Trials@uspto.gov
Tel: 571-272-7822

Paper 10
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

GALDERMA LABORATORIES, INC.,
Patent Owner.

Case IPR2015-01782
Patent 8,603,506 B2

Before ERICA A. FRANKLIN, ZHENYU YANG, and
ROBERT A. POLLOCK, *Administrative Patent Judges.*

POLLOCK, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

INTRODUCTION

Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (collectively, "Petitioner") filed a Petition (Paper 1; "Pet.") to institute an *inter partes* review of claims 1, 7, 8, 14, 15, and 20 of US 8,603,506 B2 (Ex. 1001; "the '506 patent"). Galderma Laboratories Inc. ("Patent Owner")[1] filed a Patent Owner Preliminary Response. Paper 8 ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314.

For the reasons provided below, we determine Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim of the '506 patent. *See* 35 U.S.C. § 314(a). We, therefore, deny the Petition for an *inter partes* review.

a. Related Proceedings

Petitioner indicates that the '506 patent has been asserted in the United States District Court for the District of Delaware (Civil Action No. 15-670). Pet. 2; Paper 6, 2.

In addition to the case before us, Petitioner has requested *inter partes* review of claims 1, 7, 8, 14, 15, and 20 of US 8,603,506 B2 on other grounds in Case Nos. IPR2015-01777 and IPR2015-01778.

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[1] Petitioner further indicates that the Complaint in Civil Action No. 15-670 states that Nestlé Skin Health S.A. is now the owner of the '506 patent. Pet. 2 n.1. Although Patent Owner does not directly address this assertion in the Preliminary Response, the USPTO Assignment Database indicates that patent is assigned to Galderma Laboratories, Inc. Absent additional information, we refer to Galderma Laboratories, Inc. as the Patent Owner.

b. The '506 Patent

The '506 patent is directed to the treatment of "all known types of acne," broadly defined as "a disorder of the skin characterized by papules, pustules, cysts, nodules, comedones, and other blemishes or skin lesions." Ex. 1001, 4:23–32. The genus "acne" is expressly defined as encompassing acne rosacea ("rosacea"),[2] a skin disorder "characterized by inflammatory lesions (erythema) and permanent dilation of blood vessels (telangectasia)." *Id*. at 4:31–43. The specification further states the "[t]he present invention is particularly effective in treating comedones." *Id.* at 4:23–43.[3]

By way of background, the '506 patent discloses that the efficacy of systemically-administered tetracycline compounds in the treatment of acne is commonly believed to be due, "in significant part, to the direct inhibitory effect of the antibiotics on the growth and metabolism of [] microorganisms" that "release microbial mediators of inflammation into the dermis or trigger the release of cytokines from ductal keratinocytes." Ex. 1001, 1:42–50. In addition to these antibiotic effects, the specification also notes that tetracyclines may have therapeutic anti-inflammatory effects due to, for example, the "inhibition of neutrophil chemotaxis induced by bacterial chemotactic factors," the "inhibition of [polymorphonuclear leukocyte] derived collagenase, and by scavenging reactive oxidative species produced by resident inflammatory cells." *Id.* at 2:21–32, 3:14–25.

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[2] The parties agree that the term "acne rosacea" in the specification refers to rosacea. Pet. 30–31; Prelim. Resp 15–16.

[3] Petitioner asserts, and Patent Owner does not contest, that comedones are not a feature of rosacea. Pet. 9, 25; *see* Prelim. Resp. 23–24; Ex. 1004 ¶ 13.

The ’506 patent teaches that although tetracyclines are administered in conventional antibiotic therapy, antibiotic doses of these compounds can result in undesirable side effects such as the reduction or elimination of healthy microbial flora and the production of antibiotic resistant microorganisms. *Id*. at 3:7–17, 3:31–36. To address the need for effective treatments that minimize these side effects, the ’506 patent discloses that “all known types of acne” may be treated by administering a tetracycline compound in an amount having “substantially no antibiotic activity (i.e. substantially no antimicrobial activity)” and, thus, “does not significantly prevent the growth of . . . bacteria.” *Id*. at 3:37–50; 4:31–32; 5:31–35. The ’506 patent defines “effective treatment” as “a reduction or inhibition of the blemishes and lesions associated with acne” (*id.* 5:31–33), which may be achieved by administering non-antibiotic tetracycline compounds (i.e., those lacking substantial antibiotic activity) or by using sub-antibiotic doses of tetracycline compounds having known antibiotic effects (*see, e.g., id.* at 3:26–29, 4:58–61, 5:1–9, 5:35–42). With respect to the latter, the specification indicates that a sub-antibiotic dose may comprise “10–80% of the antibiotic dose,” or “an amount that results in a serum tetracycline concentration which is 10–80% of the minimum antibiotic serum concentration.” *Id.* at 5:36–42; 6:7–12.

The specification teaches that, whereas exemplary *antibiotic* doses of tetracycline compounds include 50, 75, and 100 milligrams per day of doxycycline, in an especially preferred embodiment, doxycycline (as doxycycline hyclate) is administered as a 20 milligram dose, twice daily. *Id*. at 5:43–45; 5:59–63. The specification teaches that this 40 milligram per day dose provides the maximum non-antibiotic (i.e., sub-antibiotic) dose of

doxycycline based on steady-state pharmacokinetics. *Id*. at 5:49–52. In terms of serum concentration, doxycycline may also be administered in an amount which results in a serum concentration between about 0.1 and 0.8 μg/ml. *Id.* at 6:29–32.

Example 38 of the '506 patent discloses that in a six-month, placebo-controlled trial for the treatment of acne[4] using 20 mg doxycycline hyclate, twice daily, doxycycline-treated patients showed a statistically significant reduction in both comedones and inflammatory lesions (defined as "papules and pustules, less than or equal to 5 nodules") as compared to placebo. *Id.* at 19:54–55; 20:24–32. The six-month doxycycline treatment "resulted in no reduction of skin microflora . . . nor an increase in resistance counts when compared with placebo." *Id.* at 20:33–37; *see id.* at 5:64–6:4.

c. Representative Claim

Claim 1 of the '506 patent recites:

> 1. A method for treating papules and pustules of rosacea in a human in need thereof, the method comprising
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> administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof, in an amount that
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> (i) is effective to treat the papules and pustules of rosacea;
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> (ii) is 10–80% of a 50 mg dose of doxycycline per day; and
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> (iii) results in no reduction of skin microflora during a six-month treatment, without administering a bisphosphonate compound.

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[4] Petitioner asserts that Example 38 is directed to treating common acne (acne vulgaris), presumably based on inclusion criteria requiring the presence of comedones, non-inflammatory lesions which are not a symptom of rosacea. *See* Pet. 9, 23, 25; Ex. 1001, 1:20, 19:54; Ex. 1004 ¶ 13. Patent Owner does not dispute this characterization. *See* Prelim. Resp. 21.

The remaining asserted claims recite "an amount [of doxycycline] which provides a serum concentration in the range of about 0.1 to about 0.8 μg/ml" (claims 7, 14, and 20), "40–80% of a 50 mg dose of doxycycline per day" (claim 8), and "doxycycline, or a pharmaceutically acceptable salt thereof, in an amount of 40 mg per day" (claim 15).

d. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability.

Claims challenged	Basis	Reference
1, 7, 8, 14, 15, and 20	§ 103	Bikowski[5] PERIOSTAT[6] Golub[7]
1, 7, 8, 14, 15, and 20	§ 103	Bikowski PERIOSTAT

ANALYSIS

a. *Claim Construction*

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1278–81 (Fed. Cir. 2015), *cert. granted sub nom., Cuozzo Speed Techs., LLC v. Lee*, No. 15–446, 2016 WL 205946 (U.S. Jan. 15, 2016). Under that standard, and absent any

[5] Bikowski, *Treatment of Rosacea with Doxycycline Monohydrate*, 66(2) CUTIS 149 (2000). Ex. 1011.
[6] PERIOSTAT™, PHYSICIANS' DESK REFERENCE (54th ed. 2000). Ex. 1042.
[7] Golub et al., *Low-dose doxycycline therapy: Effect on gingival and crevicular fluid collagenase activity in humans*, 25 J. PERIODONT. RES. 321 (1990). Ex. 1048.

special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention,[8] in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). And

> [a]lthough an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity, deliberateness, and precision. 'Where an inventor chooses to be his own lexicographer and to give terms uncommon meanings, he must set out his uncommon definition in some manner within the patent disclosure' so as to give one of ordinary skill in the art notice of the change."

In re Paulsen, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (citation omitted). "In such cases, the inventor's lexicography governs." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc). Only terms which are in controversy need to be construed, however, and then only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). For this reason, we provide express constructions for only the following terms.

i. Rosacea

The parties agree that the '506 patent identifies rosacea ("acne rosacea") as a form of acne. Pet. 12, 22; Prelim. Resp. 9. Although Petitioner's expert contends that "a dermatologist of ordinary skill in the art would not lump things like acne vulgaris and rosacea together" (Ex. 1004 ¶¶

[8] Patent Owner provisionally adopts, as do we, Petitioner's definition of a person of ordinary skill in the art as "a licensed and practicing dermatologist with as little as one year of treating patients in a hospital, clinical, and/or private setting." Prelim. Resp. 7; Pet. 25 (both quoting Ex. 1004 ¶ 11).

13) we, nevertheless apply the inventor's clearly expressed definition that "acne include[s] . . . acne rosacea" (Ex. 1001 4:31–41). With respect to the symptoms of rosacea, however, neither party contends that uncommon meanings apply. Pet. 30–31; Prelim. Resp. 8–10. We therefore construe rosacea as a form of acne having symptoms including papules, pustules, erythema, and telangiectasia, where the predominant lesions are papules and pustules. *See* Ex. 1001, 4:23–43; Ex. 1004, ¶¶ 7, 19 ("'The predominant lesions [in rosacea] are papules and pustules.' ([Ex. 1056] at 680; *see also* Exh. 1046, at 852, 958; Exh. 1047, at 1023, 1175.)."

ii. Papules and pustules

The '506 patent does not define the terms "papules" and "pustules" as other than as "[i]nflammatory lesions" or blemishes of the skin. *See* Ex. 1001, 3:17–19, 4:24–27, 19:54–55. Petitioner does not expressly suggest a meaning for these terms but points to its expert's statement 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,'" whereas, "'[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 . . . .'" Pet. 23; Ex 1004 ¶ 19 (both quoting Ex. 1056, 27, 31) (italics removed). Petitioner contends that "[t]hese definitions align well with those provided by applicant during prosecution." Pet. 23 (citing Ex. 1070, 6). We, nevertheless, note that, unlike the disclosure of the '506 patent, the definition of "pustule" quoted by Petitioner's expert is not clearly defined as a lesion of the skin.

Patent Owner contends that the terms should be accorded their plain and ordinary meanings; objects to the definitions provided by Petitioner's

expert as unnecessarily limiting; and points, instead, to the definitions set forth in the prosecution leading to the issuance of the '506 patent. Prelim. Resp. 10–11 (citing Ex. 1070, 6).[9]

In view of the above, and applying the broadest reasonable definition consistent with the specification, we interpret "papules and pustules" as inflammatory lesions or blemishes of the skin, where "papules" are solid, rounded bumps rising from the skin that are each usually less than one centimeter in diameter, and "pustules" are small, inflamed, pus-filled, blister-like lesions of the dermis or epidermis.

iii. "Administering . . . [a] dose of doxycycline per day"

The parties do not expressly address the meaning "[a]dministering . . . [a] dose of doxycycline per day." The plain language of the independent claims, however, requires that the administered dose "results in no reduction of skin microflora during a six-month treatment." Consistent with the claim language, Example 38 of the Specification discloses the administration of a daily dose of doxycycline (20 mg, twice daily) for six months. Ex. 1001, 19:37–20:37. Taken in context, we construe "[a]dministering . . . [a] dose of doxycycline per day" as requiring administering a dose of doxycycline *each day*.

b. *Principles of Law*

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was

[9] U.S. Serial No. 13/277,789, Response to Office Action, dated May 14, 2012.

made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

A prima facie case of obviousness is established when the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. *In re Rinehart*, 531 F.2d 1048, 1051 (CCPA 1976). The level of ordinary skill in the art is reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

c. *The Asserted References*

We begin our discussion with a brief summary of the references asserted under grounds 1 and 2.

i. Bikowski

Bikowski, published in 2000,[10] states that "[a]lthough the exact etiology is unknown, rosacea is thought by most experts to be an

[10] The '506 patent issued from a chain of continuation and divisional applications first filed on April 5, 2002, and further claims the benefit of provisional applications including No. 60/325,489, filed April 5, 2001. Ex. 1001, 1:5–16. Although Patent Owner reserves the right to demonstrate

inflammatory process incited by vascular instability with subsequent leakage of fluid and inflammatory mediators." Ex. 1011, 149 (emphasis omitted). Bikowski teaches that oral antibiotics are a well-established treatment of rosacea, referencing Sneddon [Ex. 1006] for the use of 250 milligram doses of tetracycline, twice daily (*id*. at 1011, 149, 151), and noting that second generation tetracyclines such as doxycycline "have increased bioavailability, improved absorption when taken with food, and broader antibacterial activity" (*id*. at 151).

Bikowski teaches that "[t]he clinician's goal is to achieve rapid remission with the oral agent and to maintain remission with [a] topical medication if at all possible. . . . intermittent low-dose systemic antibiotics in addition to daily topical treatment may be necessary to maintain complete remission in the majority of patients." *Id*.

Bikowski presents case studies of two rosacea patients treated with oral doxycycline monohydrate, but not topical medications. *See id*. at 150. Patient 1 was treated with 100 milligrams of doxycycline per day for six months. *Id*. Patient 2 also elected "systemic antibiotic therapy" and was treated for two months with 50 milligrams per day, at which time "she was essentially clear" and the oral doxycycline "was decreased to 50 mg every other day for long-term maintenance therapy." *Id*.

ii. Golub

Golub, published in 1990, teaches that "[t]etracyclines are often advocated as useful adjuncts in periodontal therapy based on their

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entitlement to benefit of this earlier priority date and an invention date prior to the publication of Bikowski (Prelim. Resp. 38), we need not address that issue at this time.

effectiveness against periodontopathogens; an additional advantage is their unique ability, among antibiotics, to be highly concentrated within the fluid of the periodontal pocket." Ex. 1048, 325 (internal citations omitted). Golub further teaches that "[c]ollagen breakdown is an essential pathway in the pathogenesis of periodontal and other diseases," and posits that "tetracycline . . . can inhibit mammalian collagenases and collagen breakdown by a mechanism *independent* of the antimicrobial efficacy of these drugs." *Id*. at 321–22.

Golub states that,

> [i]n several studies on humans, routinely prescribed, antimicrobially-effective doses of tetracyclines . . . were found to reduce the collagenase activity in the fluid of the periodontal pocket which originates from the adjacent host tissues. 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[,] which would effectively inhibit collagenase activity in the *gingival tissue* as well as in the crevicular fluid.

Id. at 322 (internal citations omitted).

Golub presents the results of two studies of patients with periodontal disease. In the first study, patients administered 30 mg doxycycline, twice daily, for two weeks as an adjunct to periodontal pre-treatment and surgery, showed a statistically significant reduction in gingival collagenase activity, but not gingival pocket depth, or the severity of gingival inflammation. *Id*. at Table 1, 322, 324, 328 ("[I]n study no. 1, in which a more complex clinical protocol was followed to obtain excised gingival specimens, the severity of inflammation in the gingival tissues did not appear to be reduced by the low-dose doxycycline therapy, even though collagenase activity in these tissues was suppressed."); *see also id.* at Fig. 4 (equating gingival

index (G.I.) to inflammation). In the second study, patients administered 20 mg doxycycline, twice daily, for two weeks with no additional treatment or surgery, showed significant reductions in the collagenase activity of their gingival crevicular fluids, and in the severity of gingival inflammation. *Id*. at 323, 324-325, Table I, Abstract.

Golub also states that novel properties of tetracycline drugs

> help explain their clinical effectiveness and may also expand their future applications *beyond* their current use as antimicrobials. As one example, tetracyclines now appear to possess anti-inflammatory properties when administered to patients with certain skin diseases [ ] such as rosacea[,] . . . which are *not* believed to have a microbial etiology.

Id. at 325 (citations omitted). Golub posits that the mechanisms underlying the non-antimicrobial properties of tetracyclines may include the inhibition of prostaglandin production, superoxide radical scavenging, and the inhibition of mammalian collagenase and other metalloproteinase activities. *Id*.

iii. PERIOSTAT

Published in 2000, PERIOSTAT is a Physician's Desk Reference entry describing Periostat® as "a 20 mg capsule formulation of doxycycline hyclate for oral administration." Ex. 1042, 944. Under "Dosage and Administration," the reference states that, "Periostat 20 mg twice daily as an adjunct following scaling and root planning may be administered for up to 9 months." *Id*. at 946. "After oral administration . . . . Doxycycline is eliminated with a half-life of approximately 18 hours by renal and fecal excretion of unchanged drug." *Id*. at 945. The reference further states that "[t]he dosage of doxycycline achieved with this product during administration is well below the concentration required to inhibit

microorganisms commonly associated with adult periodontitis." *Id*.

d. *Obviousness Grounds*

Petitioner asserts that claims 1, 7, 8, 14, 15, and 20 would have been obvious over the combination of Bikowski, Golub, and PERIOSTAT. Pet. 24–41. To summarize, Petitioner argues that it would have been obvious to reduce the daily dose of doxycycline taught by Bikowski for the treatment of the papules and pustules of rosacea from 50 milligrams, to the 40 milligram daily dose taught by Golub and PERIOSTAT for the treatment of periodontal disease because (1) rosacea and periodontitis were both non-bacterial, inflammatory conditions treatable with doxycycline, and (2) "[a]nti-inflammatory doses of doxycycline were reasonably expected to be lower than those needed for traditional antibiotic treatment." *See* e.g., Pet. 5, 30, 32. Thus,

> 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)

Id. at 32.

Petitioner's arguments that claims 1, 7, 8, 14, 15, and 20 would have been obvious over the combination of Bikowski and PERIOSTAT are similar to those based on the combination of Bikowski, Golub, and PERIOSTAT. *See* Pet. 41–56. According to Petitioner:

> 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.

Pet. 5–6.

In particular, Petitioner argues that Bikowski evidences a trend toward lower doses of doxycycline to treat the papules and pustules of rosacea (*id*. at 45); expressly relies on Bikowski's use of 50 milligram dosing every other day for long-term maintenance therapy (*id*. at 53); and suggests that dermatologists were using PERIOSTAT off label for the treatment of skin diseases prior to the filing date of the '506 patent (*id*. at 9, 48–49).

Both of Petitioner's grounds are premised on the idea that rosacea is not only an inflammatory condition, but also that it was known to be "not bacterial," such that one of ordinary skill in the art would have understood that "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." *See* Pet. 7, 42, 46. Considering the evidence of record, we do not find adequate support for that position. Indeed, Bikowski itself emphasizes that the exact etiology of rosacea is unknown, and thus, does not foreclose the possibility that the underlying cause of the inflammation is bacterial. Ex. 1011, 159. To the contrary, Bikowski, expressly describes the 50 milligram per day treatment of Patient 2 as "systemic antibiotic therapy" and emphasizes the "broader antibacterial activity" of doxycyclines as compared to tetracycline. *Id*. at 150, 151.

As set forth on pages 14–18 of Patent Owner's Preliminary Response, the record before us further illustrates that not only were the underlying causes of rosacea unknown as of the filing date of the '506 patent, but that the suspected underlying causes included bacterial infection. *See e.g.*, Ex. 1010, 945, 946 (stating that the "[t]he etiology and pathogenesis of rosacea are still unknown," and suggesting a relationship between rosacea and *Helicobacter pylori* infection); Ex. 1034, 144 (stating that "[t]he exact etiology of rosacea is unknown and theories abound," including potential roles for gastrointestinal disturbances, *Helicobacter pylori infection,* and hypersenstitivity to *D. folliculorum* mites); Ex. 2008, 777 (stating that "[*R*]*osacea* is a common condition of unknown etiology," and reporting that the eradication of *Helicobacter pylori* infection with antibiotics "leads to a dramatic improvement in the symptoms of *rosacea*."). In addition, art cited by Patent Owner shows that the etiology of rosacea was still not "known" to be "not bacterial" even after the filing date of the '506 patent. *See* Pet. 16–17 (citing Ex. 2010, 479, 480; Ex. 2011, 24; Ex. 2012, 87).

Based on the evidence of record, Petitioner has not demonstrated that one of ordinary skill in the art understood that the underlying cause of the papules and pustules of rosacea was "not bacterial." Accordingly, we are not persuaded that one of ordinary skill in the art would have, with a reasonable expectation of success, found it obvious to replace Bikowski's antimicrobial 50 milligram daily dose with the sub-microbial, 40 milligram dose taught by Golub and/or PERIOSTAT.

Implicit in Petitioner's argument is that one of ordinary skill in the art would have understood that the inflammation associated with the papules and pustules of rosacea shared a common pathway with that seen in

periodontal disease. *See e.g.*, Pet. 8, 31 (citing Ex. 1004 ¶¶ 38, 39; Ex. 1048, 325–26). Petitioner's support for this position ultimately rests on Golub's limited disclosure relating to rosacea, which we do not find persuasive as it provides no details regarding the mechanisms of inflammation associated with this disease. *See* Ex. 1004 ¶¶ 38, 39; Ex. 1048, 325–26; Prelim. Resp. 18–19.

Patent Owner argues that Petitioner has failed to establish a motivation to combine the cited prior art with a reasonable expectation of success because Bikowski is directed to the treatment of rosacea of the skin, whereas Golub and PERIOSTAT are directed to the treatment periodontitis, a disease of the gums. Prelim. Resp. 24–26. We agree. Bikowski relates to a different medical specialty, describes treating a different ailment, and focus on different organ of the body as compared to Golub and PERIOSTAT. *See id*. Petitioner fails to adequately address these differences and thus fails to persuade us that one of ordinary skill in the art would have, with a reasonable expectation of success, expected that the 40 milligram daily doses of doxycycline used to treat periodontitis would have been efficacious in the treatment of rosacea.

As Patent Owner points out, a similar argument was considered by the Examiner during prosecution of the application that ultimately issued as the '506 patent. Prelim. Resp. 28–29; *see* Pet. 14–19. In particular, Applicant argued that there was no reason to combine the Perricone[11] reference, teaching the treatment of facial acne with, inter alia, an antibiotic dose of

[11] Perricone et al., U.S. 6,365,623 B1, issued April 2, 2002.

tetracycline, with the Plugfelder reference,[12] disclosing the use of sub-antimicrobial doses for the treatment of an eye disease (Meibomian gland disease or "MGD") *associated* with rosacea. Ex. 1070, 7–12; Ex. 1072.[13] In an Examiner's interview, Applicant argued that there is no reason to combine the two references because "treating Meibomian gland disease and rosacea are not related." Ex. 1071, 16. Invited to respond in writing, Applicant elaborated that, "success in treating eye disease with a sub-antibiotic treatment is not relevant to treating a skin disease with an antibiotic treatment. Medical science is much too unpredictable to make such a connection." *Id*. at 8; *see id.* at 16; *see also* Ex. 1070, 8 ("There would be no reason for a skilled artisan to believe that a treatment that is effective to treat an ocular disorder would treat a skin condition. Medicine is too unpredictable for such a conjecture.").

Similar reasoning applies in the present case. Even were we persuaded that one of ordinary skill in the art would have recognized that the inflammation associated with the papules and pustules of rosacea shared a common pathway with that associated with periodontal disease, Petitioner does not persuade us that a skilled artisan would have reasonably expected that the sub-microbial dose of doxycycline taught by Golub and PERIOSTAT for the treatment of a gum disease would be effective in treating a disease of the skin.

Underscoring the unpredictability and lack of reasonable expectation of success of applying Golub and PERIOSTAT to a different disease and

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[12] Pflugfelder et al., U.S. 6,455,583 B1, issued Sept. 24, 2002.
[13] U.S. Serial No. 13/277,789, Declaration under 37 C.F.R. § 1.132 [of Vasant Manna], dated Feb. 22, 2013.

tissue type, we note that Golub's study number one, a "more complex clinical protocol" involving 60 milligrams of doxycycline per day, showed suppressed collagen activity but did not significantly reduce inflammation. *See* Ex. 1048, 328. This suggests that the benefits of doxycycline in Golub's work may depend on the condition of the gum tissue treated, i.e., the disease state, and thus underscores the unpredictability of applying Golub's teachings to a different disease in a different tissue type.

The disparate results of Golub's two studies treating the same tissue type also undercut Petitioner's reliance on the claim that doxycycline was known to have "at least some anti-inflammatory activity at almost any dose." Pet. 47 (citing Ex. 1004 ¶ 42). This statement is supported by reference to *in vitro* studies using isolated immune cells and, as Petitioner's expert makes clear, "does not mean that one would expect virtually any dose to be clinically effective." *See* Ex. 1004 ¶ 42 (citing Ex. 1031,[14] 312; Ex. 1032,[15] 178–79). Moreover, with respect to the treatment of rosacea, neither Golub's studies on periodontal disease, nor Petitioner's expert's reliance on *in vitro* data, persuades us that "[a]nti-inflammatory doses of doxycycline were reasonably expected to be lower than those needed for traditional antibiotic treatment," as Petitioner contends. *See* Pet. 32.

With respect to Petitioner's argument that Bikowski marks a "trend" to using lower dose doxycycline in the treatment of the papules and pustules of rosacea, we note that Petitioner omits any citation to its own expert for

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[14] Naess et al., *In vivo and in vitro effects of doxycycline on leucocyte membrane receptors*, 62 CLIN. EXP. IMMUNOL. 310 (1985).
[15] Akamatsu et al., *Effect of Doxycycline on the Generation of Reactive Oxygen Species*, 72 ACTA DERM VENEREOL 178 (1992).

this proposition, but merely points to one of two case studies in a single article. *See id*. at 45, 49. One data point does not make a trend; we find this argument unpersuasive for the reasons set forth at pages 42–44 of Patent Owner's Preliminary Response.

Petitioner argues that "[i]t would have been even more obvious" to reduce the 50 milligram daily dose of doxycycline taught in Bikowski "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 consider[ation that] doxycycline's half-life is 18 hours, would be less than half of the initial dose given by the end of one day." Pet. 9–10 (citing Ex. 1004 ¶ 32); *see id*. at 6–7, 43, 44, 47–48, 53. Petitioner does not adequately support this position.

The challenged independent claims require administering a defined "dose" of doxycycline "per day." Bikowski discloses a maintenance protocol in which a patient is administered a 50 milligram dose per day, alternating with days in which no drug is administered. Ex. 1011, 150. Accordingly, when a dose is administered under Bikowski's protocol, the "dose" is always 50 milligrams "per day," which, as set forth in the specification, is an antibiotic dose. *See* Ex. 1001, 5:43–45. Alternatively, focusing on our construction of the claim language "[a]dministering . . . [a] dose of doxycycline per day," as requiring the administration doxycycline each day, we find that Bikowski's maintenance protocol does not encompass the "per day" dosing limitation.

Instead of focusing on the required "dose of doxycycline per day," as recited by the claim, Petitioner focuses on the trough blood levels expected at the end of a non-dose day. In doing so, Petitioner fails to address the

effects of peak blood levels. *See e.g.*, Pet. 9–10 (citing Ex. 1004 ¶ 32). Accordingly, Petitioner does not address the understanding of one of ordinary skill in the art with respect to whether the therapeutic effects of doxycycline are responsive to peak drug levels, and, if so, how often they must occur to maintain efficacy.

Petitioner also does not address the understanding of one of ordinary skill in the art with respect to the antibiotic effects of peak drug levels on skin microflora. The asserted independent claims expressly require that the administered amount of doxycycline "results in no reduction of skin microflora during a six-month treatment." Nowhere has Petitioner even alleged that one of ordinary skill in the art would have considered whether Bikowski's alternative-day protocol of 50 milligram daily doses of doxycycline would provide, or make obvious, this claim limitation.

Petitioner points to PERIOSTAT as evidence that one of ordinary skill in the art had ready access to "an FDA-approved low dose doxycycline product," which they were free to prescribe "off label" "for any use." *See* Pet. 8–9, 48, 49; Ex. 1004 ¶ 27. Relying on Kapes,[16] however, Petitioner further contends that "there is evidence that, before the '506 patent, dermatologists were already using PERIOSTAT 'off label.'" Pet. 9; *see id.* at 49. Petitioner's contention is not supported by the evidence. First, Petitioner admits that Kapes is not prior art for purposes of this proceeding. Pet. 9 n.3. Accordingly, we accord it little weight in our analysis. In addition, to the extent Petitioner seeks to rely on alleged off-label use, such

[16] Kapes, *Doxycycline hyclate reduces comedones by 50 percent*, Supp. 22 DERMATOLOGY TIMES S19 (2001). Ex. 1015.

evidence is not of record, and indeed, is unavailable in this proceeding as it is not a prior art "patent or printed publication." *See* 35 U.S.C. § 311(b).

CONCLUSION

For the foregoing reasons, the information presented in the Petition and accompanying evidence do not establish a reasonable likelihood that Petitioner would prevail in showing the unpatentability of claims 1, 7, 8, 14, 15, and 20 of the '506 patent.

ORDER

Accordingly, it is

ORDERED that Petitioner's request for an *inter partes* review of claims 1, 7, 8, 14, 15, and 20 of the '506 patent is *denied*.

PETITIONER:

William L. Mentlik
Michael H. Teschner
Brian R. Tomkins
Maegan A. Fuller
LITTENBERG, KRUMHOLZ & MENTLIK, LLP
WMentlik.ipr@ldlkm.com
MTeschner.ipr@ldlkm.com
BTomkins.ipr@ldlkm.com
MFuller.ipr@ldlkm.com

PATENT OWNER:

Stephen Maebius
Sujnit Talapatra
Michael Houston
FOLEY & LARDNER LLP
smaebius@foley.com
stalapatra@foley.com
mhouston@foley.com

Gerald Flattmann
PAUL HASTINGS LLP
geraldflattmann@paulhastings.com

Trials@uspto.gov
Tel: 571-272-7822

Paper 12
Entered: February 16, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

GALDERMA LABORATORIES, INC.,
Patent Owner.

Case IPR2015-01777
Patent 8,603,506 B2

Before ERICA A. FRANKLIN, ZHENYU YANG, and
ROBERT A. POLLOCK, *Administrative Patent Judges.*

POLLOCK, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

INTRODUCTION

Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (collectively, "Petitioner") filed a Petition (Paper 1; "Pet.") to institute an *inter partes* review of claims 1, 7, 8, 14, 15, and 20 of US 8,603,506 B2 (Ex. 1001; "the '506 patent"). Galderma Laboratories Inc. ("Patent Owner")[1] filed a Patent Owner Preliminary Response. Paper 9 ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314.

For the reasons provided below, we determine Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim of the '506 patent. *See* 35 U.S.C. § 314(a). We, therefore, deny the Petition for an *inter partes* review.

a. *Related Proceedings*

Petitioner indicates that the '506 patent has been asserted in the United States District Court for the District of Delaware (Civil Action No. 15-670). Pet. 2; Paper 6, 2.

In addition to the case before us, Petitioner has requested *inter partes* review of claims 1, 7, 8, 14, 15, and 20 of US 8,603,506 B2 on other grounds in Case Nos. IPR2015-01778 and IPR2015-01782.

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[1] Petitioner further indicates that the Complaint in Civil Action No. 15-670 states that Nestlé Skin Health S.A. is now the owner of the '506 patent. Pet. 2 n.1. Although Patent Owner does not directly address this assertion in the Preliminary Response, the USPTO Assignment Database indicates that patent is assigned to Galderma Laboratories, Inc. Absent additional information, we refer to Galderma Laboratories, Inc. as the Patent Owner.

b. *The '506 Patent*

The '506 patent is directed to the treatment of "all known types of acne," broadly defined as "a disorder of the skin characterized by papules, pustules, cysts, nodules, comedones, and other blemishes or skin lesions." Ex. 1001, 4:23–32. The genus "acne" is expressly defined as encompassing acne rosacea ("rosacea"),[2] a skin disorder "characterized by inflammatory lesions (erythema) and permanent dilation of blood vessels (telangectasia)." *Id*. at 4:31–43. The specification further states the "[t]he present invention is particularly effective in treating comedones." *Id.* at 4:23–43.[3]

By way of background, the '506 patent discloses that the efficacy of systemically-administered tetracycline compounds in the treatment of acne is commonly believed to be due, "in significant part, to the direct inhibitory effect of the antibiotics on the growth and metabolism of [] microorganisms" that "release microbial mediators of inflammation into the dermis or trigger the release of cytokines from ductal keratinocytes." Ex. 1001, 1:42–50. In addition to these antibiotic effects, the specification also notes that tetracyclines may have therapeutic anti-inflammatory effects due to, for example, the "inhibition of neutrophil chemotaxis induced by bacterial chemotactic factors," the "inhibition of [polymorphonuclear leukocyte] derived collagenase, and by scavenging reactive oxidative species produced by resident inflammatory cells." *Id.* at 2:21–32, 3:14–25.

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[2] The parties agree that the term "acne rosacea" in the specification refers to rosacea. Pet. 30–31; Prelim. Resp. 15–16.

[3] Petitioner asserts, and Patent Owner does not contest, that comedones are not a feature of rosacea. Pet. 9, 25; *see* Prelim. Resp. 23–24; Ex. 1004 ¶ 13.

The ’506 patent teaches that although tetracyclines are administered in conventional antibiotic therapy, antibiotic doses of these compounds can result in undesirable side effects such as the reduction or elimination of healthy microbial flora and the production of antibiotic resistant microorganisms. *Id*. at 3:7–17, 3:31–36. To address the need for effective treatments that minimize these side effects, the ’506 patent discloses that “all known types of acne” may be treated by administering a tetracycline compound in an amount having “substantially no antibiotic activity (i.e. substantially no antimicrobial activity)” and, thus, “does not significantly prevent the growth of . . . bacteria.” *Id*. at 3:37–50; 4:31–32; 5:31–35. The ’506 patent defines “effective treatment” as “a reduction or inhibition of the blemishes and lesions associated with acne” (*id.* 5:31–33), which may be achieved by administering non-antibiotic tetracycline compounds (i.e., those lacking substantial antibiotic activity) or by using sub-antibiotic doses of tetracycline compounds having known antibiotic effects (*see, e.g., id*. at 3:26–29, 4:58–61, 5:1–9, 5:35–42). With respect to the latter, the specification indicates that a sub-antibiotic dose may comprise “10–80% of the antibiotic dose,” or “an amount that results in a serum tetracycline concentration which is 10–80% of the minimum antibiotic concentration.” *Id.* at 5:36–42; 6:7–12.

The specification teaches that, whereas exemplary *antibiotic* doses of tetracycline compounds include 50, 75, and 100 milligrams per day of doxycycline, in an especially preferred embodiment, doxycycline (as doxycycline hyclate) is administered as a 20 milligram dose, twice daily, i.e., 40 milligrams per day. *Id*. at 5:43–45; 5:59–63. The specification teaches that this 40 milligram daily dose provides the maximum non-

antibiotic (i.e., sub-antibiotic) of doxycycline based on steady-state pharmacokinetics. *Id*. at 5:49–52. In terms of serum concentration, doxycycline may also be administered in an amount that results in a serum concentration between about 0.1 and 0.8 μg/ml. *Id.* at 6:29–32.

Example 38 of the '506 patent discloses that in a six-month, placebo-controlled trial for the treatment of acne[4] using 20 mg doxycycline hyclate, twice daily, doxycycline-treated patients showed a statistically significant reduction in both comedones and inflammatory lesions (defined as "papules and pustules, less than or equal to 5 nodules") as compared to placebo. *Id.* at 19:54–55; 20:24–32. The six-month doxycycline treatment "resulted in no reduction in skin microflora . . . nor an increase in resistance counts when compared with placebo." *Id.* at 20:33–37; *see id.* at 5:64–6:4.

c. *Representative Claim*

Claim 1 of the '506 patent recites:

> 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

[4] Petitioner asserts that Example 38 is directed to treating common acne (acne vulgaris), presumably based on inclusion criteria requiring the presence of comedones, non-inflammatory lesions which are not a symptom of rosacea. *See* Pet. 9, 23, 25; Ex. 1001, 1:20, 19:54; Ex. 1004 ¶ 13. Patent Owner does not dispute this characterization. *See* Prelim. Resp. 21.

(iii) results in no reduction of skin microflora during a six-month treatment, without administering a bisphosphonate compound.

The remaining asserted claims recite "an amount [of doxycycline] which provides a serum concentration in the range of about 0.1 to about 0.8 μg/ml" (claims 7, 14, and 20), "40–80% of a 50 mg dose of doxycycline per day" (claim 8), and "doxycycline, or a pharmaceutically acceptable salt thereof, in an amount of 40 mg per day" (claim 15).

d. *Asserted Grounds of Unpatentability*

Petitioner asserts the following grounds of unpatentability.

Claims challenged	Basis	Reference
1, 7, 8, 14, 15, and 20	§ 103	Sneddon[5] Golub[6] Torresani[7] PERIOSTAT[8]
1, 8, 15	§ 103	Golub Torresani Jansen[9]
7, 14, and 20	§ 103	Golub Torresani Jansen PERIOSTAT

[5] Sneddon, *A Clinical Trial of Tetracycline in Rosacea*, 78 BRIT. J. DERMATOL. 649 (1966). Ex. 1006.
[6] Golub et al., *Low-dose doxycycline therapy: Effect on gingival and crevicular fluid collagenase activity in humans*, 25 J. PERIODONT. RES. 321 (1990). Ex. 1048.
[7] Torresani et al., *Clarithromycin versus doxycycline in the treatment of rosacea*, 36 INT'L. J. DERMATOL. 938 (1997). Ex. 1010.
[8] PERIOSTAT™, PHYSICIANS' DESK REFERENCE (54th ed. 2000). Ex. 1042.
[9] Jansen and Plewig, *Rosacea: classification and treatment*, 90 J. R. SOC. MED. 144 (1997). Ex. 1034.

ANALYSIS

As an initial matter, we note that Patent Owner asserts that the Board should exercise its discretion and deny institution of this Petition as duplicative of grounds raised in IPR2015-01782. Prelim. Resp. 52–58. While we have considered Patent Owner's position, we decline to do so.

a. *Claim Construction*

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1275–79 (Fed. Cir. 2015), *cert. granted sub nom., Cuozzo Speed Techs., LLC v. Lee*, No. 15–446, 2016 WL 205946 (U.S. Jan. 15, 2016).

Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention,[10] in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). And "[a]lthough an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity, deliberateness, and precision. 'Where an inventor chooses to be his own lexicographer and to give terms uncommon meanings, he must set out his uncommon definition in some manner within the patent disclosure' so as to give one of ordinary skill in the art notice of the change."

[10] Patent Owner provisionally adopts, as do we, Petitioner's definition of a person of ordinary skill in the art as "a licensed and practicing dermatologist with as little as one year of treating patients in a hospital, clinical, and/or private setting." Prelim. Resp. 25; Pet. 36 (both quoting Ex. 1004 ¶ 11).

In re Paulsen, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (citation omitted). "In such cases, the inventor's lexicography governs." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc). Only terms which are in controversy need to be construed, however, and then only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). For this reason, we provide express constructions for only the following terms.

i. Rosacea

The parties agree that the '506 patent identifies rosacea ("acne rosacea") as a form of acne. Pet. 30–31; Prelim. Resp. 7. Although Petitioner contends that one of ordinary skill in the art would not classify rosacea as a form of acne (Pet. 22; Ex. 1004 ¶¶ 12, 13), we apply the inventor's clearly expressed definition that "acne include[s] . . . acne rosacea" (Ex. 1001 4:31–41) . With respect to the symptoms of rosacea, however, neither party contends that uncommon meanings apply. Pet. 30–31; Prelim. Resp. 6–8. We therefore construe rosacea as a form of acne having symptoms including papules, pustules, erythema, and telangiectasia, where the predominant lesions are papules and pustules. *See* Ex. 1001, 4:23–43; Ex. 1004, ¶¶ 7, 19 ("'The predominant lesions [in rosacea] are papules and pustules.' ([Ex. 1056] at 680; *see also* Exh. 1046, at 852, 958; Exh. 1047, at 1023, 1175.)."

ii. Papules and Pustules

The '506 patent does not define the terms "papules" and "pustules" as other than as "[i]nflammatory lesions" or blemishes of the skin. *See* Ex. 1001, 3:17–19, 4:24–27, 19:54–55. Petitioner does not expressly suggest a meaning for these terms but points to its expert's statement 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,'" whereas, "'[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 . . . .'" Pet. 23; Ex 1004 ¶ 19 (both quoting Ex. 1056, 27, 31). Petitioner contends that "[t]hese definitions align well with those provided by applicant during prosecution." Pet. 23 (citing Ex. 1070, 6).[11] We, nevertheless, note that, unlike the disclosure of the '506 patent, the definition of "pustule" quoted by Petitioner's expert is not clearly defined as a lesion of the skin.

Patent Owner contends that the terms should be accorded their plain and ordinary meanings; objects to the definitions provided by Petitioner's expert as unnecessarily limiting; and points, instead, to the definitions set forth in the prosecution leading to the issuance of the '506 patent. Pet. at 10–11 (citing Ex. 1070, 6).

In view of the above, and applying the broadest reasonable definition consistent with the specification, we interpret "papules and pustules" as inflammatory lesions or blemishes of the skin, where "papules" are solid, rounded bumps rising from the skin that are each usually less than 1 centimeter in diameter, and "pustules" are small, inflamed, pus-filled, blister-like lesions of the dermis or epidermis.

[11] U.S. Serial No. 13/277,789, Response to Office Action, dated May 14, 2012.

b. *Principles of Law*

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).
The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

A prima facie case of obviousness is established when the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. *In re Rinehart*, 531 F.2d 1048, 1051 (CCPA 1976). The level of ordinary skill in the art is reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

c. *The Asserted References*

We begin our discussion with a brief summary of the references asserted.

i. Sneddon

Sneddon, published in 1966, demonstrates the efficacy of tetracycline (250mg, twice daily) in the treatment of rosacea. Ex. 1006. Sneddon states

that there are "diametrically opposed views" on the underlying cause of rosacea including emotional distress, gastric or intestinal disturbances, and demodex skin mites. *Id*. at 649. Consistent with this lack of understanding regarding the etiology of rosacea, Sneddon states that "[t]he mechanism of [tetracycline's] beneficial action is as yet unknown, but the observation that it controls not only postulation but erythema suggests that it is not entirely an antibacterial or antidemodectic effect. Has it some action on intestinal absorption?" *Id*. at 652.

ii. Torresani

Torresani reports on a comparison between oral doxycycline (100 mg/twice daily for 4 weeks followed by 100 mg/once daily for 4 weeks) and clarithromycin (250 mg/twice daily for 4 weeks followed by 250 mg/once daily for 4 weeks). Ex. 1010, 942, Ex. 1004 ¶ 31. Although finding the clarithromycin regimen potentially more promising, Torresani showed that the doxycycline treatment improved the symptoms of rosacea including the number of papules and pustules. Ex. 1010, 944, 945, Figs. 3 and 4; Ex. 1004 ¶ 31.

Torresani, published in 1997, states that "[t]he etiology and pathogenesis of rosacea are still unknown," but that "[t]he therapeutic efficacy of tetracyclines seems to be related to their anti-inflammatory efficacy." Ex. 1010, 945 (citing reference 6: Martin et al., *Effect of tetracycline on leukotaxis*, 129 J. Infect. Dis. 110 (1974). Torresani also notes that an etiologic relationship between rosacea and *Helicobacter pylori* infections has been suggested based on correlations between that bacterial infection and rosacea. *Id*. at 946.

iii. Golub

Golub, published in 1990, teaches that "[t]etracyclines are often advocated as useful adjuncts in periodontal therapy based on their effectiveness against periodontopathogens; an additional advantage is their unique ability, among antibiotics, to be highly concentrated within the fluid of the periodontal pocket." Ex. 1048, 325. Golub further teaches that "[c]ollagen breakdown is an essential pathway in the pathogenesis of periodontal and other diseases," and posits that "tetracycline . . . can inhibit mammalian collagenases and collagen breakdown by a mechanism *independent* of the antimicrobial efficacy of these drugs." *Id*. at 321–22.

Golub states that,

> [i]n several studies on humans, routinely prescribed, antimicrobially-effective doses of tetracyclines . . . were found to reduce the collagenase activity in the fluid of the periodontal pocket which originates from the adjacent host tissues. The current study was carried out to determine whether a newer, semi-synthetic tetracycline, could be administered to humans in a low-dose regimen[,] which would effectively inhibit collagenase activity in the *gingival tissue* as well as in the crevicular fluid.

Id. at 322.

Golub presents the results of two studies of patients with periodontal disease. In the first study, patients administered 30 mg doxycycline, twice daily, for two weeks as an adjunct to periodontal pre-treatment and surgery, showed a statistically significant reduction in gingival collagenase activity, but not gingival pocket depth, or the severity of gingival inflammation. *Id*. at Table 1, 322, 324, 328 ("[I]n study no. 1, in which a more complex clinical protocol was followed to obtain excised gingival specimens, the severity of inflammation in the gingival tissues did not appear to be reduced

by the low-dose doxycycline therapy, even though collagenase activity in these tissues was suppressed."); *see also id*. at Fig. 4 (equating gingival index (G.I.) to inflammation). In the second study, patients administered 20 mg doxycycline, twice daily, for two weeks with no additional treatment or surgery, showed significant reductions in the collagenase activity of their gingival crevicular fluids, and in the severity of gingival inflammation. *Id*. at 323, 324-325, Table I, Abstract.

> Golub also states that novel properties of tetracycline drugs:
>
> help explain their clinical effectiveness and may also expand their future applications beyond their current use as antimicrobials. As one example, tetracyclines now appear to possess anti-inflammatory properties when administered to patients with certain skin diseases [ ] such as rosacea[,] . . . which are *not* believed to have a microbial etiology.

Id. at 325 (citations omitted). Golub posits that the mechanisms underlying the non-antimicrobial properties of tetracyclines may include the inhibition of prostaglandin production, superoxide radical scavenging, and the inhibition of mammalian collagenase and other metalloproteinase activities. *Id*.

iv. PERIOSTAT

Published in 2000, PERIOSTAT is a Physician's Desk Reference entry describing Periostat® as "a 20 mg capsule formulation of doxycycline hyclate for oral administration." Ex. 1042, 944. Under "Dosage and Administration," the reference states that, "Periostat 20 mg twice daily as an adjunct following scaling and root planning may be administered for up to 9 months." *Id*. at 946. The reference further states that "[t]he dosage of doxycycline achieved with this product during administration is well below the concentration required to inhibit microorganisms commonly associated

with adult periodontitis." *Id*. at 945.

v. Jansen

Jansen reviews the classification and treatment of rosacea as of 1997, describing rosacea generally as:

> a chronic skin disorder affecting the facial convexities, characterized by frequent flushing, persistent erythema, and telangiectases. During episodes of inflammation additional features are swelling, papules and pustules. The disease was originally called acne rosacea, a misleading term that unfortunately persists."

Ex. 1034, 144. Jansen states that "[t]he exact etiology of rosacea is unknown and theories abound." *Id*. Jansen notes that various theories include, *gastrointestinal disturbances, Helicobacter pylori infection, hypersenstitivity to D. folliculorum mites*, which may "induce[] papule or pustule formation in pre-existing rosacea," and abnormalities in the dermis surrounding blood vessels. *Id*.

Jansen teaches that although bacteriological studies of inflammatory pustules from Stage II rosacea "reveal nothing of interest" (*id*. at 145), "[r]osacea generally responds well to oral antibiotics" (*id*. at 148). Noting that "[t]etracyclines and erythromycin reduce leucocyte migration and phagocytosis," Jansen suggests that "[t]he mechanism of antibiotics may be anti-inflammatory rather than antibacterial." *Id*. With respect to specific treatments, Jansen states that doxycycline "[is] usually effective in controlling papulopustula rosacea." *Id*. "One should start with large doses," for example, 50 milligrams of doxycycline twice daily. "As soon as papulopustules are fully controlled (usually after two to three weeks) doses of . . . 50 mg . . . doxycycline, per day are generally sufficient." *Id*.

d. *Obviousness over Sneddon, Golub, Torresani, and PERIOSTAT*

Petitioner asserts that claims 1, 7, 8, 14, 15, and 20 would have been obvious over the combination of Sneddon, Golub, Torresani, and PERIOSTAT. Pet. 24–45. To briefly summarize Petitioner's argument, it would have been obvious for one of ordinary skill in the art to reduce the dose of tetracyclines taught by Sneddon——and, in particular, the dose of doxycycline taught by Torresani——for the treatment of the papules and pustule of rosacea, to the 40 milligram per day dose taught by Golub and PERIOSTAT for the treatment of periodontal disease, because (1) "the papules and pustules of rosacea were known to be inflammatory, and not bacterial;" (2) Golub taught that periodontal disease is an inflammatory condition treatable with low dose doxycycline; (3) doxycycline was known to have "at least some anti-inflammatory properties at almost any dose;" (4) reduced dosages would provide benefits including lower cost, increased patient compliance, and reduced side effects; and (5) to minimize the risk of side effects, one of ordinary skill in the art would have reason to start treatment with a low dose, "[i]f a low dose did not work, the dose could be increased until an effective dose was reached." *See* Pet. 6–8, 32–38; Ex. 1004 ¶ 43, 53.

Petitioner's argument begins with the premise that "the papules and pustules of rosacea were known to be inflammatory, and not bacterial" such that a person of ordinary skill in the art would have been motivated to treat the papules and pustules of rosacea with doses of doxycycline having anti-inflammatory, but not antibiotic activity. *See* Pet. 6, 33, 50; Ex. 1004 ¶ 43; Prelim Resp. 13–14. In support, Petitioner points to Golub's statement that "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" (Pet. 30; Ex. 1004 ¶37 (both citing Ex. 1048, 325)), and Torresani's statement that "[t]he therapeutic activity of tetracyclines seems to be related to their anti-inflammatory efficacy" (Pet. 30–31; Ex. 1004 ¶37 (both citing Ex. 1010, 945)); *see also* Ex. 1034, 148 (suggesting that the mechanism of antibiotics in treating rosacea "may be anti-inflammatory rather than antibacterial").

As set forth on pages 13–17 of Patent Owner's Preliminary Response, however, the art of record indicates that the underlying causes of rosacea were unknown at as of the filing date of the '506 patent. *See e.g.*, Ex. 1010, 945, 946 (stating that the "[T]he etiology and pathogenesis of rosacea are still unknown," and suggesting a relationship between rosacea and *Helicobacter pylori* infection); Ex. 1034, 144 (stating that "[t]he exact etiology of rosacea is unknown and theories abound," including potential roles for gastrointestinal disturbances, *Helicobacter pylori infection,* and hypersenstitivity to *D. folliculorum* mites); Ex. 2008, 777 (stating that "[*R*]*osacea* is a common condition of unknown etiology," and reporting that the eradication of *Helicobacter pylori* infection with antibiotics "leads to a dramatic improvement in the symptoms of *rosacea*."). Moreover, art cited by Patent Owner shows that the etiology of rosacea was not "known" to be "not bacterial" even after the filing date of the '506 patent. *See* Pet. 16–17 (citing Ex. 2010, 479, 480; Ex. 2011, 24; Ex. 2012, 87). Accordingly, based on the evidence of record, Petitioner has not demonstrated that one of ordinary skill in the art understood that the underlying cause of the papules and pustules of rosacea was "not bacterial."

Implicit in Petitioner's argument is that one of ordinary skill in the art would have understood that the inflammation associated with the papules and pustules of rosacea shared a common pathway with that seen in periodontal disease. *See e.g.*, Pet. 10 (citing Ex. 1004 ¶¶ 39, 57; Ex, 1048); *id*. at 33, 49. Petitioner's express conclusion that "[t]he inflammatory pathways of periodontal disease were known to exist in papules and pustules of rosacea," however, is unpersuasive in light of the evidence provided in the Petition.

As noted by Patent Owner, Golub's limited disclosure regarding rosacea provides no details regarding the mechanisms of inflammation associated with this disease. *See* Prelim. Resp. 18–19. Petitioner's expert, however, points to passages in WO 00/18230 (Ex. 1013) for support. *See* Ex. 1004 ¶57 (citing Ex. 1013:1:10–16, 5:15–20). WO 00/18230 suggests that (1) proteolytic damage to connective tissues and basement membranes is an inflammatory response that contributes to pathological changes in diverse organs and tissues; (2) extracellular protein degradation/destruction plays a prominent role a wide range of conditions and diseases, including "skin diseases such as acne . . . [and] dental diseases such as periodontal diseases," and (3) "non-antimicrobial tetracyclines [have been used]to treat tissue destructive conditions, chronic inflammation, bone destruction, cancer and other conditions associated with excess activity of metalloproteinases." Ex. 1013:1:10–16, 4:11–19; 5:15–20. The referenced passages do not persuade us that one of ordinary skill in the art would have recognized that the inflammatory response associated with the papules and pustules of rosacea involved an excess activity of metalloproteinases responsive to non-antimicrobial tetracyclines or, more broadly, that the inflammatory response

associated with the papules and pustules of rosacea shared a common pathway with that associated with periodontal disease.

Patent Owner argues that Petitioner has failed to establish a motivation to combine the cited prior art with a reasonable expectation of success because Sneddon and Torresani are directed to the treatment of rosacea of the skin, whereas Golub and PERIOSTAT are directed to the treatment periodontitis, a disease of the gums. Prelim. Resp. 25–26, 35–36. We agree. Sneddon and Torresani relate to a different medical specialty, describe treating a different ailment, and focus on different organ of the body as compared to Golub and PERIOSTAT. *See id*. Petitioner fails to adequately address these differences, and thus, fails to persuade us that one of ordinary skill in the art would have, with a reasonable expectation of success, expected that the 40 milligram daily doses of doxycycline used to treat periodontitis would have been efficacious in the treatment of rosacea.

As Patent Owner points out, a similar argument was considered during the prosecution of the application that ultimately issued as the '506 patent. Prelim. Resp. 29–30; see Pet. 16–21. In particular, Applicant argued that there was no reason to combine the Perricone[12] reference, teaching the treatment of facial acne with, inter alia, an antibiotic dose of tetracycline, with the Plugfelder reference,[13] disclosing the use of sub-antimicrobial doses for the treatment of an eye disease (Meibomian gland disease or "MGD) *associated* with rosacea. Ex. 1070, 7–12; Ex. 1072.[14] In an Examiner's

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[12] Perricone et al., U.S. 6,365,623 B1, issued April 2, 2002.
[13] Pflugfelder et al., U.S. 6,455,583 B1, issued Sept. 24, 2002.
[14] U.S. Serial No. 13/277,789, Declaration under 37 C.F.R. § 1.132, dated Feb. 22, 2013.

interview, Applicant argued that there is no reason to combine the two references because "treating Meibomian gland disease and rosacea are not related." Ex. 1071, 16. Invited to respond in writing, Applicant elaborated that, "success in treating eye disease with a sub-antibiotic treatment is not relevant to treating a skin disease with an antibiotic treatment. Medical science is much too unpredictable to make such a connection." *Id*. at 8; *see id.* at 16; *see also* Ex. 1070, 8 ("There would be no reason for a skilled artisan to believe that a treatment that is effective to treat an ocular disorder would treat a skin condition. Medicine is too unpredictable for such a conjecture.").

Similar reasoning applies in the present case. Even were we persuaded that one of ordinary skill in the art would have recognized that the inflammation associated with the papules and pustules of rosacea shared a common pathway with that associated with periodontal disease, Petitioner does not persuade us that a skilled artisan would have reasonably expected that the sub-microbial dose of doxycycline taught by Golub and PERIOSTAT for the treatment of a gum disease would be effective in treating a disease of the skin.

Underscoring the unpredictability and lack of reasonable expectation of success of applying Golub and PERIOSTAT to a different disease and tissue type, we note that Golub's study number one, a "more complex clinical protocol" involving 60 milligrams of doxycycline per day, showed suppressed collagen activity but did not significantly reducing inflammation. *See* Ex. 1048, 328. This suggests that the benefits of doxycycline in Golub's work may depend on the condition of the gum tissue treated, i.e., the disease state, and thus underscores the unpredictability of applying Golub's

teachings to a different disease in a different tissue type.

The disparate results of Golub's two studies treating the same tissue type also undercut Petitioner's reliance on the assertion that doxycycline was known to have "at least some anti-inflammatory properties at almost any dose." Pet. 35 (citing Ex. 1004 ¶ 42). This statement is supported by reference to *in vitro* studies using isolated immune cells and, as Petitioner's expert makes clear, "does not mean that one would expect virtually any dose to be clinically effective." Ex. 1004 ¶ 42 (citing Ex. 1031,[15] 312; Ex. 1032,[16] 178–79).

Finally, we note that fully seven years after the publication of Golub, Torresani continued to teach the administration of high-dose tetracyclines (doxycycline) for the treatment of rosacea. *Cf.* Ex. 1048 (published 1990) and Ex. 1010 (published 1997); *see also* Ex. 1034, 148 (teaching that, as of 1997, "[o]ne should start with large doses," e.g., 50 milligrams doxycycline twice daily.); Prelim. Resp. 28 (arguing that, as of the priority date of the '506 patent, "the prevalent teaching for using tetracyclines in treating rosacea was to us a *high, antibacterial dose*, and to reduce the dose, if at all, only *after* the papules and pustules were treated and under control") (citations omitted). That Golub was published at least a decade prior to the filing date of the '506 patent[17] underscores the impermissible hindsight

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[15] Naess et al., *In vivo and in vitro effects of doxyclycline on leucocyte membrane receptors*, 62 CLIN. EXP. IMMUNOL. 310 (1985).
[16] Akamatsu et al., *Effect of Doxycycline on the Generation of Reactive Oxygen Species*, 72 ACTA DERM VENEREOL 178 (1992).
[17] On its face, the '506 patent issued from a chain of continuation and divisional applications first filed on April 5, 2002. We take no position here

reconstruction inherent in Petitioner's argument. *See* Prelim. Resp. 40–41.

For the reasons discussed above, we conclude that Petitioner has not established a reasonable likelihood that it would prevail in showing any of the challenged claims would have been obvious over the combination of Sneddon, Golub, Torresani, and PERIOSTAT.

e. *Obviousness over Golub, Torresani, Jansen and PERIOSTAT*

Petitioner also argues that the asserted claims would have been obvious over Golub, Torresani, and Jansen (claims 1, 8, and 15), and further with respect to PERIOSTAT (claims 7, 14, and 20). Pet. 45–56. Petitioner relies on Jansen's teaching that bacteriological studies of inflammatory pustules from Stage II rosacea "reveal nothing of interest," to support its contention that the papules and pustules of rosacea "are inflammatory in nature, not bacterial." *See* Pet. 49, 50. As noted above, however, Jansen teaches that as of 1997, "[t]he exact etiology of rosacea is unknown and theories abound" (Ex. 1034, 144) and, while the mechanism of antibiotics may be anti-inflammatory rather than antibacterial, "one should start with large doses," e.g., 50 milligrams of doxycycline twice daily (*id*. at 148). For the reasons previously discussed in Section I, Petitioner does not persuade us that one of ordinary skill in the art understood that the underlying etiology of the papules and pustules of rosacea was "not bacterial."

In addition to the reliance on Jansen, the instant grounds focus first on Golub's use of low dose doxycycline for the treatment of periodontal disease, rather than the conventional high-dose treatment for rosacea taught

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regarding whether the '506 patent is entitled to benefit of the earlier filing date(s) of provisional applications Nos. 60/325,489 and 60/281,916.

by, for example, Torresani. *See, e.g.*, Pet. 5–6. This reshuffling of references fails to persuade us Petitioner has established a reasonable likelihood it would prevail in showing any of the challenged claims would have been obvious for the reasons set forth in Section I.

CONCLUSION

For the foregoing reasons, the information presented in the Petition and accompanying evidence does not establish a reasonable likelihood that Petitioner would prevail in showing the unpatentability of claims 1, 7, 8, 14, 15, and 20 of the '506 patent.

ORDER

Accordingly, it is

ORDERED that Petitioner's request for an *inter partes* review of claims 1, 7, 8, 14, 15, and 20 of the '506 patent is *denied*.

PETITIONER:

William L. Mentlik
Michael H. Teschner
Brian R. Tomkins
Maegan A. Fuller
LITTENBERG, KRUMHOLZ & MENTLIK, LLP
WMentlik.ipr@ldlkm.com
MTeschner.ipr@ldlkm.com
BTomkins.ipr@ldlkm.com
MFuller.ipr@ldlkm.com

PATENT OWNER:

Stephen Maebius
Sujnit Talapatra
Michael Houston
FOLEY & LARDNER LLP
smaebius@foley.com
stalapatra@foley.com
mhouston@foley.com

Gerald Flattmann
PAUL HASTINGS LLP
geraldflattmann@paulhastings.com