

Case IPR2015-
Patent No. 8,603,506
Petition for *Inter Partes* Review
Attorney Docket No. REDDYPP 7.1R-009

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

DR. REDDY'S LABORATORIES, LTD. and
DR. REDDY'S LABORATORIES, INC.
Requestors

v.

GALDERMA LABORATORIES, INC.
Patent Owner

Patent No. 8,603,506
Issue Date: December 10, 2013
Title: METHOD OF TREATING ACNE

Inter Partes Review No. Unassigned

**PETITION FOR *INTER PARTES* REVIEW OF
CLAIMS 1, 7, 8, 14, 15, AND 20 OF U.S. PATENT
NO. 8,603,506 AND MANDATORY NOTICES UNDER 37 C.F.R. § 42.8**

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Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. ("DRL,"
"Requestor," or "Petitioner") requests *inter partes* review of claims 1, 7, 8, 14, 15,
and 20 of U.S. Patent No. 8,603,506 ("the '506 Patent") (Exh.1001).

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NOTICE OF EACH REAL-PARTY-IN-INTEREST

The Real-Parties-In-Interest for this Petition are Requestor, Dr. Reddy's Laboratories, Ltd. ("DRL LTD") an Indian company, and Dr. Reddy's Laboratories, Inc. ("DRL Inc.") a U.S. company, and wholly owned subsidiary of DRL LTD. (collectively referred to herein as "DRL," "Requestor," or "Petitioner").

NOTICE OF RELATED MATTERS

Patent Owner¹ has asserted the '506 Patent as well as related U.S. Patent Nos. 7,211,267 and 7,232,572 in a civil action filed in the United States District Court for the District of Delaware (Civil Action No. 15-670), on July 31, 2015 ("the Litigation"). (Exh.1045.) Requestor has also filed concurrent *inter partes* review (also referred to herein as "IPR") petitions against the same claims of the

¹ Galderma is listed as the patent owner in the caption of this Petition, and as of August 18, 2015, is the recorded assignee of the '506 Patent in the USPTO Assignment Database. However, in the Litigation (defined herein), the Complaint states that Nestle Skin Health S.A. ("Nestlé") is now the owner of the '506 Patent. While the purported assignment to Nestlé is not yet recorded, Petitioner is serving both Galderma and Nestlé with this Petition, and as used herein, "Patent Owner" refers to both Galderma and Nestlé.

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‘506 Patent under different theories bearing attorney docket nos. REDDYPP 7.1R-015 and REDDYPP 7.1R-017.

NOTICE OF SERVICE INFORMATION

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GROUND FOR STANDING

Requestor certifies that the patent for which review is sought is available for *inter partes* review, and that Requestor is not barred or estopped from requesting an *inter partes* review on the grounds identified in the Petition. The Petition is filed within one year of the filing of the Complaint in the Litigation. (Exh.1045.) The Petition is thus timely under 35 U.S.C. § 315(b). The fee for this Petition has been paid. However, the U.S. Patent and Trademark Office is hereby authorized to charge Deposit Account No. 12-1095 for any fees that may be due and owing in connection with this Petition.

STATEMENT OF PRECISE RELIEF REQUESTED

Requestor requests that claims 1, 7, 8, 14, 15, and 20 of the ‘506 Patent be held unpatentable based on the following grounds:

Ground 1. Claims 1, 7, 8, 14, 15, and 20 would have been obvious over Sneddon (Exh.1006), in view of Golub (Exh.1048), Torresani (Exh.1010), and the 2000 PERIOSTAT PDR (Exh.1042). *See* 35 U.S.C. § 103(a).²

Ground 2. Claims 1, 8, and 15 would have been obvious over Golub (Exh.1048) in view of Torresani (Exh.1010) and further in view of Jansen (Exh.1034). *See* 35 U.S.C. § 103(a).

Ground 3. Claims 7, 14, and 20 would have been obvious over Golub (Exh.1048) in view of Torresani (Exh.1010), and Jansen (Exh.1034) and in further view of the 2000 PERIOSTAT PDR (Exh.1042). *See* 35 U.S.C. § 103(a).

Although Petitioner provides multiple grounds of unpatentability, they are meaningfully distinct. Ground 1 is meaningfully distinct from Grounds 2 and 3 because Ground 1 involves a different primary reference and takes a different approach to unpatentability. All of the Grounds in this Petition also represent meaningfully different arguments than those made in the corresponding IPR Petitions filed on the same date as this Petition bearing attorney docket nos. REDDYPP 7.1R-015 and REDDYPP 7.1R-017.

² The pre-AIA version of § 103 applies to each ground in this Petition, because the ‘506 Patent has an effective filing date before March 16, 2013.

Ground 1 starts with the premise that: (1) it was known to treat rosacea with tetracycline, including doxycycline (Exhs.1006, 1010); (2) it was known that the papules and pustules of rosacea were not bacterial, but more inflammatory conditions (Exhs.1010, 1048, 1004 ¶ 33); and (3) it was known that doxycycline was an effective anti-inflammatory agent at the claimed doses (Exhs.1010, 1042, 1048, 1004 ¶ 42), that is, doses below those allegedly considered to have an antibiotic effect.

Ground 2, on the other hand, starts with research showing that periodontal disease, a condition of mixed bacterial and inflammatory origin, was treated by low dose (40mg/day) doxycycline and that the inflammatory pathways of periodontal disease were also known to exist in rosacea. (Exh.1048.) Indeed, the impact of tetracyclines as anti-inflammatories for treating rosacea was offered as part of the justification for trying low dose doxycycline in periodontal disease. Both conditions are chronic conditions requiring potentially long term treatment. (Exhs.1034, at 144; 1048, at 328.) And doxycycline was known to treat papules and pustules of rosacea based on its anti-inflammatory activity. (Exhs.1010, 1004 ¶ 31.) The prospect of long-term administration of an antibiotic dose of an antibiotic drug would, in both cases, raise the very same concerns over side effects and the creation of drug resistant microorganisms. (Exhs.1004 ¶¶ 48, 49; 1048.)

Thus, it would have been obvious to use low dose doxycycline to treat rosacea based on the success in treating periodontal disease.

THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW

A petition for *inter partes* review must demonstrate “a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). This Petition meets that threshold. All of the elements of claims 1, 7, 8, 14, 15, and 20 of the ‘506 Patent are taught, either expressly or inherently, in the prior art, or are obvious in view of the prior art, as explained below in the grounds of unpatentability. The reasons to combine the cited references, where applicable, are established under 35 U.S.C. § 103(a).

STATEMENT OF REASONS FOR RELIEF REQUESTED

I. INTRODUCTION AND SUMMARY OF ARGUMENT

The claims for which this Petition was filed involve treating symptoms of a common skin condition known as rosacea. (Exh.1004 ¶ 7.) Rosacea and its various symptoms, including papules and pustules (*Id.* ¶¶ 7, 12, 13), have long been treated by tetracyclines, including doxycycline, albeit administered at what the Patent Owner alleges to be “antibiotic” doses. (*Id.* ¶¶ 28, 29, 31; Exhs.1001 col.5 ll.43-45; 1006; 1010; 1048.) Prior to the earliest application leading to the ‘506 Patent, it was known that rosacea in general, and its papules and pustules specifically, were inflammatory in nature, not bacterial. (Exhs.1004 ¶ 33; 1048, at 325; 1034, at 145.)

And before the claimed invention, it was known that tetracyclines, and in particular, doxycycline, were effective as anti-inflammatory agents (Exhs.1004 ¶¶ 34-39, 1010, 1048) including at doses lower than were allegedly used for antibiotic therapy. (Exhs.1004 ¶ 42, 1042, 1048.) As such, no medical necessity persisted for giving antibiotic doses of doxycycline to treat papules and pustules of rosacea. (Exh.1004 ¶¶ 40, 45, 58.) Indeed, just the opposite was true. Advantages of lower doses, such as cost and pill size, in addition to possibly avoiding the known antibiotic-level side effects of that drug and reducing the prospect of creating drug resistant bacteria, were well known. (*Id.* ¶¶ 46, 47, 48; Exh.1048.)

At the time of the alleged invention of the ‘506 Patent, dermatologists would have been motivated to use, or at least try, lower doses of doxycycline to treat inflammatory conditions like rosacea and its symptoms because they knew doxycycline was effective in treating rosacea, and that doxycycline was active as an anti-inflammatory at almost any level. (Exhs.1004 ¶ 40, 42, 43, 44, 45; 1031, 1032.) They also knew of both the availability of, and the success achieved by, using 40mg of doxycycline in treating periodontitis, another chronic inflammatory condition involving some of the same underlying mechanisms. (Exhs.1004 ¶¶ 38, 39, 42, 55-58, 60; 1042, 1048.) PERIOSTAT, for example, was already FDA-approved and commercially available. (Exhs.1053, 1042, 1004 ¶¶ 42, 53,

60.)³ PERIOSTAT uses allegedly subantibiotic 40mg/day doses of doxycycline just as claimed in the ‘506 Patent. (Exhs.1042, 1048, 1004 ¶¶ 42, 54, 55.)

Drugs are often thought of as falling into only one therapeutic category. But just as often, they are used to treat conditions in other categories. Gabapentin, for example, is FDA approved for treatment of epilepsy and shingles. But its “off label” uses for pain and other conditions are so prevalent, they exceed the approved uses. (Exh.1004 ¶ 25.) Aspirin is another example. Known since antiquity for treating headaches, inflammation, and fever, it more recently has been used as an antiplatelet aggregation drug for cardiac patients. (*Id.*) And doxycycline, the drug whose use is claimed in the ‘506 Patent, was similarly known for off label uses, even in dermatology, before the invention of the ‘506 Patent. (*Id.* ¶ 26.)

Before the ‘506 Patent, dosing was known to change with changes in usage as well. Returning to aspirin, it is often dosed at 500mg or more up to six times a day for fever, but it is commonly prescribed at a level of 81mg once per day for antiplatelet aggregation. (*Id.* ¶ 25.) Thus, prescribing PERIOSTAT treatment for papules and pustules of rosacea was well within the skill of any dermatologist.

³ References to PERIOSTAT were not meant to be references to the product *per se*, but rather to the published prescribing information memorialized in, *inter alia*, the 2000 PERIOSTAT PDR. (Exh.1042.)

(Exh.1004 ¶¶ 59, 60.) Indeed, there is evidence that, before the ‘506 Patent, doctors were already using PERIOSTAT “off label” in this manner. (Exh.1015⁴, at 2 (“Periostat was approved by the FDA in 1998, and it could currently be used for its anti-inflammatory benefits with excellent results.”); Exh.1004 ¶ 27.)

Importantly, prior to the ‘506 Patent, dermatologists would have known that patients could be advantaged by using lower doses of doxycycline for reasons including, but not limited to, not being needlessly exposed to antibiotic side effects and the possible development of drug resistant bacteria, lower cost, smaller pills, etc. (Exh.1004 ¶¶ 44-49.) Indeed, there would have been nothing to dissuade a dermatologist from trying lower doses, where, as here, the condition being treated is not life threatening — they were skin blemishes. (*Id.* at ¶ 50.) If lower doses were not effective, doctors could always prescribe a higher dose. (*Id.*) In the meantime, unlike when treating an infection, there would be little or no therapeutic downside to starting with a lower dose — only, at worst, a slight delay in clearing up the symptoms. (Exh.1004 ¶¶ 50-53.)

This is by no means the only path leading to the conclusion of the obviousness of these claims. For many years prior to the filing of the ‘506 Patent, research had been ongoing on the role of inflammation in periodontal disease.

⁴ Exhibit 1015 is not prior art for purposes of this *inter partes* review.

(Exhs.1004 ¶¶ 38, 39, 54-56; 1048.) Periodontal disease is a chronic condition, and a patient with this condition needs long term treatment. (*Id.*¶ 48, Exh.1048.) Research had shown that several inflammatory pathways were implicated and that doxycycline could be an effective anti-inflammatory for treating periodontal disease. (Exh.1004 ¶¶ 38, 39.) Concerns for the side effects of long term antibiotic exposure, such as traditional antibiotic side effects and the possible creation of drug resistant bacteria, prompted the exploration of the use of low dose doxycycline — *i.e.*, 40mg/day. (*Id.* ¶¶ 48, 49, 54, 56; Exh.1048.) That research proved that 40mg/day of doxycycline was effective as an anti-inflammatory in treating periodontal disease. (*Id.* ¶¶ 54-56, Exh.1048.) It also purported to address many of the concerns one might have in exposing patients with a chronic condition to antibiotics over a long term. That research eventually led to the product PERIOSTAT mentioned above. (Exhs.1004 ¶ 54, 1042, 1053.) PERIOSTAT was FDA approved and commercialized before the filing of the ‘506 Patent. (Exhs.1004 ¶¶ 7, 42, 53; 1042, 1053.)

The inflammatory pathways of periodontal disease were known to exist in papules and pustules of rosacea. (Exhs.1004 ¶¶ 39, 57; 1048.) And the concern over long term exposure and the advantages of lower dosing in treating rosacea would have been the same as found in treating periodontal disease. (Exhs.1004

¶¶ 48, 58; 1048.) Indeed, the parallels are virtually inescapable. It would have been obvious to apply a completely analogous solution to a totally analogous problem such as this without more. (Exh.1004 ¶ 60.) However, here, there was more. The art had already linked the inflammatory nature of skin conditions such as rosacea with the periodontal research furthering the obviousness case. (*Id.* ¶¶ 39, 57; Exh.1048.)

Whether because of the modification of the existing standard of care of treating rosacea with doxycycline to lower the dose based on the understanding that it was inflammatory and antibiotic doses were unnecessary, or because of the success of low dose doxycycline in treating other inflammatory conditions in an analogous way with a drug already used for treating rosacea successfully, it would have been obvious to use low dose doxycycline to treat the papules and pustules of rosacea. Thus, claims 1, 7, 8, 9, 15, and 20 of the '506 Patent are therefore unpatentable.

II. THE CLAIMS UNDER CONSIDERATION

1. A method for treating papules and pustules of rosacea in a human in need thereof, the method comprising administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof, in an amount that (i) is effective to treat the papules and pustules of rosacea; (ii) is 10-80% of a 50 mg dose of doxycycline per day; and (iii) results in no

reduction of skin microflora during a six-month treatment, without administering a bisphosphonate compound.

7. The method according to claim 1, wherein said doxycycline, or a pharmaceutically acceptable salt thereof, is administered in an amount which provides a serum concentration in the range of about 0.1 to about 0.8 µg/ml.

8. A method for treating papules and pustules of rosacea in a human in need thereof, the method comprising administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof, in an amount that (i) is effective to treat the papules and pustules of rosacea; (ii) is 40-80% of a 50 mg dose of doxycycline per day; and (iii) results in no reduction of skin microflora during a six-month treatment, without administering a bisphosphonate compound.

14. The method according to claim 8, wherein said doxycycline, or a pharmaceutically acceptable salt thereof, is administered in an amount which provides a serum concentration in the range of about 0.1 to about 0.8 µg/ml.

15. A method for treating papules and pustules of rosacea in a human in need thereof, the method comprising administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof, in an amount of 40 mg per day, wherein the amount results in no reduction of skin microflora during a six-month treatment, without administering a bisphosphonate compound.

20. The method according to claim 15, wherein said doxycycline, or a pharmaceutically acceptable salt thereof, is administered in an amount

which provides a serum concentration in the range of about 0.1 to about 0.8 µg/ml.

III. THE SPECIFICATION AND PROSECUTION HISTORY OF THE ‘506 PATENT

A. The Specification Of The ‘506 Patent

While the claims of the ‘506 Patent are clearly directed to treating the papules and pustules of rosacea, the specification is not nearly as clear on that point. Indeed, the specification does not refer to rosacea *per se*, but rather a more antiquated term no longer generally used in the dermatological community — “acne rosacea.” (Exh.1004 ¶ 12.) There are no examples of treating rosacea, symptoms of rosacea, or the use of any amount of any drug to treat rosacea or its symptoms described in the ‘506 Patent. There is not even a direct association in the specification between papules and pustules and rosacea.

It is only in the Detailed Description section of the patent that one learns that the term “acne” is a group of disorders of the skin that are characterized by, *inter alia*, comedones, papules and pustules. (Exh.1001 col.4 ll.23-27.) The ‘506 Patent then notes that the term “acne” is generic and provides a list of 30 different types of acne including, *inter alia*, acne rosacea. (*Id.* col.4 ll.31-41.) Acne rosacea, however, is not specifically described as being characterized by papules and pustules; instead “[a]cne rosacea is characterized by inflammatory lesions (erythema) and permanent dilation of blood vessels (telangectasia) [sic].” (*Id.* col.4

ll.41-43.) As this is the extent of the disclosure, one reviewing the ‘506 Patent is left to make assumptions as to which symptoms match with which species of “acne.” For instance, one might assume that since papules and pustules are symptoms of “acne” and rosacea is a species of “acne,” generally treating rosacea will treat papules and pustules. However, this relationship is not only at best inferential (nothing in the patent states this), it is not always true. In another example, comedones are identified in the specification as characterizing the genus “acne.” (*Id.* col.4 ll.23-27.) But while comedones are found in common acne (acne vulgaris), they are not a symptom of rosacea — not that the patent provides any guidance on this point. (Exh.1004 ¶¶ 13, 15.) Even as to the aspects specifically attributed to rosacea, such as telangiectasia, NO known drug treatment, let alone the claimed treatment, actually works. (*Id.* ¶ 14.)

According to the specification, “acne” is allegedly treated using a dose of a drug that the ‘506 Patent argues is “subantimicrobial.” This is a key concept to the patent. (*See* Exh.1001 col.3 ll.45-50 (“The method comprises administering . . . a tetracycline compound in an amount that is effective to treat acne but has substantially no antibiotic activity . . .”).) But the real meaning of this passage is far from clear. The patent teaches hundreds of antibiotic and nonantibiotic compounds without discussing any of them to treat rosacea or its papules and

pustules. (*See id.* col.4 l.58 to col.5 l.28, col.7 l.37 to col.8 l.13, Exs.1-36, col.20 l.45 to col.31 l.58.) Moreover, the ‘506 Patent states that “antibiotic doses” of doxycycline “include 50, 75, and 100 mg/day.” (*Id.* col.5 ll.43-44.) It also teaches that tetracycline compounds may be administered in a dose which is 10-80% of the antibiotic dose. (*See id.* col.5 ll.38-40.) So 80% of a 100mg/day dose should be “subantibiotic.” But this results in an 80mg dose which, based on the first passage mentioned above, is still antibiotic.

To confuse matters further, the specification states that a daily amount of doxycycline from 30 to 60mg maintains human plasma concentrations below the threshold for a significant antibiotic effect — thus subantibiotic. (*See id.* col.5 ll.54-58.) But just two paragraphs earlier, the same specification states that 50mg of doxycycline, which falls in this 30-60mg range, *is* antibiotic. (*See id.* col.5 ll.43-44.) Perhaps even more importantly, however, the specification identifies neither dose nor specific antibiotic (or indeed any nonantibiotic tetracycline derivative) in connection with the treatment of rosacea, let alone the papules and pustules of rosacea. It certainly does not describe that these symptoms of rosacea can be treated by any specific range of any specific compound.

To be sure, the specification says nothing about whether or not the papules and pustules of rosacea should or could be treated without co-administration of a

bisphosphonate. And nothing in the specification discusses the dose or drug necessary to accomplish the treatment of papules and pustules of rosacea without impacting the skin's microflora as claimed.

B. The Prosecution History Of The '506 Patent

While the application immediately leading to the '506 Patent (Serial No. 13/277,789) was filed on October 20, 2011, it was not until a fifth preliminary amendment filed on April 30, 2012, that its claims were directed to treating papules and pustules of rosacea. (Exh.1068.) In remarks accompanying the fifth preliminary amendment, applicants noted that the independent claims were very similar to independent claims of its parent, U.S. Patent No. 7,232,572, but specifically noted that the application's amended claims were focused on doxycycline rather than a tetracycline compound, and that the doses cited were defined differently. (*Id.* at 5.)

The claims were rejected in an Official Action mailed May 14, 2012, over Perricone, U.S. Patent No. 6,365,623 in view of Pflugfelder *et al.*, U.S. Patent No. 6,455,583. (Exh.1069.)⁵ Perricone allegedly taught a method of treatment of papules and pustules comprising orally administering an antibiotic compound. The Examiner noted, however, that Perricone did not expressly teach doxycycline or

⁵ Page numbers correspond to those in the bottom right-hand corner of exhibit.

the claimed amount of doxycycline. Pflugfelder allegedly taught a method of treating conditions associated with rosacea and comprised orally administering a tetracycline compound in a subantimicrobial amount that ranges from about 20% to about 80% of the normal antibiotic therapeutic dose. Doxycycline is one of the tetracyclines taught. Also according to the Examiner, Pflugfelder taught the use of an antibiotic compound for the treatment of a rosacea-related condition, and that long-term administration of antibiotic compounds in a subantimicrobial amount will minimize the side effects of tetracycline. (Exh.1069, at 3, 4.) According to the Examiner, it would have been obvious for one of ordinary skill in the art at the time to optimize the method of Perricone to administer an antibiotic compound in a subantimicrobial amount in view of the teachings of Pflugfelder.

On September 19, 2012, applicant responded pointing out that papules and pustules are inflammatory lesions that occur only in skin and do not occur in ocular rosacea. (Exh.1070, at 5-6.) Addressing the principal rejection, applicant argued that Perricone teaches the administration of lipoic acid, which may be added to an “antibiotic” preparation, but that in all cases an antibiotic dose would be used. (*Id.* at 7-8.) Applicant argued that Perricone acknowledges possible side effects of antibiotic compounds. Applicant also argued that Pflugfelder allegedly teaches a method of treating meibomian gland disease (MGD), all of the manifestations of

which relate to the eye, not the skin. (*See* Exh.1070, at 8-9.) Applicant further argued that there is no disclosure in the secondary reference of treating any condition or symptom outside of the eye, and in particular, a facial condition, let alone the papules and pustules of facial rosacea. And while Pflugfelder notes an association between MGD and rosacea, according to applicant, the nature of the association is not disclosed and the reference allegedly does not suggest that the treatment of MGD suggests the treatment of rosacea. (*See id.*) Applicant thus argued that there would be no reason to combine these two references because Perricone and Pflugfelder teach treating different ailments in different organs of the body. Moreover, Perricone indicates that an antibiotic dose is necessary to treat facial skin acne, while Pflugfelder suggests a nonantibiotic dose be used in treating the eye.

Applicant also cited to a number of alleged secondary considerations, including arguments that the predecessor-in-interest of Patent Owner launched the first tetracycline drug for rosacea in July 2006 and that no one had known or developed such a drug before that date. (*Id.* at 14.) Applicant also referred to a Bikowski 2003 article, noting that the author was a consultant of the predecessor-in-interest. This article is not prior art, but allegedly conveyed the state of the art in April 2001 — one that did not include treating rosacea with

subantibiotic doses of doxycycline. (Exh.1070, at 15.) Finally, applicant argued commercial success based on unsubstantiated alleged sales data and an article liberally quoting a paid consultant of Patent Owner. (*See generally id.* at 17-18.) Applicant neither provided market share data nor evidence of a nexus between the alleged commercial success of its product and some aspect of the claim that was patentably distinct. *See Cable Elec. Prods., Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1026-27 (Fed. Cir. 1985), *overruled on other grounds*; *see also* M.P.E.P. § 716.03(b) (“Gross sales figures do not show commercial success absent evidence as to market share”); *see also Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008); *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997) (“[A]sserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art.”).

The Examiner accepted neither applicant’s primary arguments for patentability nor patentability based on the alleged secondary considerations; instead finally rejecting the claims on November 19, 2012. Following an interview, applicant filed an RCE, a response dated February 22, 2013 (Exh.1071), a Terminal Disclaimer over U.S. Patent No. 7,232,572, and a declaration by

Dr. Vasant Manna (Exh.1072), a Senior Medical Advisory/Project Leader for Patent Owner, Galderma.

The claims were not amended, and the prior arguments for patentability were largely repeated. In addition to pointing out the alleged deficiencies of the references individually, applicant argued that there was no reason to combine the references. (Exh.1071, at 7-8.)⁶ Referencing the Manna declaration (Exh.1072), applicant argued the references related to different ailments and different organs of the body. Moreover, they were said to have used different treatment modalities (antibiotic versus subantibiotic). (Exh.1071, at 7.) While applicant appears to have conceded that a skilled artisan might have believed that subantibiotic doses of tetracycline may lead to fewer side effects, applicant agreed that they would have no reason to believe that subantibiotic doses would be effective in the method of Perricone, which allegedly required an antibiotic treatment. (*Id.*) Applicant also noted M.P.E.P. § 2143.01 IV, arguing that the combination could not be made because the proposed modification would change the principal operation of the primary reference, which teaches an antibiotic treatment. (*Id.* at 8.)

⁶ Page numbers reflect those at the bottom right-hand corner of the exhibit.

The Manna declaration (Exh.1072) mirrored the arguments made by applicant and provided more information regarding meibomian gland disease and any association with rosacea.

Subsequently, on October 9, 2013, a Notice of Allowability was mailed. (Exh.1012.) In its reasons for allowance, the Examiner noted that the closest prior art did not teach the claimed method for treating papules and pustules of rosacea in a human by orally administering doxycycline in a subantimicrobial amount without administering a biphosphonate compound. It further noted that the Manna declaration includes statements that the MGD taught by the secondary reference does not include the papules and pustules of rosacea. Moreover, the specification allegedly shows that the claimed method results in no reduction in skin microflora during a six-month treatment. (*Id.* at 10-11.)⁷ The Examiner did not mention reliance on any of the alleged secondary considerations.

IV. EFFECTIVE FILING DATE FOR DETERMINATION

All of the grounds of this Petition rely on prior art that is available under 35 U.S.C. §§ 102(b)/103(a). Thus, for purposes of this Petition only, Petitioner is not challenging the entitlement of the claims of the '506 Patent to the earliest

⁷ Page numbers reflect the consecutive page numbering at the bottom right-hand corner of the exhibit.

provisional filing date of April 5, 2001. However, Petitioner has advanced later effective filing dates for these claims in two other IPR Petitions filed on the same date as this Petition bearing attorney docket nos. REDDYPP 7.1R-015 and REDDYPP 7.1R-017. The fact that Petitioner is not advancing an argument for a later effective filing date here should not be taken as an admission or acknowledgement that the challenged claims are indeed entitled to an April 15, 2001 date, only that it is not an issue here.

V. **CLAIM CONSTRUCTION**

In *inter partes* review, a claim term is given its “broadest reasonable construction in light of the specification” *See* 37 C.F.R. § 42.100(b); *see also In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1279 (Fed. Cir. 2015), *reh’g en banc denied*.

A. **Rosacea**

Rosacea is identified in the ‘506 Patent as “acne rosacea.” (Exh.1001 col.4 ll.41.) The ‘506 Patent notes that “[a]cne rosacea is characterized by inflammatory lesions (erythema) and permanent dilation of blood vessels (telangectasia [sic]).” (*Id.* col.4 ll.41-43.) Rosacea is identified as a form of acne: “[f]or the purposes of this specification, acne includes all known types of acne. Some types of acne include, for example, acne vulgaris . . . and acne rosacea.” (*Id.* col.4 ll.31-41.) Acne, in turn, is defined as “a disorder of the skin characterized by papules,

pustules, cysts, nodules, comedones, and other blemishes or skin lesions.” (*Id.* col.4 ll.23-27; Exh.1004 ¶ 12.)

B. Papules And Pustules

Neither the term “papule” nor the term “pustule” appears to be specifically defined in the ‘506 Patent. Dr. Payette, Requestor’s expert dermatologist, explains that “[a] papule is a small, solid, elevated lesion . . . smaller than 1 cm in diameter, and the major portion of a papule projects above the plane of the surrounding skin. . . . The elevation can be the result of metabolic deposits, localized hyperplasia of cellular components of the epidermis or dermis, or localized cellular infiltrates in the dermis.” (Exhs.1004 ¶ 19; 1056, at 27.) “A *pustule* is a circumscribed, raised lesion that contains a purulent exudate. . . . Pus, composed of leukocytes, with or without cellular debris, may contain bacteria or may be sterile” (Exhs.1004 ¶ 19; 1056, at 31.) These definitions align well with those provided by applicant during prosecution. (Exh.1070, at 6 (“**Papules**: Small solid rounded bumps rising from the **skin** that are each usually less than 1 centimeter in diameter (less than 3/8 inch across) . . . **Pustule**: A pustule is a small collection of pus in the top layer of **skin** (epidermis) or beneath it in the dermis. Pustules frequently form in sweat glands or hair follicles”).)

Papules and pustules are extremely common to both common acne (acne vulgaris) and rosacea (as well as other skin disorders), and although the two

diseases are distinct with distinct underlying pathophysiologies, the resulting papules and pustules in both diseases share common underlying properties in that they are inflammatory in nature. (Exh.1004 ¶ 19.)

VI. ANALYSIS

A. Ground 1. Claims 1, 7, 8, 14, 15, And 20 Would Have Been Obvious Over Sneddon (Exh.1006) In View Of Golub (Exh.1048), Torresani (Exh.1010) And The 2000 PERIOSTAT PDR (Exh.1042)

The obviousness inquiry is one of law based on four factual predicates: (1) “the scope and content of the prior art,” (2) “the differences between the prior art and the claims at issue,” (3) “the level of ordinary skill in the pertinent art,” and (4) “secondary considerations” such as “commercial success, long felt but unsolved needs, failure of others, etc.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)); 35 U.S.C. § 103(a). *KSR* reaffirmed that “[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR*, 550 U.S. at 416. The Supreme Court also instructed that “any need or problem known in the field of endeavor at the time of [the] invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *Id.* at 420. “Common sense teaches, however, that familiar items may have obvious uses beyond their primary purposes, and in

many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle.” *KSR*, 550 U.S. at 420. Finally, the Court held that “[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill [in the art] has good reason to pursue the known options within his or her technical grasp.” *Id.* at 421.

A “[m]otivation to combine may be found in many different places and forms.” *Par Pharm. Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1197 (Fed. Cir. 2014) (citations omitted). Thus, for example, a challenger is not limited to the same motivation that the patentee had. *See id.* (citing *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012), *cert denied*, 133 S. Ct. 1736 (2013)).

1. The Level Of Ordinary Skill In The Art

Factors relevant to determining the level of skill in the art include: the educational level of the inventors, the types of problems encountered in the art, prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1376 (Fed. Cir. 2012).

A person of ordinary skill in the art at issue here would be a licensed and practicing dermatologist with as little as one year of treating patients in a hospital,

clinical, and/or private setting. (Exh.1004 ¶ 11.) Here, the claims are directed to methods of treating extremely common symptoms of rosacea (*i.e.*, papules and pustules), something treated virtually every day by practicing dermatologists at almost every level of experience. (*Id.* ¶ 7.) Moreover, the drug used to treat these symptoms as claimed, doxycycline, has been known since the 1960s (Exh.1054, at 21 (“doxycycline was approved for use by the FDA in 1967”)); and, as claimed, it is administered through a known route (orally) (Exhs.1042, 1051, 1004 ¶ 28.) This drug was also previously used by dermatologists in treating rosacea. (Exhs.1006, 1010, 1011, 1048, at 325; 1004 ¶¶ 30, 31, 32.) Finally, the relevant claimed doses were already FDA approved and commercially available. (Exhs.1042, at 944; 1053; 1004 ¶¶ 7, 42, 53.) Thus, the claimed invention relates to generally well-known and well-understood methods and drugs. That said, these are still methods of medical treatment raising issues that are specifically in the purview of medical doctors. (Exh.1004 ¶ 9.) And adjusting doses and understanding the mechanisms of symptomology is more than would be expected from general practitioners. (*Id.*)

The types of problems addressed by the ‘506 Patent and their solutions involve balancing the need to treat the patient while avoiding exposing the patient to side effects and/or unintended consequences. “This is a problem that is faced by

every treating physician, every time they prescribe medication, or decide not to do so.” (Exh.1004 ¶ 8.) Thus, the general problems and solutions implicated by the claims here are nothing new. And, without minimizing the import of either, in this instance, the issues are not sophisticated relative to other dermatological issues, and are well within the purview of even relatively inexperienced dermatologists. (*Id.* ¶¶ 9, 11.) Finally, Petitioner notes that the inventor, Robert A. Ashley, has a master’s degree in biochemistry, but no specific degrees in medicine in general, or dermatology specifically — arguably the most relevant discipline to the ‘506 Patent. (Exh.1052.)

2. The Scope And Content Of The Prior Art

For purposes of this analysis, all three independent claims can be discussed together, as the sole significant difference between them resides in how the dose administered is recited. Claims 1 and 8 recite a genus of doses encompassing the single 40mg/day dose described in claim 15. Accordingly, while Requestor’s comments will be principally directed to claim 15 in that it references doses of 40mg/day, Requestor’s comments are equally applicable to claims 1 and 8. Indeed, claims directed to treating papules and pustules of rosacea using, for example, 5 to 40mg of doxycycline (cls.1, 7), would be rendered obvious by the same prior art that would render obvious the use of 40mg of doxycycline in the same

treatment process. A detailed claim chart for all of the challenged claims is provided, *infra*.

With the exception of one reference (Exh.1015), all of the references discussed in connection with this ground are printed publications that were published more than one year before April 5, 2001, the filing date of the earliest provisional application from which the ‘506 Patent claims priority. All of these references therefore constitute prior art pursuant to 35 U.S.C. §§ 102(b)/103(a).

Sneddon (Exh.1006)⁸ reported in the late 1960s that: (1) tetracycline was effective in the treatment of rosacea (Exh.1006, at 652 (“successful in controlling rosacea in 87% of patients”)); (2) his group had been using the treatment since 1962 (*id.* at 649); and (3) its mechanism, though not yet known, could not be entirely antibacterial (*id.* at 652; Exh.1004 ¶ 28). Tetracycline was one of the first members of this family of antibiotic drugs, which were known as of the filing date of the ‘506 Patent as “tetracyclines.” This family was also well known to include

⁸ Sneddon (Exh.1006) was published in January-December 1966, Vol. 78, of the *British Journal of Dermatology*. The copy of Exhibit 1006 was provided by the David L. Tilderquist Memorial Medical Library. Sneddon is prior art under 35 U.S.C. § 102(b) and was not identified as being of record on the cover of the ‘506 Patent.

doxycycline. (See Exhs.1048, 1051, 1004 ¶ 30.) And members of the tetracycline family, including doxycycline, were known for the treatment of rosacea. (See Exhs.1048, at 325 (“As one example, tetracyclines now appear to possess anti-inflammatory properties when administered to patients with certain skin diseases, diseases such as rosacea”); 1010, at 945 (“Both therapies [doxycycline and clarithromycin] achieve[d] significant improvements of dermatosis in 80-90% of casesThe therapeutic activity of tetracyclines seems to be related to their anti-inflammatory efficacy.”); 1004 ¶¶ 31, 32.) As discussed in Torresani (Exh.1010)⁹, doxycycline was effective in treating papules and pustules of rosacea, and doxycycline’s action was attributed to its anti-inflammatory action. (Exhs.1010, at 944-45; 1004 ¶ 31, 37.) And it was known that the papules and pustules of rosacea were inflammatory in nature. (Exh.1004 ¶ 33.)

⁹ Torresani (Exh.1010) was published in December 1997, Vol. 36, #12 of the *International Journal of Dermatology*. Exhibit 1010 carries a date stamp from the University of Minnesota Biomedical Library of January 23, 1998. Torresani is prior art under 35 U.S.C. § 102(b). Torresani is listed as being of record on the face of the ‘506 Patent, but was not discussed during prosecution.

Prior to the filing of the first application leading to the ‘506 Patent, the doses of doxycycline typically used for treating rosacea were 100mg/day or more. (*See* Exh.1010, at 942 (100mg twice a day (“b.i.d.”) for four weeks then 100mg once daily for four weeks).) These were generally considered to be antibiotic amounts. (*See* Exhs.1048¹⁰, at 322 (At the time, when the drug “is prescribed to combat infection,” the recommended dose of doxycycline was 100mg daily or 50mg two times per day.); 1004 ¶¶ 38, 55.)

More than ten years before the earliest application leading to the ‘506 Patent was filed, Golub and collaborators disclosed that rosacea was characterized by inflammation, not bacterial infection, and was treatable by tetracyclines. (Exh.1048, at 325 (“As one example, tetracyclines now appear to possess anti-inflammatory properties when administered to patients with certain skin diseases, diseases such as rosacea . . . which are *not* believed to have a microbial etiology.” (emphasis in original, citations omitted).) This was confirmed in 1997

¹⁰ Golub (Exh.1048) was published in November 1990, Vol. 25, Issue 6 of *The Journal of Periodontal Research*. The copy of Exhibit 1048 carries a date stamp from the National Library of Medicine of January 14, 1991. Golub is prior art under 35 U.S.C. § 102(b) and was not identified as being of record on the cover of the ‘506 Patent.

by Torresani. (Exh.1010, at 945 (“The therapeutic activity of tetracyclines seems to be related to their anti-inflammatory efficacy.”).)

This link brought them to their ultimate findings that low dose doxycycline could be effective in treating periodontal conditions as well. (Exhs.1048, at 325; 1004 ¶ 39.) Specifically, they used a low dose doxycycline (20mg twice a day or “b.i.d.”) to treat the inflammatory symptoms of periodontal disease. (Exh.1048, at 323 (“20 mg capsules, b.i.d.”), *id.* at 327 (“This observation suggests that tetracycline administration, particularly in low doses, could provide a safe and effective therapeutic approach for [treating periodontal disease by] reducing pathologically excessive collagenase activity in inflammatory lesions without interfering with normal connective tissue remodeling.”); *see also id.* at 327-28 (“In addition to the effect of low-dose doxycycline on collagenase activity in inflamed human gingiva . . . this regimen also appeared to reduce the severity of inflammation assessed by the gingival index . . . ”); Exh.1004 ¶¶ 38, 39, 54, 55.)

The 20mg b.i.d. dosage of Golub is the identical regimen approved as PERIOSTAT — administration of two 20mg capsules of doxycycline per day for a total of 40mg/day of doxycycline. (Exh.1042, at 946.) PERIOSTAT was approved by the FDA and commercially available more than one year prior to the

filing date of the ‘506 Patent, as published in 2000 PERIOSTAT PDR.¹¹ (Exhs.1042, at 944-46; 1053.) Its FDA-approved label was therefore a printed publication well before the filing date of the ‘506 Patent. PERIOSTAT itself is also Patent Owner’s product and prior art. (*See* Exh.1001 col.5 ll.59-63.)

**3. The Differences Between The
 Claimed Invention And The Prior Art**

a. The Dosage

As noted above, it was known to treat inflammatory papules and pustules of rosacea with tetracyclines such as doxycycline administered orally. (Exhs.1006, at 651-52 (tetracycline); 1010, at 944 (doxycycline).) The first difference between Sneddon and Torresani and the claim is the dose of doxycycline. However, Golub and the 2000 PERIOSTAT PDR both taught the use of 40mg of doxycycline to treat another inflammatory condition, periodontal disease. (Exhs.1048, at 323;

¹¹ 2000 PERIOSTAT PDR was received by undersigned counsel’s firm in February 2000, as indicated by the library date stamp on the inner cover thereof. Further, an e-mail from the PDR Customer Service Department provided as Exhibit 1014 confirms the 2000 PDR was published in November 1999 and distribution began in December of 1999. Thus, the 2000 PERIOSTAT PDR constitutes prior art against all of the challenged claims pursuant to 35 U.S.C. § 102(b).

1042, at 946 Dosage and Administration.) And Golub taught that rosacea and periodontitis were both inflammatory conditions influenced by some of the same pathways and mechanisms that were treatable by tetracyclines. (Exh.1048, at 325-26; 1004 ¶ 39.) Indeed, Golub suggested that the anti-inflammatory activity of tetracyclines in connection with rosacea and other skin diseases provided a part of the motive to try low dose doxycycline in periodontitis. (Exh.1048, at 325; 1004 ¶ 39.) Thus, much like Golub himself, upon considering the prior art, it would have been obvious to one of ordinary skill in the art at the time to substitute the anti-inflammatory low dose amounts of PERIOSTAT, established to be successful in treating inflammatory periodontal conditions by Golub, for the higher doses used previously in treating papules and pustules of rosacea. (Exh.1004 ¶¶ 42, 43, 44, 45, 59, 60.)

To a dermatologist of ordinary skill in the art considering the prior art before April 5, 2001, a teaching and motivation existed to lower the dose of doxycycline from the levels taught in Torresani (100mg/day or more) to the 40mg/day dose of Golub and PERIOSTAT in treating the papules and pustules of rosacea. (Exhs.1004, 1006, 1010, 1042; 1048 ¶¶ 28, 31, 38, 39, 42, 60.) At the most basic level, the fact that the papules and pustules of rosacea were known to be inflammatory, and not bacterial, would raise concerns for dermatologists about

needlessly continuing to dose an antibacterial amount of doxycycline when other options were readily available. (Exh.1004 ¶¶ 43, 44, 45, 53, 58.) But this is far from the only reason to try lower doses. The art recognized other motivations in that there would be advantages to reducing the dose of doxycycline in terms of, for example, dosage form, size, cost, compliance, etc. (*Id.* ¶¶ 46, 47.) Further, the administration of antibiotic doses of tetracyclines also implicates known side effects thereby providing further motivation to consider lower dosages. (*See id.* ¶¶ 48, 49, 50, 53.)

Both the potential treatment advantages (lower dose, lower cost, smaller dosage forms, etc.) and the prospect of avoiding antibiotic level side effects, each independently, and certainly in combination, would provide ample motive to reduce the dose of doxycycline used or, in other words, look from Torresani and Sneddon to other, lower dosage levels. Indeed, for example, Torresani noted that an issue with the 100mg/day dose of doxycycline is the risk of side effects. (Exh.1010, at 945-46, Fig.6.) And a dermatologist of ordinary skill in the art would reasonably expect that lowering the dose of doxycycline used to treat papules and pustules of rosacea would provide both efficacy *and* a lower risk of the side effects associated with antibiotics, although providing either expectation would be sufficient. (Exh.1004 ¶¶ 43, 44, 45, 46, 47, 48, 53.)

It should also be recalled that papules and pustules of rosacea are symptoms that are certainly serious, but not life threatening. (*Id.* ¶ 50.) Unlike treating an infection, there likely would be no serious consequence to initially under dosing these symptoms; only lost time, at worst. (*Id.* ¶¶ 49, 50.) Indeed, while trying a lower dose, the patient would already be advantaged by not being exposed to the potentially far more serious side effects of antibiotic doses of doxycycline. (*Id.*)

Additionally, a dermatologist of ordinary skill in the art would likewise arrive at the decision to try a low dose doxycycline regimen based on the general trend of the prior art in the understanding of rosacea. First, as of the time of the alleged invention of the '506 Patent, a dermatologist of ordinary skill in the art would know that doxycycline had at least some anti-inflammatory activity at almost any dose. (*Id.* ¶ 42.) Second, the therapeutic effect of doxycycline on the papules and pustules of rosacea was due to its anti-inflammatory properties, not its antibiotic properties. (Exhs.1004 ¶¶ 37, 38, 39, 40; 1010, at 945-46; 1048, at 325.) Third, PERIOSTAT was an FDA-approved, commercially available treatment known to be effective in treating another inflammatory condition using low dose doxycycline (40mg/day). (Exhs.1042, 1053, 1004 ¶¶ 42, 54.) With this knowledge, a dermatologist of ordinary skill would have had a reasonable expectation of success. (Exh.1004 ¶¶ 42, 43, 44, 45, 53.) Indeed, a similar consideration of

rosacea led to the development of PERIOSTAT, which offers an unusually apt analogy. (*Id.* ¶¶ 54, 60.)

Like rosacea, earlier dosing of doxycycline in treating periodontitis involved allegedly antibiotic level doses. (Exhs.1004 ¶ 58; 1048, at 322.) And also as in the case of rosacea, the art had come to realize that certain aspects of periodontitis were inflammatory rather than microbial, and thus treatable with low dose doxycycline such as PERIOSTAT to take advantage of its anti-inflammatory properties without invoking its antibacterial properties or disadvantages. (Exhs.1004 ¶¶ 38, 39, 54-56; 1042, at 945; 1048, at 325-26; 1053.) Finally, as both periodontal disease and rosacea were chronic conditions (Exhs.1048, at 328; 1004 ¶ 48), the concern over the health risks of exposing a patient to antibiotic levels of doxycycline over a long term would be identical. (Exh.1004 ¶ 48, 56.)

With such similar problems and concerns involved, it should surprise no one that the solutions were the same. Golub *et al.* in 1990 disclosed using a low dose doxycycline treatment for addressing the inflammatory component of periodontal disease by administering capsules of doxycycline containing 20mg or 30mg of the active agent given twice a day. (*See* Exh.1048, at 322.) Their justification included the success of tetracyclines on rosacea. (*Id.* at 325, Exh.1004 ¶ 39.) They also discussed inflammatory mechanisms that would be just as important in treating

periodontal disease as treating rosacea. (Exh.1048, at 328 (hypothesizing that low dose doxycycline capsules could yield the same clinical efficacy without inducing the well-known side effects of long-term antibiotic usage).) And to provide further motivation and a likelihood of success in finding a treatment for the papules and pustules of rosacea, PERIOSTAT was a low dose (40mg/day) doxycycline regimen offered commercially embodying this very set of conclusions.

The similarities between the problems and solutions facing periodontists treating periodontal disease and those facing dermatologists treating the papules and pustules of rosacea are inescapable. Both sought to treat chronic conditions known to have a significant inflammatory component. And both were previously treated with doxycycline in higher doses. In both cases, medical professionals, including dermatologists, considering the appropriate treatment of patients, would expect advantages from using a lower dose and/or be justifiably concerned with the side effects of antibiotic doses of doxycycline when it was not being used as an antibiotic. (Exh.1004 ¶¶ 44, 45, 46, 47, 48, 49, 53.)

Given the foregoing, knowing that doxycycline was an active anti-inflammatory at very low doses, that 40mg/day of doxycycline was effective in addressing other inflammatory conditions, and that lower doses of doxycycline would strike a more desirable balance between efficacy and potential side effects,

it would have been obvious for a dermatologist of ordinary skill in the art to use the treatment outlined in Golub and/or PERIOSTAT in treating the papules and pustules of rosacea, precisely as claimed in the ‘506 Patent. (Exh.1004 ¶¶ 42, 43, 44, 45, 46, 47, 48, 49, 50, 53, 59, 60.) And PERIOSTAT, an FDA-approved low dose doxycycline product, was readily at hand, even if it was “off label.” (*See also* Exh.1015, at 2 (“Periostat was approved by the FDA in 1998, and it could currently be used for its anti-inflammatory benefits with excellent results.”).) In view of the periodontitis results and the known activity of these anti-inflammatory agents, there would be at least a reasonable expectation of success, whether measured by the expectation of efficacy, the expectation of reducing the exposure of the patient to side effects unique to antibiotic doses of the same drug, or both. (Exh.1004 ¶¶ 42, 43, 44, 45, 46, 47, 48, 49, 50, 53, 59, 60.)

b. Exclusion Of Bisphosphonate

A second possible difference between the claims and the art is that the claims exclude co-administering a bisphosphonate. But none of the art discussed herein suggested using a bisphosphonate — just an antibiotic. (Exhs.1006, 1010, 1048, 1042, 1004 ¶ 61.) They, therefore, taught administration *without* a bisphosphonate as claimed, either literally or by inherency.

c. No Reduction In Microflora

Finally, the independent claims of the ‘506 Patent recite that 40mg/day of doxycycline given orally to patients with rosacea as claimed would not result in a reduction of skin microflora during a six-month treatment. But the dosing of that same amount of that same drug to patients with periodontitis, something clearly known in the art (Exhs.1042, 1048, 1053), must bring about the same result. (Exh.1004 ¶ 62.) If the claimed invention of the ‘506 Patent does not result in a reduction of microflora, then neither did the prior art use of PERIOSTAT. Thus, this recitation is merely a restatement of an inherent property of administering a 40mg/dose of doxycycline to a human patient. As a matter of law, it cannot confer patentability here. “We have recognized that inherency may supply a missing claim limitation in an obviousness analysis.” *Par*, 773 at 1194-95. Indeed, the “mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not distinguish a claim drawn to those things from the prior art.” *Id.* at 1195 (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). Here, the lack of impact of 40mg of doxycycline on skin microflora is a function of that dose of that drug, not the condition for which it was prescribed. (Exh.1004 ¶ 62.) As such, doxycycline given in a low dose for treating papules and pustules of rosacea as suggested by the combined teachings of the prior art, will

necessarily and always have the same effect on skin microflora as an inherent property of the drug dosage.

Accordingly, the fact that no one previously determined the impact on skin microflora for PERIOSTAT does not diminish the fact that such impact *must* have been, and must be, the natural result flowing from administering PERIOSTAT. This limitation is therefore inherently met by the prior art.

4. Dependent Claims 7, 14, And 20

Dependent claims 7, 14, and 20 of the '506 Patent each contains an identical recitation and therefore they can be treated together. Dependent claim 7 depends from independent claim 1, dependent claim 14 depends from independent claim 8, and dependent claim 20 depends from independent claim 15. Since each dependent claim also includes all of the limitations of the independent claim from which it depends, the arguments presented above for independent claims 1, 14, and 20 apply to dependent claims 7, 14, and 20.

Each dependent claim requires that the doxycycline, or its pharmaceutically acceptable salt of the independent claim from which they depend, be administered in an amount that provides a serum concentration in the range of about 0.1 to about 0.8µg/mL. As shown in the 2000 PERIOSTAT PDR (Exh.1042, at 945), the mean peak concentration in plasma for PERIOSTAT was 790ng/mL and the average steady state concentration was 482ng/mL. For conversion, 1µg = 1000ng.

So, 482ng/mL = 0.482µg/mL and 790ng/mL = .79µg/mL, both of which overlap with the claimed range and establish a *prima facie* case of obviousness as to these claims. *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). (“[W]e and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness.”) We are aware of no evidence capable of negating this *prima facie* case. Thus, this establishes that administering 20mg doses of doxycycline twice a day, as taught by the 2000 PERIOSTAT PDR (Exh.1042) and Golub (Exh.1048) would result in a serum concentration as claimed in claims 7, 14, and 20.

5. Claim Chart

A claim chart summarizing the foregoing analysis appears below. It includes citations to the record and, where appropriate, for the ease of the Board, a citation to specific language to aid in finding the relevant passage.

Claims of the ‘506 Patent	Citation to the art for Ground 1
1. A method for treating papules and pustules of rosacea in a human in need thereof, the method comprising:	Exh.1006, at 652 (“successful in controlling rosacea in 87% of patients. . . . Observation that it controls not only pustulation”); Exh.1010, at 944-45 (Title — Clarithromycin versus doxycycline in the treatment of rosacea.), Figs.3, 4; Exh.1004 ¶¶ 28, 31, 37

Claims of the ‘506 Patent	Citation to the art for Ground 1
administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof,	Exh.1048, at 322 (“20 or 30 mg of Vibramycin® . . . take one capsule in the morning and one at night”); Exh.1042, at 944 (“Periostat ® is available as a 20 mg capsule formulation of doxycycline hyclate for oral administration”); Exh.1004 ¶¶ 28, 31, 37
in an amount that (i) is effective to treat papules and pustules of rosacea;	Exh.1006, at 652 (“successful in controlling rosacea in 87% of patients.”); Exh.1010, at 944-45, Figs.3, 4; Exh.1004 ¶¶ 31, 33, 40, 42, 43, 44, 45
(ii) is 10-80% of a 50 mg dose of doxycycline per day; and	Exh.1048, at 322 (“[s]pecial capsules of doxycycline were formulated . . . each containing 20 or 30 mg of Vibramycin® . . . subjects were instructed to take one capsule in the morning and one at night”); Exh.1042, at 946 (“Periostat® 20 mg twice daily”); Exh.1004 ¶¶ 42, 43, 53, 60
(iii) results in no reduction of skin microflora during a six month treatment,	Exh.1042, at 945 (“The dosage of doxycycline achieved with this product during administration is well below the concentration required to inhibit microorganisms commonly associated with adult periodontitis.”); Exh.1004 ¶ 62 (Inherent function of dose)
without administering a bisphosphonate compound.	Exh.1004 ¶ 61; Exhs. 1048, 1010, 1006 (References teach doxycycline monotherapy)
7. The method according to claim 1, wherein said doxycycline, or a pharmaceutically acceptable salt thereof, is administered in an amount which provides a serum concentration in the range of about 0.1 to about 0.8 ug/ml.	<i>See</i> citations for claim 1. Exh.1042, at 945 (“mean peak concentration in plasma [for PERIOSTAT] was 790 ng/mL and the average steady-state concentration was 482 ng/mL.”)

Claims of the ‘506 Patent	Citation to the art for Ground 1
8. A method for treating papules and pustules of rosacea in a human in need thereof, the method comprising	Exh.1006, at 652 (“successful in controlling rosacea in 87% of patients. . . . Observation that it controls not only pustulation”); Exh.1010, at 944-45 (Title - Clarithromycin versus doxycycline in the treatment of rosacea.), Figs.3, 4; Exh.1004 ¶¶ 28, 31, 37
administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof,	Exh.1048, at 322 (“20 or 30 mg of Vibramycin® . . . take one capsule in the morning and one at night”); Exh.1042, at 944 (“Periostat ® is available as a 20 mg capsule formulation of doxycycline hyclate for oral administration”); Exh.1004 ¶¶ 28, 31, 37
in an amount that (i) is effective to treat the papules and pustules of rosacea;	Exh.1006, at 652 (“successful in controlling rosacea in 87% of patients.”); Exh.1010, at 944-45, Figs.3, 4; Exh.1004 ¶¶ 31, 33, 40, 42, 43, 44, 45
(ii) is 40-80% of a 50 mg dose of doxycycline per day; and	Exh.1048, at 322 (“[s]pecial capsules of doxycycline were formulated . . . each containing 20 or 30 mg of Vibramycin . . . subjects were instructed to take one capsule in the morning and one at night”); Exh.1042 , at 946 (“Periostat® 20 mg twice daily”); Exh.1004 ¶¶ 42, 43, 53, 60
(iii) results in no reduction of skin microflora during a six-month treatment,	Exh.1042, at 945 (“The dosage of doxycycline achieved with this product during administration is well below the concentration required to inhibit microorganisms commonly associated with adult periodontitis.”); Exh.1004 ¶ 62 (Inherent function of dose)
without administering a bisphosphonate compound.	Exh.1004 ¶ 61; Exhs. 1048, 1010, 1006 (References teach doxycycline monotherapy)

Claims of the ‘506 Patent	Citation to the art for Ground 1
14. The method according to claim 8, wherein said doxycycline, or a pharmaceutically acceptable salt thereof, is administered in an amount which provides a serum concentration in the range of about 0.1 to about 0.8 µg/ml.	<i>See</i> citations for claim 8. Exh.1042, at 945 (“mean peak concentration in plasma [for PERIOSTAT] was 790 ng/mL and the average steady-state concentration was 482 ng/mL.”)
15. A method for treating papules and pustules of rosacea in a human in need thereof, the method comprising	Exh.1006, at 652 (“successful in controlling rosacea in 87% of patients. . . . Observation that it controls not only pustulation”); Exh.1010, at 944-45 (Title — Clarithromycin versus doxycycline in the treatment of rosacea.), Figs.3, 4; Exh.1004 ¶¶ 28, 31, 37
administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof,	Exh.1048, at 322 (“20 or 30 mg of Vibramycin® . . . take one capsule in the morning and one at night”); Exh.1042, at 944 (“Periostat ® is available as a 20 mg capsule formulation of doxycycline hyclate for oral administration”); Exh.1004 ¶¶ 28, 31, 37
in an amount of 40 mg per day,	Exh.1048, at 322 (“[s]pecial capsules of doxycycline were formulated . . . each containing 20 or 30 mg of Vibramycin® . . . subjects were instructed to take one capsule in the morning and one at night”); Exh.1042, at 946 (“Periostat® 20 mg twice daily”); Exh.1004 ¶¶ 42, 43, 53, 60
wherein the amount results in no reduction of skin microflora during a six-month treatment,	Exh.1042, at 945 (“The dosage of doxycycline achieved with this product during administration is well below the concentration required to inhibit microorganisms commonly associated with adult periodontitis.”); Exh.1004 ¶ 62 (Inherent function of dose)
without administering a bisphosphonate compound.	Exh.1004 ¶ 61; Exhs. 1048, 1010, 1006 (References teach doxycycline monotherapy)

Claims of the ‘506 Patent	Citation to the art for Ground 1
20. The method according to claim 15, wherein said doxycycline, or a pharmaceutically acceptable salt thereof, is administered in an amount which provides a serum concentration in the range of about 0.1 to about 0.8 µg/ml.	<i>See</i> citations for claim 15. Exh.1042, at 945 (“mean peak concentration in plasma [for PERIOSTAT] was 790 ng/mL and the average steady-state concentration was 482 ng/mL.”)

B. Ground 2. Claims 1, 8, And 15 Would Have Been Obvious Over Golub (Exh.1048) In View Of Torresani (Exh.1010) And Further In View Of Jansen (Exh.1034)

1. The Level Of Ordinary Skill In The Art

The level of ordinary skill in the art is the same for this ground as that discussed in connection with Ground 1.

2. The Scope And Content Of The Prior Art

As was also the case in connection with Ground 1, the independent claims can generally be discussed together, and in the context of, for example, claim 15. With the exception of one reference (Exh.1015), all of the references discussed in connection with this ground were published more than one year before April 5, 2001, and qualify as prior art pursuant to 35 U.S.C. § 102(b).

Golub (Exh.1048) reported on a study measuring the effects of low dose doxycycline on gingival and crevicular fluid collagenase activity in human patients with periodontal disease. Citing, *inter alia*, the group’s prior work, Golub explained that tetracycline antibiotics, which had long been advocated as useful

adjuncts in periodontal therapy, can inhibit mammalian collagenase and collagen breakdown by a mechanism independent of its antimicrobial efficacy. (*See id.* at 321-22.) “The current study was carried out to determine whether a newer, semi-synthetic tetracycline, doxycycline, could be administered to humans in a low-dose regimen (20 or 30 mg capsules, rather than 50 or 100 mg capsules which are commercially available) which would effectively inhibit collagenase activity in the *gingival tissue* as well as in crevicular fluid.” (*Id.* at 322 (emphasis in original), Exh.1004 ¶ 38.) “The subjects were instructed to take one capsule in the morning and one at night, but not at mealtimes.” (Exh.1048, at 322.)

The authors noted that tetracyclines had often been advocated as useful adjuncts in periodontal therapy based on their effectiveness against periodontopathogens. (*See id.* at 325.) But, Golub also spoke to why they might be used as anti-inflammatories, not as antibiotics, and in doing so, observed that experience with skin conditions, including rosacea, suggested that this might be the case. Specifically, Golub noted that “[r]ecently, novel properties of these drugs have been discovered which help explain their clinical effectiveness and may also expand their future applications *beyond* their current use as antimicrobials.” (*Id.* (emphasis in original).) “As one example, tetracyclines now appear to possess anti-inflammatory properties when administered to patients with certain skin

diseases, diseases such as rosacea . . . which are *not* believed to have a microbial etiology.” (Exhs.1048, at 325 (emphasis in original); 1004 ¶ 39.)

The authors then described several mechanisms linked to inflammation, which were known to those of ordinary skill in the art to be common to both periodontal disease and rosacea. (Exh.1004 ¶¶ 38, 39.) Specifically, Golub noted that tetracyclines have an ability to inhibit mammalian collagenase and other metalloproteinase activities, which may also contribute to the anti-inflammatory efficacy of these drugs. (*See* Exhs.1048, at 325-26; 1004 ¶ 39.) It was the effect on these pathways in periodontal disease that prompted the study. (*See* Exhs.1048, at 325-26 (“In the current study, a low-dose regimen of doxycycline appeared to substantially reduce the collagenolytic activity in the fluid of the periodontal pocket (GCF) and in the gingiva of humans with adult periodontitis.”); 1004 ¶ 39.)

In discussing its results, in the context of prior publications, the authors noted that “tetracycline administration, particularly in low doses, could provide a safe and effective therapeutic approach for reducing pathologically-excessive collagenase activity in inflammatory lesions without interfering with normal connective tissue remodeling.” (Exh.1048, at 327.) Golub also discussed studies finding that low dose doxycycline did not create tetracycline resistant microorganisms, whereas 50mg dosed twice a day did. (*Id.* at 328.) The authors

concluded by hypothesizing that “specially formulated low-dose doxycycline capsules may yield the same clinical efficacy without inducing the well-known side effects (e.g. antibiotic-resistant microorganisms . . . gastro-intestinal upset) of long-term antibiotic usage. However, further study is required.” (Exh.1048, at 328.)

Thus, Golub clearly teaches the use of 40mg doxycycline per day in patients with a condition characterized by inflammation and the successful mitigation of that inflammation. It also recognized that rosacea was another such inflammatory condition that had been treated by the same family of active ingredients. Indeed, the success in rosacea was amongst the justifications for their study. (Exh.1048, at 325.) Torresani (Exh.1010) specifically recognized that doxycycline, albeit given at higher doses, significantly reduced the papules and pustules of rosacea and also acknowledged the known anti-inflammatory activity of tetracyclines. (*See* Exh.1010, at 945, Figs.3, 4; 1004 ¶¶ 31, 37.)

Finally, Jansen¹² (Exh.1034) discusses generally the classification and treatment of rosacea, noting that it is a chronic skin disorder affecting the facial

¹² Jansen (Exh.1034) was published in March 1997, Vol. 90, No. 3 of the *Journal of the Royal Society of Medicine*. Exhibit 1034 bears a date stamp from the University of Minnesota Bio-Medical Library of March 24, 1997. Jansen is prior

convexities characterized by frequent flushing, persistent erythema and telangiectasia. “During episodes of inflammation additional features are swelling, papules and pustules.” (Exh.1034, at 144.) Jansen confirms that bacteriologic studies of the pustules of rosacea revealed nothing of interest. (*Id.* at 145, Exh.1004 ¶ 33.) Therefore, the papules and pustules of rosacea are clearly inflammatory, and not bacteriological, in nature.

3. Differences Between The Art And The Claims

Golub did not expressly discuss treating papules and pustules of rosacea. However, it did teach treating inflammatory aspects of periodontitis using 40mg/day of doxycycline administered orally. Moreover, it taught that the inflammatory pathways in periodontal disease were the same as those found in inflammatory rosacea. (Exh.1004 ¶ 38, 39.) Indeed, it offered the impact of tetracyclines on rosacea in its justifications for the study. (Exh.1048, at 325.) The fact that the condition was chronic and inflammatory (and not just bacterial) provided a reason to use a lower dose of doxycycline to capitalize on its anti-inflammatory properties without invoking its antibacterial properties or disadvantages. (Exh.1004 ¶¶ 40, 42, 43, 44, 45, 48, 49, 50, 53.) These were

art under 35 U.S.C. § 102(b) and was not listed as of record on the cover of the ‘506 Patent.

considered important in general but were particularly important given the prospect of “long-term antibiotic usage” to treat periodontal disease. (Exh.1048, at 328; 1004 ¶ 48.)

Knowing of the success observed by Golub in using low dose doxycycline to treat such a chronic inflammatory condition, it would have been obvious for one of ordinary skill in the art to at least try the same protocol to treat rosacea, another such chronic inflammatory condition already known to be responsive to doxycycline, with at least a reasonable expectation of success when doing so. (Exh.1004 ¶¶ 42, 43, 44, 45, 53.)

Golub’s teaching provides clear motivation to employ its treatment protocol when treating rosacea, and at least a reasonable expectation that it would be effective. (*Id.* ¶ 60.) What’s more, Torresani (Exh.1010) provided additional support for the expectation of success, as it showed that doxycycline was already known to be effective in treating papules and pustules of rosacea, that it was believed that this therapeutic effect was due to doxycycline’s efficacy as an anti-inflammatory, not an antibiotic, and that higher doses of doxycycline had an increased risk of antibiotic side effects (Exh.1010, at 944, 945, Fig.6). Further, Jansen (Exh.1034) confirmed that rosacea and, in particular, its papules and pustules, are inflammatory in nature, not bacterial.

A person of ordinary skill in the art would have reason and incentive to combine Torresani and Jansen with Golub. To begin with, all three are directed to treating inflammatory conditions with tetracyclines, specifically doxycycline. And all three were successful in treating their respective inflammatory conditions. Given the success that a reduced dose of doxycycline exhibited in periodontitis, its link to rosacea, and the fact that papules and pustules of rosacea were known specifically to be inflammatory and treatable by the same active ingredient, a person of ordinary skill in the art would have a reasonable expectation that employing a lower dose protocol, such as was successfully used for periodontal conditions, would produce similarly advantageous results in connection with rosacea. (Exh.1004 ¶¶ 42, 43, 44, 45.) And, as extensively noted in Ground 1 (*see* Part VI.A, *supra*), the possible advantages of a reduced dose in terms of schedule, compliance, cost, and potential reduction in side effects would each provide additional strong motivation in this instance (Exh.1004 ¶¶ 46-53).

A second difference between the claims and the art is that none of this art discussed above explicitly taught administering doxycycline without a bisphosphonate. But they did teach administering only doxycycline. (Exhs.1010, 1034, 1042, 1048, 1004 ¶ 61.) They therefore taught administration *without* a bisphosphonate as claimed, either literally or by inherency.

Finally, the results in terms of allegedly not reducing skin microflora, recited in the independent claims, are inherent for the reasons explained in connection with Ground 1. (*See* Part VI.A.3.c, *supra*; Exh.1004 ¶ 62.)

4. Claim Chart

A claim chart summarizing the foregoing analysis appears below. It includes citations to the record and, where appropriate, for the ease of the Board, a citation to specific language to aid in finding the relevant passage.

Claims of the ‘506 Patent	Citation to the art for Ground 2
1. A method for treating papules and pustules of rosacea in a human in need thereof, the method comprising:	Exh.1048, at 325 (“tetracyclines . . . when administered to patients with certain skin diseases, diseases such as rosacea”); Exh.1034, at 144 (“Rosacea is a chronic skin disorder . . . features are swelling, papules and pustules.”); Exh.1010, at 944-45, Figs.3, 4; Exh.1004 ¶¶ 31, 37
administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof,	Exh.1034 at 148 (“Rosacea generally responds well to oral antibiotics . . . doxycycline”); Exh.1048, at 322 (“20 or 30 mg of Vibramycin®...take one capsule in the morning and one at night”); Exh.1004 ¶¶ 31, 37
in an amount that (i) is effective to treat papules and pustules of rosacea;	Exh.1048, at 322 (“20 or 30 mg of Vibramycin®...take one capsule in the morning and one at night”); Exh.1034, at 148 (“Rosacea generally responds well to oral antibiotics . . . doxycycline”); Exh.1010, at 944-45, Figs.3, 4; Exh.1004 ¶¶ 31, 33, 40, 42, 43, 44, 45
(ii) is 10-80% of a 50 mg dose of doxycycline per day; and	Exh.1048, at 322 (“[s]pecial capsules of doxycycline were formulated . . . each containing 20 or 30 mg of Vibramycin® . . . subjects were instructed to take one capsule in the morning and

Claims of the ‘506 Patent	Citation to the art for Ground 2
	one at night”); Exh.1004 ¶¶ 38, 39, 42, 43, 44, 45, 53
(iii) results in no reduction of skin microflora during a six month treatment,	Exh.1004 ¶ 62 (Inherent function of dose); Exh.1048, at 322 (“[s]pecial capsules of doxycycline were formulated . . . each containing 20 or 30 mg of Vibramycin® . . . subjects were instructed to take one capsule in the morning and one at night”)
without administering a bisphosphonate compound.	Exh.1004 ¶ 61; Exhs. 1048, 1010 (References teach doxycycline monotherapy)
8. A method for treating papules and pustules of rosacea in a human in need thereof, the method comprising	Exh.1048, at 325 (“tetracyclines . . . when administered to patients with certain skin diseases, diseases such as rosacea”); Exh.1034, at 144 (“Rosacea is a chronic skin disorder . . . features are swelling, papules and pustules.”); Exh.1010, at 944-45, Figs.3, 4; Exh.1004 ¶¶ 31, 37
administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof,	Exh.1034, at 148 (“Rosacea generally responds well to oral antibiotics . . . doxycycline”); Exh.1048 at 322 (“20 or 30 mg of Vibramycin® . . . take one capsule in the morning and one at night”); Exh.1004 ¶¶ 31, 37
in an amount that (i) is effective to treat the papules and pustules of rosacea;	Exh.1048, at 322 (“20 or 30 mg of Vibramycin® . . . take one capsule in the morning and one at night”); Exh.1034, at 148 (“Rosacea generally responds well to oral antibiotics . . . doxycycline”); Exh.1010, at 944-45, Figs.3, 4; Exh.1004 ¶¶ 31, 33, 40, 42, 43, 44, 45
(ii) is 40-80% of a 50 mg dose of doxycycline per day; and	Exh.1048, at 322 (“[s]pecial capsules of doxycycline were formulated . . . each containing 20 or 30 mg of Vibramycin® . . . subjects were instructed to take one capsule in the morning and one at night”); Exh.1004 ¶¶ 38, 39, 42, 43, 44, 45, 53

Claims of the ‘506 Patent	Citation to the art for Ground 2
(iii) results in no reduction of skin microflora during a six-month treatment,	Exh.1004 ¶ 62 (Inherent function of dose); Exh.1048, at 322 (“[s]pecial capsules of doxycycline were formulated . . . each containing 20 or 30 mg of Vibramycin® . . . subjects were instructed to take one capsule in the morning and one at night . . .”)
without administering a bisphosphonate compound.	Exh.1004 ¶ 61; Exhs. 1048, 1010 (References teach doxycycline monotherapy)
15. A method for treating papules and pustules of rosacea in a human in need thereof, the method comprising	Exh.1048, at 325 (“tetracyclines . . . when administered to patients with certain skin diseases, diseases such as rosacea . . .”); Exh.1034, at 144 (“Rosacea is a chronic skin disorder . . . features are swelling, papules and pustules.”); Exh.1010, at 944-45, Figs.3, 4; Exh.1004 ¶¶ 31, 37
administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof,	Exh.1034, at 148 (“Rosacea generally responds well to oral antibiotics . . . doxycycline . . .”); Exh.1048, at 322 (“20 or 30 mg of Vibramycin® . . . take one capsule in the morning and one at night . . .”); Exh.1004 ¶¶ 31, 37
in an amount of 40 mg per day,	Exh.1048, at 322 (“[s]pecial capsules of doxycycline were formulated . . . each containing 20 or 30 mg of Vibramycin® . . . subjects were instructed to take one capsule in the morning and one at night . . .”); Exh.1004 ¶¶ 38, 39, 40, 42, 43, 44, 45, 53
wherein the amount results in no reduction of skin microflora during a six-month treatment,	Exh.1004 ¶ 62 (Inherent function of dose); Exh.1048, at 322 (“[s]pecial capsules of doxycycline were formulated . . . each containing 20 or 30 mg of Vibramycin® . . . subjects were instructed to take one capsule in the morning and one at night . . .”)
without administering a bisphosphonate compound.	Exh.1004 ¶ 61; Exhs. 1048, 1010 (References teach doxycycline monotherapy)

Dependent claims 7, 14, and 20 are discussed in Part VI.C, *infra*.

C. Ground 3. Dependent Claims 7, 14, And 20 Would Have Been Obvious Over Golub (Exh.1048) In View Of Torresani (Exh.1010) And Jansen (Exh.1034), And Further In View Of 2000 PERIOSTAT PDR (Exh.1042)

Dependent claims 7, 14, and 20 of the '506 Patent each contains an identical recitation and therefore they can be treated together. Furthermore, each dependent claim also includes all of the limitations of the independent claim from which it depends. As such, the arguments presented above in Ground 2 for independent claims 1, 14, and 20 apply to dependent claims 7, 14, and 20.

Each dependent claim requires that the doxycycline, or its pharmaceutically acceptable salt of the independent claim from which they depend, be administered in an amount that provides a serum concentration in the range of about 0.1 to about 0.8 μ g/mL. As shown in the 2000 PERIOSTAT PDR (Exh.1042, at 945), the mean peak concentration in plasma for PERIOSTAT was 790ng/mL and the average steady-state concentration was 482ng/mL. 1 μ g = 1000ng, so 482ng/mL = 0.482 μ g/mL and 790ng/mL = .79 μ g/mL, both of which are within the claimed range and establish a *prima facie* case of obviousness as to these claims. *Peterson*, 315 F.3d at 1330. We are aware of no evidence capable of negating this *prima facie* case. Thus, this establishes that administering 20mg doses of doxycycline twice a day, as taught by the 2000 PERIOSTAT PDR (Exh.1042) and

Golub (Exh.1048) would result in a serum concentration as claimed in claims 7, 14, and 20.

Claims of the '506 Patent	Citation to the art for Ground 3
7. The method according to claim 1, wherein said doxycycline, or a pharmaceutically acceptable salt thereof, is administered in an amount which provides a serum concentration in the range of about 0.1 to about 0.8 µg/ml.	<i>See supra</i> Part VI.B.4, citations for claim 1 in the claim chart for Ground 2. Exh.1042, at 945 (“mean peak concentration in plasma [for PERIOSTAT] was 790 ng/mL and the average steady-state concentration was 482 ng/mL”)
14. The method according to claim 8, wherein said doxycycline, or a pharmaceutically acceptable salt thereof, is administered in an amount which provides a serum concentration in the range of about 0.1 to about 0.8 µg/ml.	<i>See supra</i> Part VI.B.4, citations for claim 8 in the claim chart for Ground 2. Exh.1042, at 945 (“mean peak concentration in plasma [for PERIOSTAT] was 790 ng/mL and the average steady-state concentration was 482 ng/mL”)
20. The method according to claim 15, wherein said doxycycline, or a pharmaceutically acceptable salt thereof, is administered in an amount which provides a serum concentration in the range of about 0.1 to about 0.8 µg/ml.	<i>See supra</i> Part VI.B.4, citations for claim 15 in the claim chart for Ground 2. Exh.1042, at 945 (“mean peak concentration in plasma [for PERIOSTAT] was 790 ng/mL and the average steady-state concentration was 482 ng/mL”)

VII. CONCLUSION

For the foregoing reasons, Requestor requests that *inter partes* review be instituted for claims 1, 7, 8, 14, 15, and 20 of the '506 Patent and that those claims be held unpatentable over each of the grounds discussed in Part VI hereof.

Dated: August 20, 2015

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**CERTIFICATE OF COMPLIANCE
WITH TYPE-VOLUME LIMITATION**

Pursuant to Rule 37 C.F.R. 42.24(d), the undersigned hereby certifies that, based upon the word count of the word-processing system used to prepare this petition, the number of words in this petition is 13,606. Pursuant to 37 C.F.R. 42.24 (a), this word count does not include “a table of contents, a table of authorities, a certificate of service or word count, exhibits, appendix, or claim listing.”

Dated: August 20, 2015

By: /Brian R. Tomkins/
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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing **PETITION FOR *INTER PARTES* REVIEW OF CLAIMS 1, 7, 8, 14, 15, AND 20 OF U.S. PATENT NO. 8,603,506 AND MANDATORY NOTICES UNDER 37 C.F.R. § 42.8**, together with all exhibits, the Power of Attorney, and all other papers filed therewith, was served on August 20, 2015, as follows.

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