

Case IPR2015-
Patent No. 8,603,506
Petition for *Inter Partes* Review
Attorney Docket No. REDDYPP 7.1R-017

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).

NOTICE OF LEAD AND BACKUP COUNSEL

Lead Counsel:	Backup Counsel:
William L. Mentlik (Reg. No. 27,108) WMentlik.ipr@ldlkm.com <u>Postal and Hand-Delivery Address</u> 600 South Avenue West Westfield, NJ 07090 Telephone: 908.518.6305 Fax: 908.654.7866	Michael H. Teschner (Reg. No. 32,862) MTeschner.ipr@ldlkm.com <u>Postal and Hand-Delivery Address</u> 600 South Avenue West Westfield, NJ 07090 Telephone: 908.518.6313 Fax: 908.654.7866 Brian R. Tomkins (Reg. No. 58,550) BTomkins.ipr@ldlkm.com <u>Postal and Hand-Delivery Address</u> 600 South Avenue West Westfield, NJ 07090 Telephone: 908.518.6380 Fax: 908.654.7866 Maegan A. Fuller (Reg. No. 71,596) MFuller.ipr@ldlkm.com <u>Postal and Hand-Delivery Address</u> 600 South Avenue West Westfield, NJ 07090 Telephone: 908.518.6324 Fax: 908.654.7866

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 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 19, 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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Petition for *Inter Partes* Review

Attorney Docket No. REDDYPP 7.1R-017

‘506 Patent under different theories bearing attorney docket nos. REDDYPP 7.1R-009 and REDDYPP 7.1R-015.

NOTICE OF SERVICE INFORMATION

Please address all correspondence to the lead and backup counsel at the address shown above. Requestor also consents to electronic service by e-mail at: WMentlik.ipr@ldlkm.com, MTeschner.ipr@ldlkm.com, BTomkins.ipr@ldlkm.com, and MFuller.ipr@ldlkm.com.

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 are obvious over Bikowski (Exh.1011) in view of the 2000 PERIOSTAT PDR (Exh.1042) and Golub *et al.* (Exh.1048). *See* 35 U.S.C. § 103(a).²

Ground 2. Claims 1, 7, 8, 14, 15, and 20 are obvious over Bikowski (Exh.1011) and the 2000 PERIOSTAT PDR (Exh.1042). *See* 35 U.S.C. § 103(a).

Although Petitioner provides multiple grounds of unpatentability, they are meaningfully distinct from each other and from those made in the corresponding IPR Petitions filed on the same date as this Petition bearing attorney docket nos. REDDYPP 7.1R-009 and REDDYPP 7.1R-015.

Grounds 1 and 2 herein are based on the premise that claims 1, 7, 8 and 14 of the ‘506 Patent are entitled to a priority date no earlier than April 5, 2002, the filing date of the earliest nonprovisional application in its chain, now U.S. Patent No. 7,211,267 (Exh.1016). The provisional applications from which priority is also claimed on the face of the ‘506 Patent do not disclose a dose range that is some fraction of a 50mg dose — that disclosure, which is embodied in independent claims 1 and 8 of the ‘506 Patent was only added when the nonprovisional

² The pre-AIA version of 35 U.S.C. § 103 applies to each ground in this proceeding, because the ‘506 Patent has an effective filing date before March 16, 2013.

application was filed. Bikowski (Exh.1011) is a printed publication published in August 2000, Vol. 66, No. 2 of *CUTIS, Cutaneous Medicine for the Practitioner*. The copy of Bikowski in this Petition bears a date stamp from the University of Minnesota Bio-Medical Library of August 18, 2000. Bikowski was listed as of record on the cover of the '506 Patent, but was not discussed during its prosecution. As such, Bikowski (Exh.1011) is prior art against claims 1, 7, 8, and 14 pursuant to 35 U.S.C. § 102(b) and against claims 15 and 20 pursuant to 35 U.S.C. § 102(a). Even if claims 1, 7, 8 and 14 are accorded the benefit of the provisional applications, Bikowski is still prior art pursuant to 35 U.S.C. §§ 102(a)/103(a) against all of the challenged claims.

For Ground 1, Bikowski teaches the oral administration of 50mg of doxycycline to a patient to treat rosacea, including its papules and pustules, and that rosacea is an inflammatory condition. This combined with the knowledge that periodontal disease, known to be another inflammatory condition treatable with doxycycline, and which was successfully treated by PERIOSTAT, a 40mg/day doxycycline product of Patent Owner, renders the claims obvious.

Ground 2 starts with the premise that by April 5, 2001: (1) it was known to treat rosacea with doxycycline (Exh.1004 ¶ 31, 32; 1011)); (2) it was known that the papules and pustules of rosacea were not bacterial, but more inflammatory

conditions (Exh.1004 ¶ 33, 1011); and (3) it was known that doxycycline was an effective anti-inflammatory agent at the claimed doses (Exhs.1004 ¶ 42, 1042, 1048), that is, doses below those allegedly considered to have an antibiotic effect.

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

It was known to treat rosacea with doxycycline. (Exhs.1011, at 149-50; 1004 ¶¶ 31, 32.) Historically, tetracyclines, including doxycycline, were administered to treat rosacea, albeit at what the Patent Owner alleges to be “antibiotic doses.” (Exhs.1004 ¶¶ 28, 29, 31; 1001 col.5 ll.43-45; 1048.) However, as of the ‘506 Patent’s earliest asserted effective filing date (April 5, 2001), doxycycline had already been successfully used to treat rosacea at doses as little as 50mg daily and 50mg every other day, which, given that doxycycline’s half-life is 18 hours, the

expected dose at the end of one day would be less than half of the initial does given. (Exhs.1011, at 149; 1042, at 945; 1004 ¶ 32). Rosacea was known by April 5, 2001, to be an inflammatory condition, not bacterial. (*Id.*; *see also* Exh.1004 ¶ 33, 1048.) And, it was known that doxycycline's success in treating the papules and pustules of rosacea was attributed to its anti-inflammatory properties, not its antibiotic properties. (Exh.1004 ¶ 37, 40; 1048)

In treating rosacea, there was no medical necessity for using an antibiotic amount of an antibiotic drug if less was needed to take advantage of its anti-inflammatory properties. (Exh.1004 ¶¶ 40, 42, 43, 44, 45, 58.) This strongly suggests using a lower dose of an antibiotic in treating rosacea. (*Id.*) But there were several other readily apparent advantages that would motivate one to try giving an allegedly sub-antibiotic dose of an antibiotic with anti-inflammatory properties, such as doxycycline (itself already known to successfully treat rosacea). These included possible reduced drug cost, smaller dosage forms, and reduced potential exposure to antibiotic level side effects and reducing the prospect of creating drug resistant bacteria, all of which were well known. (*Id.* ¶¶ 46, 47, 48; Exh.1048.) 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. (Exh.1004 ¶ 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.)

It was also known at the time of the earliest asserted effective filing date that using 40mg/day of doxycycline successfully treated another chronic inflammatory condition, periodontal disease, whose underlying inflammatory pathways were known to be similar to those found in the papules and pustules of rosacea. (Exhs.1048, 1004 ¶ 39.) And a commercial product used for that exact treatment, PERIOSTAT, made that dose readily available. (Exhs.1042, 1053.)

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. (Exh.1004 ¶ 25.) Furthermore, a dermatologist may prescribe an FDA-approved medication for any use. (*Id.*) Thus, prescribing PERIOSTAT treatment for papules and pustules of rosacea was well within the skill of any dermatologist. (*Id.* ¶ 59-60.) Indeed, there is evidence that, before the ‘506 Patent, dermatologists were already using PERIOSTAT “off label.” (Exh.1015³, 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.)

Accordingly, in view of these combined teachings, it would have been obvious to reduce the 50mg daily dose of doxycycline taught in Bikowski , which was already a significant decrease from historical dosage levels, to 40mg/day (as claimed). (Exhs.1011; 1042; 1004 ¶¶ 42-45, 53, 59, 60.) This is an even more obvious step when taking into account that Bikowski reported that a maintenance level of doxycycline could be as low as 50mg every other day, which taking into considering doxycycline’s half-life is 18 hours, would be less than half of the

³ Exhibit 1015 is not prior art for purposes of this IPR.

initial dose given by the end of one day. (Exh.1004 ¶ 32.) All of the treatments in question were done without a bisphosphonate (as claimed). Finally, if, as the challenged claims allege, treating a patient with 40mg/day of doxycycline does not reduce skin microflora after six months of treatment, then that would have been the inherent result of using the recommended dosage of prior art PERIOSTAT. (Exh.1004 ¶ 62.) In light of these teachings, 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 particular drug to

treat rosacea or its symptoms described in the ‘506 Patent. There is not even a direct association in the specification of papules and pustules with 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,” 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. (Exhs.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. (Exh.1004 ¶ 14.)

According to the specification, “acne” is allegedly treated by using a dose of a drug that the ‘506 Patent argues is “subantimicrobial.” This is a key concept to the patent. (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 phrase 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 Exh.1001 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, for example, “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 is 80mg 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 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 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 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 are very similar to independent claims of its cousin, U.S. Patent No. 7,232,572, but

specifically noted that the application's amended claims were more specifically defined to 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.)⁴ 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 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. (*Id.* at 3, 4.) According to the Examiner, it would have been obvious for one of ordinary skill in the art at the

⁴ Page numbers correspond to those in the bottom right-hand corner of the exhibit.

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 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 id.* 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 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 and

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. (*Id.* 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 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 neither accepted 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 and 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)⁵. 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). (*Id.* at 7.) While applicant appears to have conceded that a skilled artisan might have believed that subantibiotic doses of

⁵ Page numbers reflect those at the bottom right-hand corner of exhibit.

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.)

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.)⁶ The Examiner did not mention reliance on any of the alleged secondary considerations.

IV. EFFECTIVE FILING DATE FOR CLAIMS 1, 7, 8 AND 14

Claims 1, 7, 8, and 14 are not entitled to any effective filing date earlier than April 5, 2002. Independent claim 1 of the '506 Patent requires administering doxycycline or a pharmaceutically acceptable salt thereof in an amount of "10 to 80% of a 50mg dose of doxycycline per day . . . ,” *i.e.*, 5 to 40mg/day (Exh.1001 col.31 l.67.) Independent claim 8 contains a similar recitation, but instead specifies that the amount "is 40-80% of a 50mg dose of doxycycline per day . . . ,” *i.e.*, 20 to 40mg/day (*Id.* col.32 l.26.) There is no recitation of a "50mg" dose at all in either of the provisional applications upon which the '506 Patent claims benefit under 35 U.S.C. § 119(e). (Exhs.1002 Serial No. 60/281,916, filed Apr. 5, 2001; 1003 Serial No. 60/325,489, filed Sept. 26, 2001.) There is also no support in either provisional application for administering the particular range of percentages of a 50mg dose specifically. (*See, e.g.*, Exhs.1002 p.7 ll.10-15, 1003 p.8 ll.14-20.) Nor is there any disclosure of the corresponding dosage ranges stated as 5-40 or 20-40mg/day.

⁶ Page numbering reflects the consecutive page numbering at the bottom right-hand corner of the exhibit.

In order to take advantage of an earlier priority date under 35 U.S.C. § 119(e), the provisional application must comply with the written description requirement by providing sufficient disclosure of the invention so that it is clear to those skilled in the art that the inventor was in possession of the invention as of the filing date. *New Railhead Mfg., LLC v. Vermeer Mfg Co.*, 298 F.3d 1290, 1295 (Fed. Cir. 2002). No such disclosure is present here.

Accordingly, the earliest alternative possible effective date for independent claims 1 and 8 of the '506 Patent is the filing date of its initial nonprovisional ancestor filed on April 5, 2002, which later issued as U.S. Patent No. 7,211,267. (Exh.1016.) Claims 7 and 14, which depend from claims 1 and 8, respectively, are similarly deficient and therefore are entitled to no earlier date than April 5, 2002, as well. For these reasons, the earliest effective date of claims 1, 7, 8, and 14 of the '506 Patent for this petition can be no earlier than April 5, 2002.

Note that Petitioner has discussed prior art which would be effective with an earlier effective filing date for these claims in another *inter partes* review petition filed on the same date as this Petition bearing attorney docket no. REDDYPP 7.1R-009. However, that date is only applicable to that petition. Similarly, the arguments presented in another *inter partes* review petition filed on the same date as this Petition bearing attorney docket no. REDDYPP 7.1R-015

advanced a later effective filing date for these claims. The arguments presented in these other petitions are separate and apart from the arguments set forth in this Petition, and particular to the petition bearing attorney docket no. REDDYPP 7.1R-009, such arguments are not admissions of the Petitioner and should not be treated as such for the purposes of this Petition.

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 Bikowski (Exh.1011), In View Of The 2000 PERIOSTAT PDR (Exh.1042) And Golub *et.al.* (Exh.1048)

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.” *Id.* 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 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, Exh.1004 ¶¶ 28, 29). 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. Requestor’s comments directed to claim 15, which recites doses of 40mg/day, 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 claims is provided, *infra*.

All references discussed in connection with this ground, except for Bikowski, as discussed *supra* in “Statement of Precise Relief Requested” and

Part IV, were published more than one year before April 5, 2001, and qualify as prior art pursuant to 35 U.S.C. § 102(b). Further, with the exception of Bikowski, none of the prior art used herein was identified on the cover sheet of the ‘506 Patent.

Bikowski reports two case studies of treating rosacea patients with doxycycline in an amount of either 100mg/day or 50mg/day for several months.⁷ It describes and illustrates how the patients’ papules and pustules were essentially cleared by this treatment. It also teaches that rosacea is an inflammatory condition. Dr. Bikowski also teaches that rosacea was a form of inflammatory dermatosis. (Exh.1011, at 149 (“Rosacea is an inflammatory condition of the skin, classically presenting with a history of flushing and/or blushing along with the clinical findings of erythema, edema, telangiectasia, papules, pustules, and nodules of the face.”).) He stated that “[a]lthough the exact etiology is unknown, rosacea is thought by most experts to be an inflammatory process incited by vascular instability with subsequent leakage of fluid and inflammatory mediators into the genus.” (*Id.*)

⁷ Depending on which definition of “subantimicrobial” applies, Bikowski’s use of 50mg/ day of doxycycline could be subantimicrobial. (Exh.1004 ¶¶ 23, 24.)

PERIOSTAT is a prescription treatment approved by the FDA for the treatment of periodontal disease — another known inflammatory condition. As explained in the 2000 PERIOSTAT PDR, PERIOSTAT involves the twice daily (also referenced as “b.i.d.” or “bid”) oral administration of 20mg capsules of doxycycline for a total of 40mg/day. Further, the mean peak concentration in plasma for PERIOSTAT was 790ng/mL and the average steady-state concentration was 482ng/mL. $1\mu\text{g} = 1000\text{ng}$, so $482\text{ng/mL} = 0.482\mu\text{g/mL}$ and $790\text{ng/mL} = .79\mu\text{g/mL}$. (Exh.1042, at 945.) Additionally, PERIOSTAT was FDA approved on September 30, 1998. (Exh.1053, at 2.) and was commercially available before April 5, 2000.⁸ (Exh.1042, at 944-46.) PERIOSTAT is also Patent Owner’s product.

⁸ 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).

More than ten years before the earliest application leading to the ‘506 Patent was filed, Golub (Exh.1048)⁹ 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 also confirmed by Bikowski. (Exh.1011, at 149 (“rosacea is thought by most experts to be an inflammatory process” treated with, *inter alia*, 50mg of doxycycline).)

Golub also taught that low dose doxycycline (20mg twice a day or “b.i.d.”) was known and used to treat another inflammatory condition, periodontitis. (Exh.1048, at 327 (“This observation suggests that tetracycline administration, particularly in low doses, could provide a safe and effective therapeutic approach for reducing pathologically excessive collagenase activity in inflammatory lesions

⁹ Golub (Exh.1048) was published in November 1990, Vol. 25, No. 6:321-377 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.

without interfering with normal connective tissue remodeling”); *see also* Exh.1048, 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.) Golub and his collaborators looked at doxycycline’s effect on certain inflammatory pathways, which they noted were common to both periodontitis and rosacea, to develop the low dose treatment for periodontitis. (Exhs.1004 ¶ 38, 39; 1048, at 325-26.) The treatment of periodontitis described in 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; 1004 ¶ 54.)

3. Differences Between The Art And The Claims

The only elements of the independent claims of the ‘506 Patent arguably missing from Bikowski are: (1) the use of a 40mg/day dose of doxycycline instead of a 50mg/day dose described by Bikowski; (2) treatment without concomitant bisphosphonate; and (3) the observation of the impact of that dose on skin microflora. But changing the dose was, at a minimum, obvious to try. Bikowski did not concomitantly administer a bisphosphonate, and the result in terms of skin microflora was merely an inherent consequence of the treatment.

Simply stated, rosacea was known from Bikowski to be an inflammatory condition. Accordingly, there would be no *per se* reason to use an antibiologically effective amount of doxycycline to treat rosacea — only an amount that was anti-inflammatory. (Exh.1004 ¶¶ 44, 45, 58.) And knowing that 50mg/day was effective, and that an antibiotic dose of doxycycline, with all of its attendant side effects (Exh.1050 col.3 ll.58-62; Exh.1051, at 943 (*see* “Warnings” and “Adverse Reactions”; *see also* Exh.1004 ¶¶ 48), was unnecessary, a dermatologist of ordinary skill in the art would have found it obvious to at least try commercially available slightly lower doses of doxycycline such as PERIOSTAT, and would have had more than a reasonable expectation of achieving anti-inflammatory efficiency when doing so. (Exhs.1042, at 944-46; 1053; *see also* Exh.1004 ¶¶ 40, 42, 53, 54, 60)

Anti-inflammatory doses of doxycycline were reasonably expected to be lower than those needed for traditional antibiotic treatment. In fact, the anti-inflammatory properties of doxycycline were known to be effective at concentrations just above 0µg/ml. (Exh.1004 ¶ 42.) PERIOSTAT had already successfully treated another inflammatory condition, periodontitis, at 40mg/day. (Exh.1042, at 945.) Golub had the same result. (Exh.1048, at 325-26.) That being the case, there was at least a reasonable expectation that lowering the dose from

50mg/day to 40mg/day would be effective and would immediately reduce a patient's exposure to antibiotic side effects. Thus, there was ample motive to try the available lower doses of doxycycline, and, again, more than a reasonable expectation of success from doing so. (Exh.1004 ¶¶ 42, 43, 44, 45, 53, 60.)

Despite the fact that PERIOSTAT is FDA-approved for periodontitis, doctors are of course free to prescribe such medication for other indications. (Exh.1004 ¶ 25, 59.) And there is evidence that dermatologists were already doing so. (*Id.* ¶ 27.) Thus, before April 5, 2001, indeed more than a year before that date, doctors had at their disposal FDA-approved and commercially available lower doses of the very active agent known to be useful to treat rosacea and its papules and pustules — doses falling within the scope of claims 1, 8, and 15 of the '506 Patent. (Exh.1042, Exh.1053) Indeed, the prospect of using a lower dose offered other immediate possible advantages in terms of drug dose, dosage form, size, and compliance, any of which would justify its use. (Exh.1004 ¶ 46, 47)

As a further matter, it is fundamental to the practice of medicine that doctors always must balance the prospect of efficacy and potential side effects every time they make a treatment decision. (Exh.1004 ¶¶ 48, 49, 50.) Particularly in the case of rosacea, there is good reason to try a low dose and increase it as needed. (*Id.*) If a low dose of doxycycline were ineffective in treating a patient, there would be no

long-term consequence to the patient's health, other than the continuing rosacea. In that case, the dose could be merely increased until efficacy was obtained. On the other side of the balance, using an initially low dose would have the immediate impact of minimizing the exposure of the patient to side effects, in particular those linked to antibiotically effective amounts of that drug. (*Id.* ¶¶ 49-53.) As Dr. Payette observed, "[b]alancing providing the claimed symptomatic relief from a nonlife threatening dermatological condition with the possible side effects, in this case, more heavily counsels starting with a low dose and titrating the patient to the lowest dose that treats the patient's papules and pustules." (*Id.* ¶ 50.) As Dr. Payette further states, this approach is not unique to dermatology. (*Id.* ¶ 51.)

Although Bikowski did not expressly state that the administration of doxycycline should be done without concomitant bisphosphonate, only doxycycline monotherapy was disclosed. Thus, it was known from Bikowski to treat papules and pustules of rosacea with doxycycline and *without* bisphosphonates. (*See also* Exh.1004 ¶ 61.) The same is true for the Dosage and Administration of PERIOSTAT disclosed in the 2000 PERIOSTAT PDR. (Exh.1042.)

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/day 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. 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.

In summary, a person of ordinary skill in the art would be motivated to prescribe a 40mg/day dose of doxycycline instead of a 50mg/day dose, and thus such decrease in dose would be obvious to try and would meet all of the limitations of the independent claims of the '506 Patent.

4. Dependent Claims 7, 14 and 20

Dependent claims 7, 14, and 20 of the '506 Patent all contain identical recitations and therefore they can be treated together. Claim 7 depends from independent claim 1, claim 14 depends from independent claim 8, and 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 0.12 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. 1µg = 1000ng, so 482ng/mL =

0.482µg/mL and 790ng/mL = .79µg/mL, both of which are within 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). 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.1011, at 150-51 patients 1 and 2 and Figs.3-5, at 149 (“Two cases of inflammatory rosacea...these patients improved dramatically within 1 to 2 months of beginning treatment, exclusively with doxycycline monohydrate”); Exh.1004 ¶ 32
administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof,	Exh.1011, at 150 “doxycycline monohydrate” “systemic antibiotic therapy” (<i>id.</i>), “oral antibiotics” (<i>id.</i> at 149.); Exh.1042, at 944 (“Periostat® is available as a 20 mg capsule formulation of doxycycline hyclate for oral administration”); Exh.1004 ¶¶ 29, 32
in an amount that (i) is effective to treat papules and pustules of rosacea;	Exh.1011, at 150 Fig.2; p.151 Figs.4, 5; p.150 (“At follow-up she was essentially clear.”); Exh.1004 ¶¶ 40, 42, 43, 44, 45, 52, 60

Claims of the '506 Patent	Citation to the art for Ground 1
(ii) is 10-80% of a 50 mg dose of doxycycline per day; and	Exh.1011, at 150 (“Therapy with doxycycline monohydrate 50 mg/day was initiated”); Exh.1042 (“Periostat® 20 mg twice daily”)(40mg is 80% of a 50mg dose); Exh.1048, at 322 (“Special 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 ¶¶ 32, 40, 42, 43, 44, 45, 53, 59, 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 associated with periodontitis.”); Exh.1004 ¶ 62 (Inherent result of dose).
without administering a bisphosphonate compound.	Exh. 1011, at 149 (“Two cases of inflammatory rosacea...these patients improved dramatically within 1 to 2 months of beginning treatment, exclusively with doxycycline monohydrate”); Exh.1004 ¶ 61
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.	See 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.”)
8. A method for treating papules and pustules of rosacea in a human in need thereof, the method comprising	Exh.1011, at 150-51 patients 1 and 2 and Figs.3-5, at 149 (“Two cases of inflammatory rosacea...these patients improved dramatically within 1 to 2 months of beginning treatment, exclusively with doxycycline monohydrate”); Exh.1004 ¶ 32

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.1011, at 150 “doxycycline monohydrate” “systemic antibiotic therapy” (<i>id.</i>), “oral antibiotics” (<i>id.</i> at 149.); Exh.1042, at 944 (“Periostat® is available as a 20 mg capsule formulation of doxycycline hyclate for oral administration”); Exh.1004 ¶ 32
in an amount that (i) is effective to treat the papules and pustules of rosacea;	Exh.1011, at 150 Fig.2; p.151 Figs.4, 5; p.150 (“At follow-up she was essentially clear.”); Exh.1004 ¶¶ 40, 42, 43, 44, 45, 52, 60
(ii) is 40-80% of a 50 mg dose of doxycycline per day; and	Exh.1011, at 150 (“Therapy with doxycycline monohydrate 50 mg/day was initiated”); Exh.1042 (“Periostat® 20 mg twice daily”)(40mg is 80% of a 50mg dose); Exh.1048, at 322 (“Special 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 ¶¶ 32, 40, 42, 43, 44, 45, 53, 59, 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 associated with adult periodontitis.”); Exh.1004 ¶ 62 (Inherent result of dose)
without administering a bisphosphonate compound.	Exh. 1011, at 149 (“Two cases of inflammatory rosacea...these patients improved dramatically within 1 to 2 months of beginning treatment, exclusively with doxycycline monohydrate”); Exh.1004 ¶ 61

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.	See 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.1011, at 150-51 patients 1 and 2 and Figs.3-5, at 149 (“Two cases of inflammatory rosacea...these patients improved dramatically within 1 to 2 months of beginning treatment, exclusively with doxycycline monohydrate”); Exh.1004 ¶ 32
administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof,	Exh.1011, at 150 “doxycycline monohydrate” “systemic antibiotic therapy” (<i>id.</i>) “oral antibiotics” (<i>id.</i> at 149); Exh.1042 (“Periostat® is available as a 20 mg capsule formulation of doxycycline hydrate for oral administration”); Exh.1004 ¶ 32
in an amount of 40 mg per day,	Exh.1011, at 150 (“Therapy with doxycycline monohydrate 50mg/day was initiated”); Exh.1042 (“Periostat® 20 mg twice daily”); Exh. 1048, at 322 (“Special 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 ¶¶ 32, 40, 42, 43, 44, 45, 53, 59, 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 associated with adult periodontitis.”); Exh.1004 ¶ 62 (Inherent result of dose)

Claims of the ‘506 Patent	Citation to the art for Ground 1
without administering a bisphosphonate compound.	Exh. 1011, at 149 (“Two cases of inflammatory rosacea...these patients improved dramatically within 1 to 2 months of beginning treatment, exclusively with doxycycline monohydrate”); Exh.1004 ¶ 61
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.	See 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, 7, 8, 14, 15, And 20 Would Have Been Obvious Over Bikowski (Exh.1011) And The 2000 PERIOSTAT PDR (Exh.1042)

1. The Level Of Ordinary Skill In The Art

The level of skill in the art set forth in Ground 1 applies here as to Ground 2 as well.

2. The Scope And Content Of The Prior Art

As discussed above relative to Ground 1, all three independent claims can be discussed together, with Requestor’s comments directed principally to independent claim 15 in that it references doses of 40mg/day, though Requestor’s comments are equally applicable to claims 1 and 8.

All references discussed in connection with this ground, except for Bikowski, were published more than one year before April 5, 2001, and qualify as

prior art pursuant to 35 U.S.C. § 102(b). Further, while Bikowski was identified on the cover sheet of the '506 Patent, 2000 PERIOSTAT PDR was not.

Tetracycline was one of the first members of a family of antibiotic drugs known as of the filing date of the '506 Patent as "tetracyclines." (Exh.1004 ¶ 28.) This family was also well known to include doxycycline. (*See* Exhs.1042, 1051, 1004 ¶ 30.) And members of the tetracycline family, including doxycycline, were well known for decades to treat rosacea. (Exhs.1004 ¶¶ 28-31.) 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. (Exh.1004 ¶¶ 28-31.) These were generally considered to be antibiotic amounts. (Exh.1004 ¶¶ 58.)

It was also known prior to April 5, 2001 that the papules and pustules of rosacea were inflammatory in nature, not bacterial. (Exh.1004 ¶ 33.) Further, it was known that tetracyclines, including doxycycline, possessed not just antibiotic properties, but anti-inflammatory properties as well. (*Id.* ¶¶ 34, 35, 36, 37). In fact, the art concluded that doxycycline was effective as an anti-inflammatory at concentrations just above 0µg/mL. (*Id.* ¶ 42) As such, doxycycline's effectiveness in treating the papules and pustules of rosacea was being attributed to its anti-inflammatory properties, not its antibiotic properties. (*Id.* ¶¶ 37, 38, 39, 40.)

Prior to the earliest application leading to the '506 Patent was filed, lower doses of tetracyclines started being used. Bikowski for instance, taught that lower doses of doxycycline (50mg/day) were effective in treating rosacea, and a decreased dose of 50mg every other day for ongoing maintenance therapy. (Exhs.1011, at 150; 1004 ¶ 32.) Bikowski also confirmed earlier findings in that, “[r]osacea is an inflammatory condition of the skin, classically presenting with . . . clinical findings of erythema . . . papules, pustules, and nodules of the face.” (Exh.1011, at 149.) And further, Bikowski confirmed that a well-documented treatment includes an oral antibiotic such as tetracyclines, doxycycline and minocycline. (*Id.* at 150-51.) Bikowski also noted that the “second-generation tetracyclines,” such as minocycline, doxycycline hyclate and doxycycline monohydrate, all have “increased bioavailability, improved absorption when taken with food, and broader antibacterial activity.” (Exh.1011, at 151.) These “systemic antibiotics will usually clear the inflammatory lesions of moderately severe . . . rosacea.” (*Id.*) Further, while “the ultimate goal is to taper down and/or discontinue oral therapy, intermittent low-dose systemic antibiotics in addition to daily topical treatment may be necessary to maintain complete remission in the majority of patients.” (*Id.*)

Low dose doxycycline products were also known in the marketplace prior to April 5, 2001. One such product is PERIOSTAT — administrated via 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. (Exh.1042, at 944-46; Exh.1053.) PERIOSTAT itself is also Patent Owner’s product and prior art. (See Exh.1001 col.5 ll.59-63.) The 2000 PERIOSTAT PDR also discloses the half-life of doxycycline to be “approximately 18 hours by renal and fecal excretion of unchanged drug.”¹⁰ (*Id.*) Thus, not only was there a 50mg/day dose known in the art and a 40mg/day dose commercially available, but, given that the half-life of doxycycline is 18 hours, the effectiveness of the 50mg dose every other day taught in Bikowski is expected to be less than half of the initial dose after one day. (Exh.1004 ¶ 32.)

¹⁰ PERIOSTAT is doxycycline hyclate, while the treatment in Bikowski describes doxycycline monohydrate. However, the half-life is about 18 hours for doxycycline hyclate and doxycycline monohydrate. (Exh.1073, at 2082, 2385.)

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

a. The Dosage

As noted above, it has been known for decades to treat inflammatory papules and pustules of rosacea with tetracyclines, including doxycycline, administered orally. (Exh.1004 ¶¶ 28-31.) However, over this timeframe, a trend had emerged as to the dosage administered to treat the papules and pustules of rosacea. Previously, much higher doses of 100mg to 250mg/day of doxycycline were given for the treatment of rosacea. (*Id.* 1004 ¶ 28-31.) Fast forward to Bikowski and the dose had dropped as low as 50mg/day, and even 50mg every other day as a maintenance dose for the treatment of rosacea. (Exh.1011.) Moreover, the same year as Bikowski published, PERIOSTAT, as discussed above, was commercially available in a 40mg/day doxycycline dose readily available on the market, FDA approved, and indicated for use in treating patients with periodontitis, but should “not be used for reducing the numbers of or eliminating those microorganisms associated with periodontitis,” even though doxycycline was widely known to be in the tetracycline class of antibiotics and thus have antibiotic properties. (Exhs.1042, at 945; 1053, at 12.)

Given this trend towards a lower dose of doxycycline to treat the papules and pustules of rosacea, an inflammatory condition, coupled with the knowledge

that doxycycline was effective as an inflammatory at levels even just above concentrations of 0µg/mL, it would have been obvious to a person of ordinary skill in the art to use a 40mg/day dose, or lower, to treat the papules and pustules of rosacea in accordance with the claimed invention. (Exh.1004 ¶¶ 40, 42, 43, 44, 45, 59, 60.) Importantly, 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. (*Id.* ¶¶ 42, 48, 53, 60.) But this is far from the only reason to try lower doses. The art recognized 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. (*See id.* ¶ 48.)

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. 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 ¶¶ 44, 45, 48, 53.)

With the above motivations in mind, in combination with the general knowledge one of ordinary skill in the art would possess based on the prior art, arriving at the purported invention of the '506 Patent would be painfully obvious. 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. (Exh.1004 ¶ 42.) Second, the use of a 50mg/day dose, and even a 50mg every other day dose, had been documented by this time (Exh.1011), which established a precipitous drop in dosage level from earlier studies (Exh.1004 ¶¶ 28-31, 58). This decrease in dosage level to treat the papules and pustules of rosacea would only serve as confirmation that lower-dose doxycycline treatments still provide sufficient anti-inflammatory activity. Third, PERIOSTAT was an FDA-approved, commercially available treatment known to be effective in treating another inflammatory condition (periodontitis) using low dose doxycycline in 20mg tablets twice a day for a recommended daily dose of 40mg. (Exhs.1042; 1053; Exh.1004 ¶¶ 38 42, 54.) The 2000 PDR PERIOSTAT also taught a half-life of doxycycline to be about 18 hours (Exh.1042, at 945), thus as noted above, the maintenance dose of 50mg every other day in Bikowski was

expected to be less than half the initial 50mg dose at the end of one day. (Exh.1004 ¶ 32.) As such, Bikowski not only taught lowering the dose to 50mg/day, but also taught that an even lower dose of about 40-50% of a 50mg/day dose would be effective. Such guidance confirmed the aforementioned general understanding that doxycycline was effective as an inflammatory at levels even just above concentrations of 0µg/ml. (Exh.1004 ¶ 42.)

A dermatologist of ordinary skill in the art would be motivated to look to commercially available low dose doxycycline products in light of the teachings of the prior art. (Exh.1004 ¶¶ 42, 60.) PERIOSTAT, despite being FDA-approved for periodontitis, is one such low dose commercial offering, and doctors are of course free to prescribe such medication for other indications. (*Id.* ¶¶ 25, 59.) And there is evidence that dermatologists were already doing so. (*Id.* ¶ 27.) Reviewing these factors together, a person of ordinary skill in the art would understand that lower doses of doxycycline can successfully treat the papules and pustules of rosacea, and further these factors provide a reasonable expectation of success in doing so. (*Id.* ¶¶ 42, 43, 44, 45, 60.) In addition, medical professionals, including dermatologists, considering the appropriate treatment of patients, would be justifiably concerned with the side effects of antibiotic doses of doxycycline when

it was not being used as an antibiotic, and therefore look to lower doses of antibiotic treatment. (*Id.* ¶¶ 48, 53, 58.)

Given the foregoing, knowing that doxycycline was an active anti-inflammatory at very low doses, that there would be no *per se* reason to use an antibiotically effective amount of doxycycline to treat rosacea, that a 40mg/day dose of doxycycline was FDA-approved and commercially available in effectively addressing other inflammatory conditions, and that such 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 a treatment incorporating a lower dose of doxycycline, such as PERIOSTAT, in treating the papules and pustules of rosacea, precisely as claimed in the '506 Patent. (Exh.1004 ¶¶ 40, 42, 43, 44, 45, 46, 47, 48, 53, 58, 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 trend in rosacea treatment towards a lower dose, the known activity of these anti-inflammatory agents at almost any dose, and the availability of an even lower dose of doxycycline in PERIOSTAT, 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 ¶¶ 40, 42, 43, 44, 45, 53, 60.)

It should also be recalled that papules and pustules of rosacea are symptoms that are certainly serious, but not life threatening. (Exh.1004 ¶ 50.) Unlike treating an infection, there likely would be no serious consequence to initially under dosing these symptoms; only lost time, at worst. (*Id.* ¶¶ 50, 53.) 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.* ¶¶ 49, 50.)

a. 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.1011, 1042; 1004 ¶ 61.) They, therefore, taught administration *without* a bisphosphonate as claimed, either literally or by inherency.

b. 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, 1053), must bring about the same result. 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. 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 0.12 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 1329. 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)

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 2
1. A method for treating papules and pustules of rosacea in a human in need thereof, the method comprising:	Exh.1011, at 150-51 patients 1 and 2 and Figs.3-5, at 149 (“Two cases of inflammatory rosacea...these patients improved dramatically within 1 to 2 months of beginning treatment, exclusively with doxycycline monohydrate”); Exh.1004 ¶ 32
administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof,	Exh.1011, at 150 “doxycycline monohydrate” “systemic antibiotic therapy” (<i>id.</i>) “oral antibiotics” (<i>id.</i> at 149); Exh.1042, at 944 (“Periostat ® is available as a 20 mg capsule formulation of doxycycline hyclate for oral administration”); Exh.1004 ¶ 32
in an amount that (i) is effective to treat papules and pustules of rosacea;	Exh.1011, at 150 Fig. 2; p.151 Figs. 4, 5; p.150 (“At follow-up she was essentially clear.”); Exh.1004 ¶¶ 32, 40, 42, 43, 44, 45, 60
(ii) is 10-80% of a 50 mg dose of doxycycline per day; and	Exh.1011, at 150 (“Therapy with doxycycline monohydrate 50 mg/day was initiated”), (“The doxycycline monohydrate was decreased to 50 mg every other day for long-term maintenance”); Exh.1042, at 944 (“Periostat® 20 mg twice daily”)(40mg is 80% of a 50mg dose), at 945 (“doxycycline is eliminated with a half-life of approximately 18 hours by renal and fecal excretion of unchanged drug”); Exh.1004 ¶¶ 32, 40, 42, 43, 44, 45, 53, 59, 60

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.1042, at 945 (“The dosage of doxycycline achieved with this product during administration is well below the concentration required to inhibit microorganisms associated with adult periodontitis.”); Exh.1004 ¶ 62 (Inherent result of dose)
without administering a bisphosphonate compound.	Exh. 1011, at 149 (“Two cases of inflammatory rosacea...these patients improved dramatically within 1 to 2 months of beginning treatment, exclusively with doxycycline monohydrate”); Exh.1004 ¶ 61;
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.”)
8. A method for treating papules and pustules of rosacea in a human in need thereof, the method comprising	Exh.1011, at 150-51 patients 1 and 2 and Figs.3-5, at 149 (“Two cases of inflammatory rosacea...these patients improved dramatically within 1 to 2 months of beginning treatment, exclusively with doxycycline monohydrate”); Exh.1004 ¶ 32
administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof,	Exh.1011, at 150 “doxycycline monohydrate” “systemic antibiotic therapy” (<i>id.</i>) “oral antibiotics” (<i>id.</i> at 149); Exh.1042, at 944 (“Periostat ® is available as a 20 mg capsule formulation of doxycycline hyclate for oral administration”); Exh.1004 ¶ 32
in an amount that (i) is effective to treat the papules and pustules of rosacea;	Exh.1011, at 150 Fig. 2; p.151 Figs.4, 5; p.150 (“At follow up she was essentially clear.”); Exh.1004 ¶¶ 32, 40, 42, 43, 44, 45, 60

Claims of the ‘506 Patent	Citation to the art for Ground 2
(ii) is 40-80% of a 50 mg dose of doxycycline per day; and	Exh.1011, at 150 (“Therapy with doxycycline monohydrate 50mg/day was initiated”), (“The doxycycline monohydrate was decreased to 50 mg every other day for long-term maintenance”); Exh.1042, at 944 (“Periostat® 20 mg twice daily”)(40mg is 80% of a 50mg dose), at 945 (“doxycycline is eliminated with a half-life of approximately 18 hours by renal and fecal excretion of unchanged drug”); Exh.1004 ¶¶ 32, 40, 42, 43, 44, 45, 53, 59, 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 associated with adult periodontitis.”); Exh.1004 ¶ 62 (Inherent result of dose)
without administering a bisphosphonate compound.	Exh. 1011, at 149 (“Two cases of inflammatory rosacea...these patients improved dramatically within 1 to 2 months of beginning treatment, exclusively with doxycycline monohydrate”); Exh.1004 ¶ 61
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.	See 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.1011, at 150-51 patients 1 and 2 and Figs.3-5, at 149 (“Two cases of inflammatory rosacea...these patients improved dramatically within 1 to 2 months of beginning treatment, exclusively with doxycycline monohydrate”); Exh.1004 ¶ 32

Claims of the ‘506 Patent	Citation to the art for Ground 2
administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof,	Exh.1011, at 150 “doxycycline monohydrate” “systemic antibiotic therapy” (<i>id.</i>) “oral antibiotics” (<i>id.</i> at 149.); Exh.1042, at 944 (“Periostat ® is available as a 20 mg capsule formulation of doxycycline hyclate for oral administration”); Exh.1004 ¶ 32;
in an amount of 40 mg per day,	Exh.1011, at 150 (“Therapy with doxycycline monohydrate 50mg/day was initiated”), (“The doxycycline monohydrate was decreased to 50 mg every other day for long-term maintenance”); Exh.1042 at 944 (“Periostat® 20 mg twice daily”), at 945 (“doxycycline is eliminated with a half-life of approximately 18 hours by renal and fecal excretion of unchanged drug”); Exh.1004 ¶¶ 32, 40, 42, 43, 44, 45, 53, 59, 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 associated with adult periodontitis.”); Exh.1004 ¶ 62 (Inherent result of dose)
without administering a bisphosphonate compound.	Exh. 1011, at 149 (“Two cases of inflammatory rosacea...these patients improved dramatically within 1 to 2 months of beginning treatment, exclusively with doxycycline monohydrate”); Exh.1004 ¶ 61
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.	See 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”)

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

By: /Brian R. Tomkins/
Brian R. Tomkins
Registration No. 58,550

**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 13,372 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/
Brian R. Tomkins
Registration No. 58,550

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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:

VIA FEDEX

Quintin Cassady, Esq.
Vice President & General Counsel
Galderma Laboratories, L.P.
14501 North Freeway
Fort Worth, TX 76177
Tel: 866.735.4137.

Humberto C. Antunes
Chief Executive Officer
Nestlé Skin Health S.A.
Avenue Gratta Paille 2
1018 Lausanne, CH
Tel: +41 21 924 1111

Gerald J. Flattmann, Jr., Esq.
Evan D. Diamond, Esq.
Vanessa Y. Yen, Esq.
Paul Hastings LLP
75 East 55th Street
New York, NY 10022
Tel: 212.318.6000

Susan A. Sipos, Esq.
Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791
Tel: 516.822.3550

Dated: August 20, 2015

By: /Brian R. Tomkins/
Brian R. Tomkins
Registration No. 58,550

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