. As discussed in subsection II.A.3, there is no statistically significant evidence to show gender-by-treatment interaction in CollaGenex' bioequivalence study, and the CollaGenex bioequivalence study, in fact, suggests that the male subjects showed larger variability than the female subjects. Therefore, FDA believes that, in this case, a finding of bioequivalence using an all-male study population can be generalized to reasonably predict bioequivalence in subjects or patients of either gender.

FDA has reviewed the bioequivalence studies of Mutual and West-ward and determined that the studies meet the statutory and regulatory requirements for demonstrating bioequivalence to Periostat.

3. *The Mutual and West-ward Study Populations Did Not Inappropriately Exclude Female Subjects.*

To determine whether inclusion of females indeed resulted in higher variability in CollaGenex' study as it has claimed, and whether a gender-by-treatment interaction exists in the disposition of doxycycline hyclate, FDA performed various analyses of the relevant data from CollaGenex, Mutual, and West-ward.

a. Labeling

The labeling for Periostat refutes CollaGenex' assertion that bioequivalence studies involving Periostat must include both men and women because of pharmacokinetic differences in the sexes. As stated in the approved labeling for Periostat 20-mg tablets under *Gender*:

> Doxycycline pharmacokinetics were compared in 9 men and 11 women under fed and fasted conditions. While female subjects had a higher rate (Cmax) and extent of absorption (AUC), these differences are thought to be due to differences in body weight/lean body mass. Differences in other pharmacokinetic parameters were not significant.

In addition, one of the references cited in the Periostat labeling stated, "There do not seem to be any sex-related modifications in the pharmacokinetic parameters of doxycycline" (Savain, S. and G. Houin, Clinical Pharmacokinetics of Doxycycline and Minocycline, Clinical Pharmacokinetics, 1988, 15:355-366). Although CollaGenex relies on its own bioequivalence study, comparing Periostat tablets to capsules, to support its assertions about gender differences, FDA's medical review for Periostat 20-mg tablets indicates that CollaGenex did not conduct an analysis to account for subject variability such as differences in weight of male and female

subjects in its studies. Thus, as stated in the approved labeling of Periostat, the differences in certain pharmacokinetic parameters between males and females are thought to be due to differences in body weight/lean body mass, and the suggestion that the differences are due to gender is unsubstantiated.

b. Gender-by-Treatment Interaction

You claim that females should not be excluded from bioequivalence studies involving Periostat "because doxycycline hyclate is known to exhibit different pharmacokinetics in women than in men, with women having a higher extent of absorption (Cmax) under both fasted and fed conditions" (Docket No. 2003P-0372/CP1 at 5) (see also Docket Nos. 2003P-0315/CP1 at 3 and 2004P-0517/PSA1 at 4). You base your claims on a CollaGenex study that was used to show that Periostat tablets are bioequivalent to Periostat capsules. As explained in subsection II.A.2, gender differences in bioequivalence comparisons are not unexpected. If there is a difference in variation because of gender alone, the difference is not a primary concern in a bioequivalence study unless it indicates the existence of a gender-by-treatment interaction rather than variability. A gender-by-treatment interaction indicates that males and females respond differently to treatment, for example, whether females handle either the generic or innovator product differently than males do. If a gender-by-treatment interaction exists, this could mean that bioequivalence may be established in one gender but not in the other.

The CollaGenex study report mentioned that a gender difference in treatment effect was observed for the comparison between capsule and tablet under fasting conditions and for the comparison between fed and fasted conditions for the tablets. However, you did not report a formal statistical analysis for the claimed gender-by-treatment interaction. Therefore, we conducted our own analysis to determine if a gender-by-treatment interaction existed for CollaGenex' tablet and capsule drug products under fasting conditions. We used an analysis of variance (ANOVA) model that included (1) gender; (2) sequence; (3) period and treatment effects, as well as subject effect nested in gender-by-sequence combinations; and (4) gender-by-treatment interaction and gender-by-sequence interaction. Our analysis of variance included all the observed data from the CollaGenex study. The p-values[3] for this analysis are as follows (see Table 1):

Table 1: Pair-wise treatment by gender interaction (p-value)

	p-values for interaction
LAUCt	0.122
LAUCinf	0.955

[3] A p-value is a statistical term used to quantify the probability of obtaining results as extreme as or more extreme than the one observed, given or assuming that the null hypothesis is true. The null hypothesis here is that there is no gender-by-treatment interaction. A large p-value means that it is less likely to have gender-by-treatment interaction and a small p-value means that it is more likely to have gender-by-treatment interaction.

LCmax	0.220

Based on these p-values we determined that there was no statistically significant gender-by-treatment interaction between the Periostat tablet and capsule under fasting conditions at the level of 0.10 for the three bioequivalence parameters, AUCinf, AUCt, and Cmax (analyzed after log transformation).[4]

c. Geometric Means

To assess gender differences between Periostat capsules and tablets, we also examined, by gender, the geometric means (AUC in nanograms (ng) per milliliter (mL) times hour (h) (ng.h/mL), Cmax in ng/mL) for the two dosage forms under fasting conditions. The geometric means, cited in Table 12.2-2 of the CollaGenex bioequivalence study report, are set forth in Table 2 as follows:

Table 2: Geometric means of AUC and Cmax by formulations (under fasting conditions) and genders[a]

	Formulations	Female	Male	Ratio
AUCt				
	Capsule	5556	3593	1.55
	Tablet	4780	4616	1.04
AUCinf				
	Capsule	6068	4925	1.23
	Tablet	5691	5259	1.08
Cmax				
	Capsule	428	244	1.75
	Tablet	410	294	1.39

[a] CollaGenex bioequivalence study report, Table 12.2-2.

The differences between the female and male population geometric means were consistently higher for the three bioequivalence pharmacokinetic parameters for the capsule formulation

4 The statistical significance level for two-sided tests is usually set at the level of 0.05. The choice of a statistical significance level depends on the level of risk the investigator/reviewer/researcher would like to take to reject the null hypothesis, in this case, that there is no gender-by-treatment interaction. For testing interactions, the significance level is usually set at the level of 0.10. When the p-value is smaller than the significance level, the null hypothesis is rejected, which in this case, would mean that there is statistically significant evidence for gender-by-treatment interaction. However, because the p-values in Table 1 are higher than the significance level of 0.10, we cannot reject the null hypothesis to claim that there is gender-by-treatment interaction.

compared to the tablet formulation. This observation has been acknowledged in the CollaGenex study report (page 28, volume 8) as follows: "These gender differences appear to be more marked for the fasted capsule condition compared to the fasted tablet condition." Clearly, the observed gender differences are primarily due to the differences between female and male subjects when taking the capsule under fasting conditions. However, compared to the capsule under fasting conditions, the gender differences of the tablet under fasting conditions are small. Therefore, we conclude that the gender differences observed by analysis of the geometric means for the capsule under fasting conditions cannot be generalized to all doxycycline hyclate formulations under all conditions.

d. Coefficient of Variation Values

You assert that a comparison of the coefficient of variation (CV) values[5] in Cmax and AUCinf for Periostat reported in the Mutual study, and a comparison of the Cmax values in the West-ward study with the corresponding CV values for Periostat in CollaGenex bioequivalence study, demonstrate the likelihood that Mutual's and West-ward's study designs, by excluding females, are biased in favor of showing bioequivalence. CollaGenex reports that the CV for Cmax from Periostat in the Mutual study was 26.6 percent. The corresponding CV for Cmax in the CollaGenex bioequivalence study was 28 percent. For the parameter AUCinf, the CV for the Mutual study was 25.56 percent but in the CollaGenex bioequivalence study the CV was 37.1 percent. The CV for Cmax from Periostat in West-ward's study was 19.8 percent. The corresponding CV for Cmax from Periostat capsules in CollaGenex' study was 31 percent. CollaGenex asserts that these results, demonstrating that Periostat exhibited higher variability in Cmax and AUCinf in its study, which included women, were artificially reduced in the male-only Mutual and West-ward studies. CollaGenex concludes that a finding of bioequivalence for the Mutual and West-ward studies is therefore suspect (Docket Nos. 2003P-0315/CP1 at 3 to 4, 2003P-0372/CP1 at 5).

FDA disagrees that these values in Cmax and AUCinf evidence a bias of Mutual's and West-ward's studies toward a finding of bioequivalence because females were excluded from the

[5] In bioequivalence studies, the variability of log-transformed pharmacokinetic (PK) endpoints is sometimes expressed as a coefficient of variation (%CV) for the untransformed PK endpoints, using the formula

$$\%CV = 100 * \sqrt{\exp(\hat{\sigma}^2) - 1}$$

where $\hat{\sigma}^2$ is the estimated variance (Error Mean Square from the crossover design analysis of variance) for the log-transformed data. The calculated %CV can properly represent variability only if the data is truly log normally distributed, in which case, %CV is just a simple increasing function of the estimated standard deviation $\hat{\sigma}$. The qualitative comparison of the %CVs (under log normality) will therefore be the same as the direct comparison of standard deviations. For ease of communication, we use standard deviation, a commonly used statistical term, to quantify variability of the log-transformed data in this response.

studies. We believe it was inappropriate for CollaGenex to make comparisons of CV values from different studies. Variability across two different studies might not be comparable due to factors such as differences in study designs, drug formulations, and location where the studies are conducted. If the difference in variability is to be compared between genders, the difference should be assessed within a study rather than across studies. FDA analyzed CollaGenex' study to assess the difference in variability between genders. As the intra-subject variance of the log-transformed pharmacokinetic endpoints is the source of variability affecting the demonstration of bioequivalence in crossover trials, we have calculated this intra-subject variance in the form of the standard deviation (square-root of variance) from the analysis of the tablet and capsule formulations under fasting conditions for females and males, respectively, in CollaGenex' study. Our calculations included all the observed data.

The estimated intra-subject standard deviations (square root of variance) are listed in Table 3 for both female and male subjects.

Table 3: Intra-subject variabilities in CollaGenex' study by genders

	Female Standard Deviation	Male Standard Deviation
LAUCt	0.254	0.310
LAUCinf	0.240	0.381
LCmax	0.112	0.233

Table 3 shows that in CollaGenex' study the male subjects had somewhat higher estimated variability than the female subjects for the three log-transformed endpoints (LAUCt, LAUCinf, and LCmax). Thus, our analysis presents no evidence that exclusion of female subjects from a study on doxycycline hyclate, 20-mg, will result in an increased likelihood of a finding of bioequivalence.

e. Variability Comparison of Males in CollaGenex' and West-ward's Bioequivalence Studies

We compared only male subject data from West-ward and CollaGenex studies to determine the difference in variability between studies. In West-ward's study, conducted using all male subjects (sample size = 26), the standard deviations of log AUCt, log AUC ∞, and log Cmax of the reference product Periostat (doxycycline hyclate capsules, 2 x 20-mg dose) were 0.211, 0.200, and 0.196, respectively. In CollaGenex' bioequivalence study, which compared bioequivalence of capsules and tablets under fasted conditions and bioavailability of the tablets under fed and fasted conditions, the standard deviations for log AUCt, log AUC∞, and log Cmax for Periostat (doxycycline hyclate capsules, 20-mg, in 9 male subjects) were 0.444, 0.386, and

0.320, respectively. Our analysis noted large differences in variability between the studies. The observed differences could be due possibly to factors such as study design, recruited subjects, dose levels, and/or study conduct. However, these differences cannot be attributed to the absence of female subjects, in that no females were included in the analysis. Therefore, it is misleading to attribute the variability difference between West-ward's and CollaGenex' bioequivalence studies to the exclusion of female subjects from West-ward's study.

B. The West-ward Bioequivalence Study Used An Appropriate Dose of Doxycycline Hyclate.

You claim that West-ward, by comparing two of its 20-mg capsules to two Periostat 20-mg capsules, used an inappropriate dose to establish bioequivalence (Docket No. 2003P-0372/CP1 at 3 to 4). You assert that West-ward should have compared a single 20-mg capsule of its doxycycline hyclate to a single 20-mg capsule of Periostat. To support your claim, you refer to the BA/BE guidance's recommendation that a bioequivalence study be conducted between the proposed product and the reference listed drug using the strength or strengths specified in *FDA's Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), in this case Periostat 20 mg. You acknowledge that multiple-unit doses, as recommended by the BA/BE guidance, are sometimes necessary, but you assert there is no "scientific or technical reason" to justify West-ward using a two-unit dose in its bioequivalence study.

We believe that West-ward was justified in using a 40 mg dose for comparison in its bioequivalence study. The BA/BE guidance recommends the use of multiple units of the highest strength if warranted for analytical reasons, provided the total single dose remains within the labeled dose range. In bioequivalence trials, it is common practice to administer multiple units up to the maximum allowable daily dose to achieve adequate plasma levels, that is, if the assay sensitivity is considered inadequate to characterize plasma level profiles. Because the assay plasma level of doxycycline is 15 ng/mL, we allowed West-ward to use a dose equal to the maximum daily dose. This approach would ensure measurable plasma levels throughout the plasma sampling period which would result in meaningful pharmacokinetic parameters for bioequivalence evaluation. Thus, we believe that the dose used by West-ward was appropriate to demonstrate bioequivalence of generic doxycycline hyclate products to Periostat.

C. Periostat Is Not a Narrow Therapeutic Index Drug.

In the conclusion of two of your petitions, you claim that Periostat has "a narrow therapeutic range," 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." CollaGenex claims that, because the bioequivalence studies of Mutual and West-ward did not include female subjects and West-ward's study compared two 20-mg capsules instead of one, there is a risk that Mutual's and West-ward's doxycycline hyclate drug products might result in antibiotic serum concentrations of doxycycline because of doxycycline's higher rate and extent of

absorption in women (Docket Nos. 2003P-0315/CP1 at 4 and 2003P-0372/CP1 at 5 to 6). FDA regulations at 21 CFR 320.33(c) define *narrow therapeutic ratio* as follows:

- There is less than a 2-fold difference in median lethal dose (LD_{50}) and median effective dose (ED_{50}) values, or

- There is less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and

- Safe and effective use of the drug products requires careful titration and patient monitoring.

FDA's guidance for industry, *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*,[6] defines *narrow therapeutic range drug products* as "those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation" (page 9).

We disagree with your claims that Periostat is a narrow therapeutic index drug for the following reasons:

- You did not submit any data to show that Periostat is a narrow therapeutic index drug, nor is FDA aware of any evidence that Periostat is a drug for which there is a narrow ratio between toxicity and efficacy.

- The labeling of Periostat does not indicate that the drug requires frequent titration and careful patient monitoring. Such labeling is commonly associated with drug products that have a narrow therapeutic ratio.

- Periostat does not require pharmacodynamic monitoring.

- Periostat does not require a minimum drug concentration for effectiveness.

Even if doxycycline hyclate were a narrow therapeutic index drug, the requirements for demonstrating bioequivalence of narrow therapeutic range drugs are the same as for other drugs.

Whether or not Periostat is an antibiotic is not relevant here because as Periostat's labeling indicates, at the recommended daily dosage, resistant bacteria do not develop.[7] Thus, generic

[6] Available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

[7] We note that CollaGenex contested FDA's determination that Periostat is an "old" antibiotic drug that falls within the scope of section 125(d) of Title I of the 1997 Food and Drug Administration Modernization Act (FDAMA) and

doxycycline hyclate drug products that are bioequivalent and therapeutically equivalent to Periostat will have the same safety and efficacy profile as Periostat.

III. Petitions for Stay (PSA)

In your PSA submitted in Docket No. 2003P-0315/PSA1, you request that the FDA stay approval of Mutual's ANDA until the Agency has responded to your citizen petition (Petition at 2). In your PSA submitted in Docket No. 2004P-0517/PSA1, you request that FDA stay approval of any ANDA for which Periostat is the RLD unless such ANDA is supported by a bioequivalence study or studies conducted on both male and female subjects (Petition at 4). You claim that the petitions for stay of action should be granted because they satisfy the criteria set forth in 21 CFR 10.35(e) for a mandatory or discretionary stay of action (Docket Nos. 2003P-0315/PSA1 at 2 to 5 and 2004P-0517/PSA1 at 4 to7).

Section 10.35(e) provides that the Commissioner may grant a stay of any proceeding, in whole or in part, "if it is in the public interest and in the interest of justice" to do so. Section 10.35(e) further provides that the Commissioner shall grant a stay of administrative 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 submitted 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 interests.

FDA need not address your claims of irreparable injury or whether your petitions have been filed in good faith and are not frivolous, because the Agency finds that neither the public interest, public policy, nor the interest of justice requires the issuance of a mandatory or discretionary stay of either petition.

You maintain that public policy, the public interest, and the interest of justice would best be served by FDA refusing to approve any ANDA referencing Periostat that does not include both male and female subjects in its bioequivalence study. You contend that data from such a study

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is therefore not eligible for certain patent and exclusivity protections described in section 505(c) and (j) of the Act. In January 2005, the U.S. District Court for the District of Columbia agreed with FDA's determination that Periostat is an old antibiotic drug subject to section 125(d) of FDAMA. *CollaGenex v. Thompson, et al*, 2005 WL 256561 (D.D.C.). CollaGenex has appealed the district court decision.

would be inherently biased and "detrimental to public policy because it would expose the public to unacceptable health risks while unlawfully relieving the ANDA applicant of its evidentiary burden" (Docket Nos. 2003P-0315/PSA1 at 4 and 2004P-0517/PSA1 at 6). You state that an all male study population is inadequate to establish bioequivalence to Periostat and fails to meet statutory and regulatory requirements for approval. You contend that the public interest and the interest of justice "demand that FDA not approve any ANDA relying on Periostat as the reference listed drug unless its studies establish bioequivalence in both male and female subjects" (Docket No. 2004P-0517/PSA1 at 7).

We disagree with your position. As discussed in subsection II.A.2 of this letter, FDA's evaluation of relevant data has determined that an all male study population is not inherently biased and is sufficient to demonstrate the bioequivalence of a generic doxycycline hyclate drug product to Periostat. Generic doxycycline hyclate drug products shown to be bioequivalent and therapeutically equivalent to Periostat can be expected to have the same safety and efficacy profile as Periostat. Because the underlying policy of Congress expressed in section 505 of the Act is to approve products that meet requirements for approval, there is no public policy supporting a stay in this matter.

The Hatch-Waxman Amendments to the Act were intended to promote the entry into the market of lower-cost versions of innovator drug products. Section 505(j) establishes the criteria for FDA approving ANDAs, including a showing of bioequivalence. FDA believes that your request for a stay of approval of ANDAs for doxycycline hyclate is outweighed by other interests, including providing access by the public to additional bioequivalent doxycycline hyclate drug products that are demonstrated to be as safe and effective as Periostat.

Because you have not demonstrated that you have met the criteria for a mandatory or discretionary stay of action, your petition requesting that FDA stay approval of any ANDA for which Periostat is the RLD unless such ANDA is supported by a bioequivalence study or studies conducted on both male and female subjects is denied. FDA did not approve Mutual's ANDA before the date of this response. Now that FDA has responded to your citizen petition 2003P-0315, your petition for stay of action in Docket No. 2003P-0315/PSA1, which requests a stay of approval of the Mutual ANDA until FDA has responded to the citizen petition, is moot.

IV. Conclusion

We deny your request that FDA refuse to approve any ANDA submitted by Mutual and Westward for doxycycline hyclate tablets and capsules, respectively, in which the ANDAs rely on a bioequivalence study conducted on an all male population. You have not submitted any persuasive data, and FDA is not aware of any data to support your claim that a study that uses an all male population is incapable of establishing bioequivalence to Periostat. Thus, your claim that a study design for doxycycline hyclate that excludes female subjects is biased toward a

finding of bioequivalence is unsupported. FDA also disagrees with your claim that West-ward used an inappropriate dose of doxycycline hyclate in its bioequivalence study. FDA will approve ANDAs for generic doxycycline hyclate drug products in which the applicants meet applicable statutory and regulatory requirements for approval.

Sincerely,

Randall W. Lutter, Ph.D.
Acting Associate Commissioner
for Policy and Planning