

B



DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

DATE: September 23, 2003

FROM: Janet Woodcock, Director
Center for Drug Evaluation and Research

SUBJECT: CDER Antibiotic Drug Classification and Classification of Periostat (doxycycline hyclate) 20 mg

TO: NDA 50-783 and 50-744 Files

In November 2002, CollaGenex renewed a request that Periostat® (doxycycline hyclate 20 mg) be considered a non-antibiotic drug, and thus subject to all of the provisions of section 505. I understand that, since then, CollaGenex has sued FDA in U.S. District Court challenging the agency's decision, when it approved Periostat on September 30, 1998, to classify Periostat as an antibiotic drug subject to the exemption provisions of the 1997 FDA Modernization Act. At the time, Dr. Murray Lumpkin, CDER's Deputy Director for Review Management, was the CDER official who handled the determination that Periostat is an antibiotic drug.

Because CollaGenex has asserted that the 1998 decision was incorrect, CDER staff have reviewed the history of CDER antibiotic drug classifications and the status of Periostat as an antibiotic drug to determine whether FDA's decision was in error. The review of this decision began in November 2002. There is no contemporaneous memorandum of the 1998 decision explaining the basis for CDER's decision, although I understand that Dr. Lumpkin is preparing a document that describes the reasons for that decision.

I have reviewed the attached report and analysis dated September 22, 2003. Based on my review of that report, I find that the 1998 decision by CDER staff that Periostat (doxycycline hyclate) 20 mg is an antibiotic drug was correct.

Janet Woodcock, MD
Director,
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



MEMORANDUM

TO: Janet Woodcock, MD, Director, Center for Drug Evaluation and Research

FROM: David Roeder, Associate Director for Regulatory Affairs, Office of Drug Evaluation IV *EMC for DR 9/23/03*

Edward Cox, MD, MPH, Deputy Director, Office of Drug Evaluation IV *EMC 9/23/03*

THROUGH: Mark Goldberger, MD, MPH, Director, Office of Drug Evaluation IV
Jonca Bull, MD, Director, Office of Drug Evaluation V
Helen Winkle, Director, Office of Pharmaceutical Science
John Jenkins, MD, Director, Office of New Drugs
Jane Axelrad, Director, Office of Regulatory Policy

RE: CDER Antibiotic Drug Classification and Classification of Periostat® (doxycycline hyclate) 20 mg

DATE: September ³ 22, 2003 *EMC*

SUMMARY

FDA's classification of Periostat® (doxycycline hyclate) 20 mg as an antibiotic drug has been challenged by the sponsor, CollaGenex Pharmaceuticals, Inc. We have reviewed FDA precedents for classification of antibiotics, and the classification of Periostat, and have concluded that Periostat was properly classified as an antibiotic drug.

Section 201(jj) of the Federal Food Drug and Cosmetic Act (FFDCA or the Act) defines an antibiotic drug as follows:

any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof.

Doxycycline was first approved in 1967 as an antibiotic drug under section 507 of the FFDCA. Doxycycline is synthetically derived from oxytetracycline, a substance

produced by a micro-organism. Antibiotic drug products containing doxycycline have been approved for antimicrobial use to treat infections. Thus, the drug substance doxycycline has the capacity to inhibit micro-organisms in dilute solution.

Periostat is an antibiotic drug for two reasons. First, Periostat is approved for use at a dose of 20 mg orally twice daily for a total daily dose of 40 mg. The serum levels that are attained with Periostat at this dose exceed the doxycycline drug levels that inhibit some micro-organisms as determined by *in vitro* susceptibility testing. Therefore, at its approved dose of 20 mg twice daily, Periostat has the capacity to inhibit micro-organisms. Second, the statutory definition of antibiotic drug is most reasonably read to mean that any drug intended for human use containing any quantity of an antibiotic substance is considered to be an antibiotic drug. Periostat (doxycycline hyclate) 20 mg contains a quantity of the antibiotic substance doxycycline, which we know to have the capacity to inhibit or destroy microorganisms in dilute solution, because other antibiotic drug products containing doxycycline as the active ingredient are approved for such anti-infective use. Thus, Periostat meets the definition of an antibiotic drug on two grounds.

Finally, that a drug may be indicated for a non-antimicrobial use is not dispositive as to whether the drug is classified as an antibiotic drug. There are clearly examples of immunomodulating drugs and cancer therapies that are not used for the treatment of infections that meet the definition of antibiotic drug in the Act and are appropriately classified as antibiotic drugs.

FDA's classification of Periostat (doxycycline hyclate) 20 mg is correct under the statutory definition of antibiotic drug and is consistent with FDA's precedent.

GENERAL BACKGROUND

Recently FDA was sued by CollaGenex in U.S. District Court challenging the agency's classification of the CollaGenex product Periostat (doxycycline hyclate) 20 mg as an antibiotic drug subject to the exception provisions of the 1997 FDA Modernization Act (FDAMA). The Periostat new drug application (NDA) was originally submitted to FDA by CollaGenex on August 30, 1996, under section 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA or the Act), and was given a "20 series" (non-antibiotic drug) NDA number (20-642). (Attachment 1) Shortly thereafter, FDA informed CollaGenex that the application for doxycycline was subject to approval as an antibiotic drug, and the NDA should be amended by CollaGenex to make it a submission under section 507 of the FFDCA. CollaGenex resubmitted the application on September 18, 1996, under section 507, and FDA gave it the "50 series" antibiotic NDA number (50-744). (Attachment 2)

On September 11, 1997, CollaGenex submitted to the FDA Ombudsman in the Office of the Commissioner, a request for designation, seeking to have Periostat reviewed and approved as a section 505 application, not as an antibiotic drug under section 507. (Attachment 3) The Ombudsman's Office determined that this request for designation properly belonged in CDER and transferred the matter to the Center. (Attachment 4)

On November 20, 1997, Congress passed FDAMA which, among other things, amended the FDCA to remove section 507, making antibiotic drug approvals subject to section 505. FDAMA also included a "Transition" provision that declared an application approved under 507 before enactment of FDAMA will be considered to be an application submitted, filed, and approved under section 505. This transition created an exception provision in section 125(d)(2) of Title I. This provision exempted certain applications for antibiotic drugs from those provisions of 505 that provide, for example, for new drug exclusivity, patent listing, patent certification, and 30 month stays on approval of abbreviated new drug applications (ANDAs). The applications that fall within this exception are those for drugs that contain an antibiotic drug, and the antibiotic drug was the subject of any application received under section 507 before enactment of FDAMA. On July 8, 1998, CollaGenex sent Dr. Murray Lumpkin in CDER a letter renewing some of the arguments made in the letter to the Ombudsman, and discussing the effect of FDAMA on the Periostat application. (Attachment 5)

FDA approved Periostat (doxycycline hyclate capsules) 20 mg on September 30, 1998, and stated in the approval letter that Periostat was approved under section 505, but was subject to the exception provisions in section 125(d)(2) of Title I of FDAMA. (Attachment 6)

Periostat contains doxycycline hyclate. Doxycycline was first approved as an antibiotic drug in 1967. (Attachment 7) Prior to passage of FDAMA, there were doxycycline antibiotic monographs set forth at 21 CFR 446.120(a) and 446.121(a) (1998). Doxycycline is approved as an antimicrobial to treat a number of infections, including infections of the respiratory tract, several different types of sexually transmitted infections, urinary tract infections due to selected microorganisms, anthrax, plague, cholera, gastrointestinal infections, selected infections acquired from tick bites caused by infecting microbes listed in the product labels, and for the prophylaxis of malaria.^{1,2,3,4}

After FDA approved Periostat in September 1998, it did not receive additional correspondence from CollaGenex regarding the classification of Periostat as an antibiotic drug until November 2002. At that time, CollaGenex's attorneys brought FDA's decision on this matter to the attention of FDA's Chief Counsel, through a series of submissions and a meeting at which CollaGenex representatives, Office of Chief Counsel staff, and CDER staff were present. (Attachments 12, 13) In response to CollaGenex's concerns, CDER staff began a review of the 1998 decision. CollaGenex sued FDA on June 26, 2003, seeking to bar FDA from approving any ANDA referencing Periostat on the

¹ Product Labeling for Vibramycin® Monohydrate (doxycycline monohydrate) for Oral Suspension, NDA 50-006; Vibramycin (doxycycline hyclate) Capsules, NDA 50-007; Vibramycin Calcium (doxycycline calcium oral suspension) Syrup, NDA 50-480; Vibra-Tabs (doxycycline hyclate) Film Coated Tablets, NDA 50-533. Combined label revised May 2002. (Attachment 8)

² Product Labeling for Vibramycin (doxycycline hyclate for injection) Intravenous, NDA 50-442; Revised November 2001. (Attachment 9)

³ Product Labeling for Monodox (doxycycline monohydrate) Capsules, NDA 50-641; revised January 12, 1999. (Attachment 10)

⁴ Product Labeling for Doryx (coated doxycycline hyclate pellets) Capsules, NDA 50-582; revised October 2002. (Attachment 11)

grounds that Periostat should be subject to the provisions of 505 regarding new drug exclusivity, patent listings, patent certifications, etc., which would prevent any ANDA referencing Periostat from being approved at this time. On July 22, 2003, Judge Rosemary M. Collyer, of the U.S. District Court for the District of Columbia, issued an order restraining and enjoining FDA from approving any ANDA referencing Periostat until the court ruled on CollaGenex's challenge to FDA's classification of Periostat, and ordering the agency to submit within 60 days the administrative record for its 1998 approval of the NDA for Periostat.

FDA's 1998 decision to classify Periostat as an antibiotic drug subject to the exception provisions of FDAMA was made by Murray Lumpkin, MD. At the time, Dr. Lumpkin was CDER's Deputy Center Director for Review Management. FDA has been unable to locate a contemporaneous memorandum explaining the basis for that decision. Accordingly, Dr. Lumpkin, who is currently FDA's Principal Associate Commissioner, is preparing a document explaining the reasoning at the time the decision was made to classify Periostat as an antibiotic drug product. Dr. Lumpkin's explanation of the basis for the decisions leading up to the 1998 Periostat NDA approval is independent of the review described in this memorandum.

This memorandum is a general survey of FDA's classification and approval decisions regarding antibiotic drug products, and a review of whether CollaGenex's doxycycline hyclate 20 mg product is an antibiotic drug under section 201(jj) of the FDCA. The review and analysis of past classification decisions was necessary in part because the agency does not have regulations or guidance detailing its interpretation of that portion of the FDCA definition, which defines "antibiotic drug" as "any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof." The agency has implemented this statutory antibiotic drug definition on a case-by-case basis, based upon a review of the characteristics of the particular drug involved. Many of these decisions have been sufficiently straightforward that they do not appear to have warranted a documented analysis.

Our review of the agency's decisions regarding antibiotic drugs was intended to determine whether FDA's interpretation of the statute has been consistent, and whether the classification of Periostat as an antibiotic drug is in line with FDA precedent. In addition, to determine whether the classification of Periostat as an antibiotic drug was an error, we reviewed the arguments made by CollaGenex in the 1997 and 1998 submissions to the FDA Ombudsman's Office and to Dr. Lumpkin, and additional information provided in CollaGenex's communications with the Chief Counsel.

We conclude that FDA has been consistent in its approach to antibiotic drugs, that the Periostat decision was consistent with past precedent and correct under the statute, and

that none of the arguments advanced by CollaGenex, either before the Periostat approval or after, require a change in the classification.⁵

STATUTORY BACKGROUND

Section 507 of the FFDCA was enacted in 1945 to provide for batch certification of antibiotics. Batch certification of antibiotics was intended to ensure the strength, quality, and potency of successive batches of these drugs, which were at that time all produced by fermentation, a manufacturing process that could be unpredictable. Unlike other drugs, antibiotic drug products were not approved in section 505 new drug applications. Monographs were later established and published in the Code of Federal Regulations to provide standards for certification of bulk antibiotics and their finished dosage forms.

Initially, section 507 applied only to penicillin or any derivative of penicillin; other named antibiotic drugs were added to the statute as they were developed.⁶ The more general definition was added to the statute in the 1962 amendments to the Act, which precluded the need for a statutory change with the discovery of additional new antibiotics.

The current definition of “antibiotic drug” found in section 201(jj) of the Act contains both the early substance-specific list of antibiotic drugs and the 1962 general definition. In section 201(jj), an antibiotic drug is defined as

“any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof.”

Of note is that the definition lists certain specific antibiotic drug substances first, and then defines antibiotic drugs by reference to the origin and the chemical characteristics of the substance. Neither part of the definition includes any reference to the intended use of the drug, for example to treat a particular disease or condition. Also, the definition specifically states that, if the drug contains “any quantity” of a substance having certain

⁵ This review did not examine every decision the agency has made regarding classification of antibiotics. We have focused on decisions where issues were raised as to whether a drug product was to be regulated under section 505 or 507 of the Act, and for which we could locate adequate records. In documenting the approach that CDER has historically taken in the classification of antibiotic drugs, a review was conducted of the FDA archival files of drugs thought to have significance in that regard. These applications included drugs for which the classification was either controversial or for which the decision demonstrates one or more of the fundamental principles that make up the FDA’s policy regarding the classification of antibiotics. Relevant available information from this search was compiled to prepare this report.

⁶ Streptomycin was added in 1947; aureomycin, chloramphenicol, and bacitracin were added in 1949; chlortetracycline was substituted for aureomycin (a trade name for chlortetracycline) in 1953.

characteristics (produced by micro-organisms and having the capacity to inhibit or destroy micro-organisms in dilute solution), that drug is an antibiotic drug.⁷

Because the antibiotic drug definition does not include any reference to the intended use of the drug for an anti-microbial or anti-infective indication, and instead defines an antibiotic drug by reference to the nature of the drug substance, a number of drug products that are not intended to be used for antimicrobial purposes have been classified by FDA as antibiotic drugs. These include, for example, bleomycin, doxorubicin, and daunorubicin, which are antibiotic drugs originally approved under section 507 and indicated for cancer therapy. (Attachment 14) Conversely, a number of antimicrobial drug products are not antibiotic drugs, because they fail the first test of the general definition (any chemical substance which is produced by a micro-organism ... (including a chemically synthesized equivalent of any such substance) or any derivative thereof). Examples of these drugs include the quinolone antibacterial products (e.g., Cipro, Levaquin, and Trovan) and most antiviral products; these have been regulated under section 505. (Attachment 15)

FDA'S HISTORIC INTERPRETATION OF SECTION 507

CDER does not have a formal, written statement of its policy regarding the classification of antibiotic drugs under the second, general, definition of antibiotic drug. Consequently, any documentation of a "working policy" has largely been generated in response to specific challenges to FDA's classification of individual drugs. These challenges can be divided into four general classes: a) drugs that are made by chemical synthesis and/or modification of antibiotic drug substances, b) antimicrobial drugs that do not fit the statutory definition of antibiotic drug, c) drugs that meet the definition of antibiotic drug, but are not indicated for antimicrobial use, and d) drugs in which the drug substance or moiety has been classified as an antibiotic drug and used for antimicrobial therapy, but subsequently were submitted for a non-antimicrobial use, or for use at a dose incapable of antimicrobial activity.

The Periostat challenge does not currently involve issues of a) the nature of the chemical synthesis of doxycycline⁸ or b) whether doxycycline is a drug indicated for anti-microbial use that is not an antibiotic drug. Therefore, our analysis focuses on FDA's treatment of two of the four general classes of drugs as to which antibiotic drug questions have been raised: c) drugs that meet the definition of antibiotic drug, but are not indicated for antimicrobial use, and d) drugs in which the drug substance has been classified as an antibiotic drug and used for antimicrobial therapy, but for which an application is subsequently submitted for a non-antimicrobial use, and/or for a dose that is not capable of antimicrobial activity.

⁷ FDA interprets the term "microorganism" to include bacteria, fungi, viruses, and other microscopic organisms.

⁸ The 1997 letter argued that doxycycline was not an antibiotic because it did not meet the "source" requirements in the general definition ("produced by micro-organisms..."). The later CollaGenex correspondence abandons this argument, and it is not at issue in the lawsuit.

Drugs that meet the statutory definition of antibiotic drug, but are not indicated for antimicrobial use

The statutory definition of antibiotic drug does not refer to the intended clinical use of a substance, and the FDA has consistently interpreted the definition to preclude consideration of how the drug product is intended to be used as the dispositive factor in whether the product is an antibiotic drug. Many drug products have been approved for non-antimicrobial uses and, nevertheless, classified as antibiotic drugs. Most of these are agents for cancer therapy or immunomodulators (e.g., drugs used to prevent organ rejection in transplant patients). Cancer therapies approved under section 507 include dactinomycin, plicamycin, bleomycin, doxorubicin, daunorubicin, streptozocin, idarubicin, epirubicin, and mitomycin. (Attachment 14) Immunomodulator drugs that have been approved under section 507 are cyclosporine, tacrolimus, and mycophenolate mofetil. (Attachment 16)

Note that there were a number of monographs for antibiotic drugs that are indicated only for oncologic (non-antimicrobial) uses, for example, mitomycin, doxorubicin, bleomycin and daunorubicin. These are listed at 21 CFR 430.4(a)(1998).

When a drug that contains "any quantity of any chemical substance which is produced by a micro-organism (including a chemically synthesized equivalent of any such substance) or any derivative thereof" is indicated for an antimicrobial use, it is a straightforward matter to determine that the drug "has the capacity to inhibit or destroy micro-organisms in dilute solution," because it is precisely that use for which the drug is intended.

Based upon our review of available decisions to classify drugs as antibiotic drugs, it appears the agency has interpreted "dilute solution" to correspond to concentrations that are found in human tissue at proposed or approved human dosing levels. As Dr. James Ramsey, the Microbiology Team Leader in the Division of Antiviral Drug Products, noted at page 2 of an August 1997 review regarding whether lovastatin is an antibiotic drug, "the term dilute solution has been generally accepted as the drug concentration in pre-clinical studies that elicits inhibitory activity against micro-organisms that correlates with clinically relevant human tissue concentrations. Human tissue concentrations considered relevant are those that are achieved from doses administered to the human target populations for the indicated use of the drug." (Attachment 17) As noted above, for a drug that is indicated for use as an antimicrobial agent, there is no question of its antimicrobial activity at these concentrations. For drugs that are not indicated for use as antimicrobial therapy, the determination of whether a substance has the capacity to inhibit or destroy micro-organisms in dilute solution requires additional analysis.

This is well illustrated with the case of the Sandoz immunomodulator, cyclosporine. Sandoz originally submitted two NDAs in 1982 under 505(b), for the use of cyclosporine for prevention of organ rejection (heart, kidney, and liver). (Attachment 18) After reviewing cyclosporine's microbial origins and early studies that showed *in vitro* anti-fungal activity, the FDA reclassified these applications as antibiotic drugs submitted under 507. The cyclosporine applications were subsequently approved under section 507

in 1983. In October 1994, and again on March 19, 1997, Sandoz challenged the classification of cyclosporine as an antibiotic drug. In the 1997 challenge, Sandoz argued that, if the FDA were to apply its classification criteria consistently, lovastatin should also have been classified as an antibiotic drug. FDA disagreed. (Attachment 19)

Lovastatin, an HMG-CoA reductase inhibitor, was approved as a cholesterol lowering agent in 1987. (Attachment 20) This drug was originally isolated from the microbe, *Penicillium citrinum*, but the first publications reporting lovastatin's antimicrobial activity appeared in 1988, a year after its approval. These publications provided no evidence that lovastatin has antimicrobial activity in humans; such activity was observed in animal studies only. In its response to Sandoz's challenge, FDA researched the literature to confirm that lovastatin has antimicrobial activity in animals. Since human data were not available, the FDA compared the level of drug expected to be found in humans at approved doses to levels that were shown to inhibit or destroy micro-organisms in *in vitro* tests. It was estimated that, at concentrations found in humans treated at recommended doses as a cholesterol lowering agent, lovastatin would not be expected to inhibit or destroy micro-organisms. The review of these issues is contained in an August 1, 1997 Memorandum from James Ramsey, Ph.D., to Dr. Murray Lumpkin, entitled "Antimicrobial Activity of Lovastatin and Related Drugs." (Attachment 17)

It should be noted that the concentration of lovastatin found in humans, when dosed according to labeling, is about 0.1 micromolar (μM), or about 4 parts per 10 million. A conservative estimate of the concentration of lovastatin needed to inhibit or destroy micro-organisms is about 3- to 25-fold the actual concentration found in humans, or about 12 to 100 parts per 10 million.

Simvastatin is another HMG-CoA reductase inhibitor that has microbial origins and possesses antimicrobial activity. The literature on simvastatin was also reviewed and similar conclusions were drawn concerning its inability to inhibit or destroy micro-organisms at levels achieved with recommended doses as a cholesterol lowering drug. (Attachment 17)

Cyclosporine is in many ways similar to lovastatin and simvastatin, but with important differences that influence how it is classified. It is produced by a micro-organism, and it has been shown to have antimicrobial activity. Also, as with lovastatin, there are inadequate human data to show that cyclosporine has antimicrobial activity in humans. However, in evaluating the antifungal properties of cyclosporine in animal models as well as in *in vitro* tests, the agency has concluded that cyclosporine has antifungal activity against the human pathogens, *Cryptococcus neoformans* and *Coccidioides immitis* at levels that are found in human plasma at the recommended doses. FDA therefore concluded that cyclosporine was appropriately classified as an antibiotic, whereas lovastatin was not classified as an antibiotic drug because it did not have adequate antimicrobial activity at concentrations corresponding to the recommended human dose and therefore did not meet the "dilute solution" criterion of the definition. A December 15, 1994 Memorandum from Dr. James Ramsey, then Supervisory Microbiologist, Division of Antiviral Drug Products, to Dr. Murray Lumpkin, Deputy

Director for Review Management, CDER, entitled "Cyclosporine –Request for Reclassification" describes the agency's analysis. (Attachment 21)

One could reasonably argue that a concentration of lovastatin of 12 to 100 parts per 10 million that is capable of inhibiting or destroying micro-organisms would constitute a dilute solution, as would a solution of much higher concentration. Although the statutory language is broad, the agency has, as demonstrated by the cyclosporine and lovastatin cases, narrowed the definition in application so that "dilute solution" is interpreted as a solution that corresponds with clinically relevant concentrations, that is concentrations that correlate to those achieved with a proposed or approved dose. This interpretation, which refers to concentrations indicated for human use, provides a reasonable and objective line for making antibiotic drug determinations for drugs intended for human use. Based upon our review of the agency's antibiotic drug decisions, the agency has not interpreted "dilute solution" such that, if there is any concentration at which the substance would have the capacity to inhibit or destroy micro-organisms, that substance is an antibiotic. Instead, in making its determination, the agency has looked at whether there is a proposed or approved human dose that corresponds to a concentration at which the substance would have the capacity to inhibit or destroy micro-organisms.

Drugs in which the drug substance has been classified as an antibiotic drug and used for antimicrobial therapy, but for which an application is subsequently submitted for a non-antimicrobial use and/or for a dose that is not capable of antimicrobial activity

The Periostat matter poses two additional questions: 1) can, or must, FDA change the classification of a drug substance or active moiety as an antibiotic drug or non-antibiotic drug if an application for a drug product containing the substance is submitted for a new non-antimicrobial indication and, 2) can, or must, FDA change the classification of a drug substance or active moiety as an antibiotic drug or non-antibiotic drug if an application is submitted at a new non-antimicrobial dose?

Change of indication

CollaGenex does not contend that doxycycline is not an antibiotic drug at the 50 mg, 75 mg, 100 mg, and 200 mg dose formulations previously approved by FDA to treat a number of infections (including infections of the respiratory tract, several different types of sexually transmitted infections, urinary tract infections due to selected micro-organisms, anthrax, plague, cholera, gastrointestinal infections, selected infections acquired from tick bites caused by infecting microbes listed in the product labels, and for the prophylaxis of malaria).^{1,2,3,4} However, Periostat, CollaGenex's doxycycline hyclate 20 mg product, is approved 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. Doxycycline has been shown to inhibit the activity of collagenase *in vitro* and to reduce the elevated collagenase activity in the gingival crevicular fluid of patients with adult

periodontitis. The clinical significance of these *in vitro* findings is unknown.⁹ We note that some authors postulate that doxycycline's inhibitory activity on collagenase [i.e., a non-antimicrobial activity of doxycycline] is the mechanism for doxycycline's therapeutic activity as adjunctive therapy for adult periodontitis.¹⁰

Even if we assume that a non-antimicrobial activity is responsible for Periostat's clinical effect, this would not have been dispositive as to Periostat's classification. The agency has consistently interpreted the statutory definition of antibiotic drug such that intended or labeled use of the drug is not dispositive in determining whether a drug is an antibiotic (e.g., cancer therapies). The use of doxycycline as Periostat, as adjunctive therapy for adult periodontitis, is no exception. Even if Periostat is neither indicated for an antimicrobial indication, nor acting as an antimicrobial drug in the treatment of adult periodontitis, this does not mean that Periostat is, for that reason, not an antibiotic drug within the definition in the FDCA.

Change of dose

We have been unable to locate documents in which the agency has discussed the question of whether a drug that has previously been correctly classified as an antibiotic drug can, or must, subsequently be classified as a non-antibiotic drug if it is later used for a non-antimicrobial use at doses that correspond to a dilute solution concentration that lacks the capacity to inhibit or destroy micro-organisms. This is, however, an important question.¹¹ The statute clearly links the antibiotic definition to the specific properties of the chemical substance, not to the particular indication or dose. Once a substance is found to meet the statutory criteria as a chemical substance 1) which is produced by a micro-organism, and 2) which has the capacity to inhibit or destroy micro-organisms in dilute solution, then the statutory language is most reasonably read to mean that any drug intended for human use containing any quantity of that substance is considered to be an antibiotic.¹² Thus, even if doxycycline hyclate at the 20 mg dose did not correspond with a concentration that has the capacity to inhibit or destroy micro-organisms in dilute solution, Periostat contains a quantity of doxycycline, and doxycycline is known to have the capacity to inhibit or destroy micro-organisms in a dilute solution corresponding to

⁹ Product Labeling for Periostat® (doxycycline hyclate tablets) 20 mg, NDA 50-783; Revised April 2001. (Attachment 22)

¹⁰ Walker C, Thomas J, Nango S, et al. Long-Term Treatment with Subantimicrobial Dose Doxycycline Exerts No Antibacterial Effect on the Subgingival Microflora Associated with Adult Periodontitis. *J Periodontol* 2000;71:1465-1471. (Attachment 23)

¹¹ In the case of Periostat, this question is not dispositive because, as demonstrated later in this memorandum, doxycycline does have antimicrobial activity at concentrations found with Periostat's recommended dose.

¹² 21 CFR 314.3 (b) (2003) provides the following definitions of "drug substance" and "drug product". "Drug substance means an active ingredient that is intended to furnish pharmacologic activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use[d] in the synthesis of such ingrediens." "Drug Product means a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients."

approved human doses (ranging from 100 to 200 mg per day taken orally) at which it is indicated for use for the treatment of a variety of infections.^{1,2,3,4}

One might think that this interpretation conflicts with the agency's decision regarding lovastatin. That is not the case, however. Lovastatin was not shown to have antimicrobial activity in dilute solution corresponding with an approved human dose, so it was not found to have the innate characteristics of an antibiotic drug that meets the "dilute solution" criterion. Once a drug like doxycycline has clearly been shown to have antimicrobial activity in dilute solution, that drug is an antibiotic; therefore, any quantity of that drug would still be an antibiotic.¹³

CDER PRECEDENT SUMMARY

The cases and analysis described above relate to the FDA's interpretation of the statutory definition of antibiotic drug. In review, the following points are important:

- The fact that a drug is not indicated for an antimicrobial use is not dispositive as to whether that drug is to be classified as an antibiotic. The clearest examples of this policy would be the immunomodulators and cancer therapies. The decision to classify Periostat as an antibiotic is consistent with this approach.
- "Dilute solution" has been interpreted to be a concentration that correlates with the level expected to be found in human tissue at any proposed or approved dose. This is the principle used to distinguish cyclosporine from lovastatin.
- The classification of a drug as an antibiotic is based on the specific characteristics of the chemical drug substance or moiety. Therefore, an antibiotic drug cannot be reclassified if it is used, in a particular drug product, at a sub-antimicrobial dose.

The remainder of this memorandum is an analysis of whether Periostat (doxycycline hyclate) 20 mg meets the statutory definition of an antibiotic drug, and a review of the arguments that Periostat is not an antibiotic made by CollaGenex in 1997, 1998, and in the past year.

PERIOSTAT IS AN ANTIBIOTIC DRUG

As discussed above, the definition of an antibiotic drug at section 201(jj) of the Act identifies two general categories: specific named antibiotic drug substances and antibiotic

¹³ FDA has never addressed the case in which a drug produced by micro-organisms and previously classified as a non-antibiotic was later found to have the capacity to inhibit or destroy micro-organisms in a dilute solution corresponding to an indicated human dose different from that dose at which it was evaluated for the first product. It is possible that in that case, a drug previously classified as a non-antibiotic drug would be reclassified as an antibiotic drug.

drugs defined by the characteristics of the chemical substance. Specifically, the term "antibiotic drug" means

- 1) any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or
- 2) any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance)

or any derivative thereof.

We, in consultation with CDER staff, including chemistry, microbiology, and dental reviewers, have analyzed Periostat under both categories in the definition, and conclude that Periostat is an antibiotic drug under the second, general, definition of antibiotic drug.

Doxycycline is a derivative of a chemical substance produced by a micro-organism

Doxycycline is a well-known, broad-spectrum antibiotic substance that is synthetically derived from oxytetracycline.^{1,2,3,4} Prior to the passage of FDAMA and the subsequent withdrawal of FDA regulations describing specific antibiotics, the applicable FDA regulation defined oxytetracycline as follows:

Oxytetracycline. Each of the several antibiotic substances produced by the growth of *Streptomyces rimosus* and each of the same substances produced by any other means is a kind of oxytetracycline.

21 CFR 430.4(a)(21)(1998). Hence, doxycycline is a semi-synthetic substance derived from oxytetracycline, a substance produced by a micro-organism.

Doxycycline has the capacity to inhibit or destroy micro-organisms in dilute solution

This memorandum has already discussed how FDA has applied the concept of "in dilute solution." This assessment examines the particular capacity to inhibit or destroy micro-organisms at the concentrations achieved in serum by Periostat (doxycycline hyclate tablets) at its approved dosage of 20 mg orally twice daily (for a total daily dose of 40 mg).

A number of doxycycline formulations are approved for adults at usual doses of 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg/day. The approved dosing regimen also notes that the maintenance dose may be increased to 200 mg/day in adults for the treatment of more severe infections. The approved indications for these various formulations include a number of infections, including infections of the respiratory tract, several different types

of sexually transmitted infections, urinary tract infections due to selected micro-organisms, anthrax, plague, cholera, gastrointestinal infections, selected infections acquired from tick bites caused by infecting microbes listed in the product labels, and for the prophylaxis of malaria.

CollaGenex's Periostat (doxycycline hyclate) 20 mg is indicated 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.⁹ The dosage for this indication is Periostat (doxycycline hyclate) 20 mg orally twice daily as an adjunct following scaling and root planing.⁹ Periostat may be administered for up to 9 months.⁹ Note that Periostat at a dose of 20 mg twice daily provides a total daily dose of 40 mg, which is 40% of the approved usual daily maintenance dose of 100 mg daily for doxycycline formulations that are approved to treat a number of different types of infections.^{1,3,4}

Doxycycline concentrations that inhibit micro-organisms

Doxycycline has activity against a variety of microbes (e.g., bacteria). The concentrations of doxycycline that have activity against (inhibit growth of) the various microbes vary by the particular microbe and even for particular isolates within a particular group of microbes. For example, some bacterial isolates (e.g., a particular bacteria isolated from a particular patient) may be more or less susceptible than other isolates of the same bacteria from other patients. A sampling from the published literature of the concentration ranges of doxycycline that inhibit bacterial growth for particular types of bacteria as summarized from several references is provided in table 1.

From examination of table 1, the lower extent of the ranges of concentrations of doxycycline that inhibit certain micro-organisms are as low as 0.06 or 0.03 micrograms per milliliter ($\mu\text{g}/\text{mL}$). For some bacterial strains the lowest concentration of doxycycline that inhibits bacterial growth for some bacterial isolates was not specifically determined (e.g., bacterial isolates inhibited by $\leq 0.015 \mu\text{g}/\text{mL}$). Clearly there are bacterial strains that are inhibited by low concentrations of doxycycline. For example, in table 1, the range of concentrations of doxycycline that inhibit *Chlamydia psittaci* are from 0.03 to 0.06 $\mu\text{g}/\text{mL}$ of doxycycline.

Table 1. Range of Doxycycline Concentrations with Inhibitory Activity for Selected Bacterial Micro-organisms^a

Micro-organism(s) ^a	Range of Concentrations of Doxycycline with Inhibitory Activity (µg/mL) ^b	Reference
<i>Actinobacillus actinomycetemcomitans</i>	0.5 - 4	19
<i>Bacteroides forsythus</i>	<0.06-0.12	14
<i>Bergeyella zoohelcum</i>	≤0.015-0.5	15
<i>B. catarrhalis</i> (non-B-lactamase producers)	0.06 - 0.25	16
<i>Chlamydia psittaci</i>	0.03-0.06	17
<i>Chlamydia trachomatis</i>	0.03-0.06	17
<i>Corynebacterium</i> spp. ^c	≤0.015-4	15
<i>Fusobacterium</i> spp. ^d	≤0.015-0.125	15
<i>Klebsiella pneumoniae</i>	0.5 - 256	16
Miscellaneous gram-negative bacteria ^e	≤0.015-0.5	15
<i>Mycoplasma hominis</i>	≤0.03-8	18
<i>Neisseria gonorrhoeae</i>	0.09 - 3.1	21
<i>Porphyromonas</i> spp.	≤0.25 - 1	19
<i>Prevotella melaninogenica</i>	≤0.5 - >8	20
<i>Providencia stuartii</i>	8 - 512	16
<i>Staphylococcus aureus</i>	0.06-0.06	15
<i>Staphylococcus aureus</i>	≤0.4 - >6.4	20
<i>Staphylococcus</i> , coagulase negative	0.03-16	15
<i>Streptococcus pneumoniae</i>	0.04 - 0.39	21
<i>Streptococcus pyogenes</i>	0.09 - 25.0	21
<i>Ureaplasma urealyticum</i>	≤0.03-≥16	18
87 bacterial isolates from odontogenic abscesses	0.016-32	22

- a. The word "micro-organism" is used to represent a specific group of micro-organisms (e.g., a type of bacteria)
- b. One microgram (µg) equals 0.001 milligram (mg) or 1 mg equals 1000 µg therefore 20 mg equals 20,000 µg.
- c. *C. accolens*; *C. argentoratense*; *Corynebacterium* Grp. F1, Grp. G, and Grp. G2; *C. jeikeium*; *C. minutissimum*; *C. propinquum*; *C. ulcerans*; *Corynebacterium* spp., no good fit.
- d. *F. necrophorum* and *F. russii*.
- e. *Bordetella bronchiseptica*, *Capnocytophaga* sp., CDC NO-1, *Haemophilus aphrophilus*, *Haemophilus parainfluenzae*, *Neisseria cinerea* or *N. flavescens*, *Neisseria elongata*, *Neisseria* species, *Rimerella anatipestifer*.

¹⁴ Takemoto T, Kurihara H, Dahlen G. 1997. Characterization of *Bacteroides forsythus* isolates. J Clin Micro. 35:6; 1378-1381. (Attachment 24)

¹⁵ Goldstein EJC, Citron DM, Merriam CV, et al. 2000. Comparative *in vitro* activities of GAR-936 against aerobic and anaerobic animal and human bite wound pathogens. Antimicrob Agents and Chemother. 44:10; 2747-2752. (Attachment 25)

¹⁶ Wiedemann B, H Grimm. 1996. Susceptibility to Antibiotics: Species Incidence and Trends, pg. 900-1168. In V Lorian (ed.). Antibiotics in Laboratory Medicine, 4th edition, Williams & Wilkins. p. 1000. (Attachment 26)

¹⁷ Donati M, Pollini GM, Sparacino M, et al. 2002. Comparative *in vitro* activity of garenoxacin against *Chlamydia* spp. J of Antimicrob Chemotherap. 50. 407-410. (Attachment 27)

¹⁸ Ullman U, Schubert S, Krausse R. 1999. Comparative *in-vitro* activity of levofloxacin, other fluoroquinolones, doxycycline and erythromycin against *Ureaplasma urealyticum* and *Mycoplasma hominis*. (Attachment 28)

¹⁹ Eick S, W Pfister, E Straube. 1999. Antimicrobial susceptibility of anaerobic and capnophilic bacteria isolated from odontogenic abscesses and rapidly progressive periodontitis. International J Antimicrob Agents 12:41-46. (Att. 29)

²⁰ Standiford, HC. 1999. Tetracyclines and Chloramphenicol, pg. 336-348. In GL Mandell, JE Bennett, and R Dolin (ed.), Principles and Practice of Infectious Diseases, 5th edition, Churchill Livingstone, Philadelphia. (Attachment 30)

²¹ Kucers A, Crowe SM, Grayson ML, Hoy JF. The use of antibiotics: A clinical review of antibacterial, antifungal and antiviral drugs. Butterworth and Heinemann, Oxford., 5th Edition. 1997. Chapter "Tetracyclines." p. 730. (Att. 31)

²² Sobottka I, Cachovan G, Sturenburg E, et al. 2002. *In vitro* activity of moxifloxacin against bacteria isolated from odontogenic abscesses. Antimicrob Agents and Chemother. 46:12; 4019-4021. (Attachment 32)

Doxycycline concentrations attained in serum

The approved labeling for Pfizer's Vibramycin® (brand name) oral formulations of doxycycline state that the administration of a 200 mg oral dose of doxycycline to normal adult volunteers resulted in peak serum levels²³ of 2.6 µg/mL at 2 hours decreasing to 1.45 µg/mL at 24 hours.¹ The product label does not provide an estimate of the maximum serum concentration after repeated doses, but an author estimates the levels attained to be approximately 4 µg/mL.²⁴ The approved labeling for Pfizer's Vibramycin (brand name) oral formulations of doxycycline states that bacteria that are inhibited by doxycycline concentrations of 4 µg/mL or less, based upon results from *in vitro* susceptibility testing, are considered susceptible to doxycycline treatment at the approved adult doses of 100 to 200 mg orally administered daily.²⁵

The concentrations of doxycycline in the serum that are attained by Periostat (doxycycline hyclate tablets) are described in the Periostat product label. Administration of a single 20 mg oral dose of doxycycline hyclate to volunteers resulted in mean peak serum levels of 0.3 µg/mL. After repeated doses of Periostat 20 mg orally twice daily (i.e., at steady-state) resulted in mean peak serum levels of 0.790 µg/mL.⁹

Periostat achieves concentrations that will inhibit some bacterial strains

The ranges of doxycycline concentrations that inhibit a variety of different types of bacteria are summarized in Table 1. The concentrations that will inhibit some microorganisms are within the range of the serum concentrations attained with Periostat (doxycycline hyclate tablets) 20 mg orally twice daily, indicating that Periostat could be expected to have inhibitory activity against susceptible isolates of these particular types of bacteria. Even if the effective concentration of doxycycline is only one tenth of the achieved doxycycline serum level of 0.79 µg/mL, Periostat retains its capacity to inhibit bacteria. For example, in table 1, the range of concentrations of doxycycline that inhibit *Chlamydia psittaci* are from 0.03 to 0.06 µg/mL of doxycycline. The ranges reported in table 1 provide the concentrations of doxycycline that inhibit the different isolates of a particular type of bacteria that have been tested. Other isolates of specific types of bacteria included in table 1 that have been reported to be inhibited by low concentrations of doxycycline include *Bacteroides forsythus*, *Bergeyella zoohelcum*, *Chlamydia trachomatis*, *Corynebacterium* spp., *Fusobacterium* spp. and others.

In conclusion, Periostat (doxycycline hyclate tablets) when administered using a dosage regimen of 20 mg orally twice daily has the capacity to inhibit or destroy strains of

²³ For purposes of our analysis, serum concentrations are being used as the index tissue concentrations.

²⁴ Kucers A, Crowe SM, Grayson ML, Hoy JF. The use of antibiotics: A clinical review of antibacterial, antifungal and antiviral drugs. Butterworth and Heinemann, Oxford., 5th Edition. 1997. Chapter "Tetracyclines." p. 730. (Attachment 31)

²⁵ We note that, in examining the serum concentrations attained and the criteria for considering a bacterial isolate susceptible, there is no specific adjustment for the protein bound and free drug fractions of doxycycline.

bacteria (i.e., micro-organisms) susceptible to low concentrations of doxycycline. Therefore, doxycycline in Periostat is an antibiotic drug.

A human drug that contains any quantity of doxycycline is an antibiotic drug

We have determined that Periostat (doxycycline hyclate) when administered using a dosage regimen of 20 mg orally twice daily has the capacity to inhibit or destroy micro-organisms susceptible to low concentrations of doxycycline. However, it is also important to note that the Act defines an antibiotic drug as “containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof” [emphasis added]. Therefore, even if the dose of doxycycline for Periostat did not itself correspond to a dilute solution concentration that was capable of inhibiting or destroying micro-organisms, Periostat contains a quantity of doxycycline, which is known to inhibit or destroy micro-organisms in dilute solution corresponding to an approved dose.

Periostat (doxycycline hyclate tablets) is an antibiotic drug

- Doxycycline is a derivative of oxytetracycline, a substance produced by a micro-organism. Some bacterial strains are inhibited or destroyed at low concentrations of doxycycline. Doxycycline has the capacity to inhibit or destroy these susceptible micro-organisms in dilute solution, including at the serum concentrations attained by Periostat at a dose of 20 mg orally twice daily (the approved dosing regimen for Periostat).
- The definition of an antibiotic drug states that a drug containing any quantity of the antibiotic substance that inhibits or destroys micro-organisms in dilute solution is an antibiotic drug; antibiotic status is not contingent upon the specific administered dose or therapeutic use. Therefore, Periostat (doxycycline hyclate) 20 mg, which contains the substance doxycycline, is an antibiotic drug.
- Periostat meets the definition of an antibiotic drug described in section 201(jj) of the Act.

ADDITIONAL POINTS RAISED BY COLLAGENEX IN CORRESPONDENCE

In its September 11, 1997, July 8, 1998, November 18, 2002, and January 21, 2003, letters to FDA, CollaGenex made a number of points regarding Periostat and its classification as an antibiotic drug. In the following sections these points are addressed.

CollaGenex asserts that Periostat does not contain an antibiotic drug

As noted in the analysis above, we have concluded that Periostat® (doxycycline hyclate) 20 mg is an antibiotic drug as defined by section 201(jj) of the Act.

CollaGenex asserts doxycycline hyclate 20 mg has no antibiotic effect

The Periostat (doxycycline hyclate tablets) 20 mg product label states the following:

The dosage of doxycycline achieved with this product [Periostat] during administration is well below the concentration required to inhibit micro-organisms commonly associated with adult periodontitis. Clinical studies with this product demonstrated no effect on total anaerobic and facultative bacteria in plaque samples from patients administered this dose regimen for 9 to 18 months. This product should not be used for reducing the numbers of or eliminating those micro-organisms associated with periodontitis.

Although the approved Periostat labeling notes that no effect was demonstrated on total anaerobic and facultative (capable of growth under anaerobic and aerobic conditions) bacteria in plaque samples, this does not preclude a finding that Periostat has antimicrobial activity. The assessment of whether an antibiotic substance has activity against micro-organisms should not be limited to examining only certain types or categories of bacteria. Even if no effect was observed on certain types or categories of bacteria associated with periodontitis, this does not exclude the drug's capacity to inhibit or destroy other types of micro-organisms or individual bacterial strains. As shown above, the concentrations achieved with doxycycline 20 mg orally twice daily have the capacity to inhibit or destroy micro-organisms susceptible to low concentrations of doxycycline. This point is discussed above under the heading "Periostat achieves concentrations that will inhibit some bacterial strains."

That Periostat's postulated mechanism of action for the treatment of periodontal disease does not involve the inhibition or destruction of micro-organisms also does not make Periostat (doxycycline hyclate tablets) a non-antibiotic drug. That doxycycline has the capacity to inhibit or destroy micro-organisms in dilute solution is a property of doxycycline, an antibiotic substance; even if doxycycline therapy is being used for some other non-antimicrobial mechanism of action, doxycycline remains an antibiotic substance.

The product label for Periostat notes the following regarding collagenase activity:

Mechanism of Action: Doxycycline has been shown to inhibit collagenase activity *in vitro*. Additional studies have shown that doxycycline reduces the elevated collagenase activity in the gingival crevicular fluid of patients with adult periodontitis. The clinical significance of these findings is not known.⁹

The product label makes it clear that the clinical significance of the findings (i.e., doxycycline's ability to inhibit collagenase) is not known. The basis for the clinical effects of Periostat (i.e., the mechanism of action) has not been clearly established.

The January 21, 2003 letter also cites a publication by Walker, Thomas, Nango, et al.²⁶ The letter states that the study concluded that “no antimicrobial effect resulted during or following a treatment regimen with 20 mg doxycycline bid.” Review of this publication helps to put the authors' conclusion into perspective and also reveals that, although the authors posit that the most likely explanation is their hypothesis that this is not an antimicrobial effect, the authors also note that other explanations for the effects observed in the study are possible. The authors note that “the small and large spirochetal groups (a particular category of micro-organisms) were found to be significantly lower at certain periods in the SDD [“subantimicrobial dose doxycycline”] treatment group than in the corresponding placebo group.”²⁶ The authors then go on to state that the possible explanations for the observed findings are as follows:

- “The levels of doxycycline obtained in the periodontal pocket are inhibitory for these organisms.”
- The decrease in the quantity of spirochetal organisms is due to the change in the periodontal pocket becoming more aerobic.
- Reduction in the degree of inflammation in the periodontal pocket leading to a healthier periodontal pocket and in turn a reduction in spirochetes.

The authors favor the third hypothesis as the most likely of these possible explanations. However, the other two hypotheses (microbial inhibition by the antibiotic doxycycline and/or an increasingly aerobic periodontal pocket) remain possible explanations or contributing factors to explain the observed reduction in spirochetal organisms. It is notable that the first of these three hypotheses involves the antimicrobial activity of doxycycline.

The pathophysiology of periodontal disease is described to result from “the interaction between bacterial products and the host's immune system and inflammatory responses.”²⁷ Hence, it remains plausible that an antimicrobial effect could play a role in altering the disease process.

²⁶ Walker C, Thomas J, Nango S, et al. Long-Term Treatment with Subantimicrobial Dose Doxycycline Exerts No Antibacterial Effect on the Subgingival Microflora Associated with Adult Periodontitis. *J Periodontol* 2000;71:1465-1471. (Attachment 23)

²⁷ Seymour RA, Meehan JG, Yates MS. *Pharmacology and Dental Therapeutics*. Oxford University Press, New York. 1999. Chapter 12 “Pharmacological Control of Dental Caries and Periodontal Disease,” p. 182. (Attachment 33)

The January 21, 2003 letter also states in a footnote that “The lowest plasma concentration that results in antimicrobial activity levels in tissue is 1 microgram per milliliter”²⁸ and refers to what we presume to be an abstract of a presentation titled “Reduced Doxycycline Blood Levels in Humans Fail to Promote Resistant Organisms” that was made at the “International Conference on Periodontal Disease: Pathogens & Host Immune Responses in Osaka, Japan” in 1990 by McNamara, Golub, and Ramamurthy. The abstract from this 1990 conference in Osaka, Japan was not provided. Therefore we are unable to provide specific comment on the cited abstract for the presentation. However, we have provided in table 1 the range of susceptibilities reported for a number of microorganisms and the range of susceptibilities go well below 1 microgram per milliliter for most of the organisms in the table.

The January 21, 2003 letter, also in footnote 11, states that “when FDA gave notice of doxycycline’s uses as an antibiotic to treat anthrax, it specifically exempted doxycycline hyclate 20 mg.” (Attachment 13) The Federal Register (FR) notice on Doxycycline and Penicillin G Procaine Administration for Inhalational Anthrax does exclude doxycycline hyclate 20 mg for the treatment of this specific infection (i.e., anthrax due to *Bacillus anthracis*). The purpose of the notice was to clarify that the currently approved indications for doxycycline and penicillin G procaine (at the time of the FR notice) for Anthrax due to *Bacillus anthracis* includes uses in cases of inhalational exposure to *Bacillus anthracis*.²⁹ Periostat (doxycycline hyclate) did not and does not include an indication for treatment of Anthrax due to *Bacillus anthracis* and therefore the FR notice clarified that the FR notice does not apply to Periostat, as explained in the following footnote from the FR notice.

Doxycycline hyclate tablets, equivalent to 20 milligrams (mg) base, and doxycycline hyclate, 10 percent, for controlled release in subgingival application are not subjects of this notice because they have periodontal indications and do not have indications for anthrax or infections caused by *Bacillus anthracis*.²⁹

The reason for exemption was not because Periostat is not an antibiotic drug, but instead because it lacks an indication for anthrax. This statement in the FR notice does not support the argument that Periostat is not an antibiotic drug.

CollaGenex asserts that doxycycline free drug concentrations are not sufficient to inhibit even profoundly susceptible microorganisms

In the letter of January 21, 2003, CollaGenex's counsel notes the following:

At our recent meeting, one of the FDA participants suggested that Periostat might have antibiotic effect on micro-organisms not associated with

²⁸ Footnote 10 of the January 21, 2003 letter from Buc & Beardsley to Daniel E. Troy, Esq. (Attachment 13)

²⁹ Prescription Drug Products: Doxycycline and Penicillin G Procaine Administration for Inhalational Anthrax (Post-Exposure), 66 Fed. Reg. 55679, 55680 (Nov. 2, 2001) (notice).

periodontitis, referencing pharmacokinetic data showing steady state mean maximum doxycycline plasma levels of 0.79 micrograms/mL after Periostat administration, which he believed would be adequate to kill certain micro-organisms. He failed to note, however, distribution data, also referenced in the package insert, showing that doxycycline is greater than 90% bound to plasma proteins. Thus only 10% is freely available; an effective level of 0.079 micrograms/mL in plasma, Periostat does not inhibit or destroy micro-organisms even if they retain a profound susceptibility to doxycycline.

Table 1 in this document provides the concentration ranges for inhibitory activity of doxycycline against selected bacterial micro-organisms based upon published reports. As noted in the table for some susceptible strains of a number of types of micro-organisms, even a concentration of 0.079 µg/mL would be inhibitory for some very susceptible strains of these organisms. For example, in table 1, there are several micro-organisms for which the range of concentrations of doxycycline that inhibit some isolates extend to concentrations below 0.079 µg/mL. The range of concentrations of doxycycline reported to inhibit *Chlamydia psittaci* in *in vitro* testing range from 0.03 to 0.06 µg/mL of doxycycline; concentrations lower than 0.079 µg/mL. Other organisms for which the range of doxycycline concentrations that extend below 0.079 µg/mL include *Bacteroides forsythus*, *Bergeyella zoohelcum*, *Chlamydia trachomatis*, *Corynebacterium* spp., *Fusobacterium* spp. Hence, the concentrations of free doxycycline attained with Periostat 20 mg orally twice daily are sufficient to retain inhibitory activity against strains of bacteria susceptible to low concentrations of doxycycline.

Lorabid and Azactam

The 1998 and 2003 letters also identify two examples of products that CollaGenex claims were not treated as antibiotics, but should have been: Lorabid (loracarbef) and Azactam (aztreonam for injection). These products have "50 series" (antibiotic) numbers. However, it appears that, because of an error, the approval letters for Lorabid and Azactam stated that the applications were submitted pursuant to section 505(b). Despite this error, the drugs are listed in the Orange Book with antibiotic series NDA numbers and subsequent correspondence regarding those applications has stated that the applications were submitted pursuant to section 507. (Attachment 34)