

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

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

GALDERMA LABORATORIES, INC.
Patent Owner

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

Inter Partes Review No. Unassigned

(Exhibit 1004)
DECLARATION OF MICHAEL PAYETTE, M.D., M.B.A.

Dr. Reddy's Laboratories, Ltd., et al. v. Galderma Laboratories, Inc. IPR2015-_____ Exhibit 1004

I, MICHAEL PAYETTE, hereby declare as follows:

1. I am a U.S. citizen and a resident of the state of Connecticut.
2. I am a board-certified dermatologist and an assistant professor for the Department of Dermatology at the University of Connecticut School of Medicine. I hold a B.A. from Dartmouth College in Biochemistry in 2002, an MBA from the University of Connecticut focusing on healthcare management in 2008, and my medical degree is also from the University of Connecticut in 2008. My current *curriculum vitae* is provided. (Exh. 1005.)
3. I am primarily a clinical dermatologist and 70% of my time is dedicated to direct patient care in an academic university setting. My clinical areas of interest are complex medical dermatology and skin cancer, but I treat the entire spectrum of dermatologic diseases and all age groups, from newborns to geriatricians. I almost always have dermatology residents, residents in primary care specialties, and/or medical students working with me in clinic. The nonclinical 30% of my time is dedicated to resident and medical student education as well as to administrative duties inherent in running an ACGME (Accreditation Council for Graduate Medical Education)-certified dermatology residency program.
4. Outside of my clinical and administrative roles, I am an active publisher in the field of dermatology. I have an interest in cost efficacy and medical ethics. I serve as a peer-reviewer for submitted manuscripts for leading

dermatology journals. I am a consultant to several pharmaceutical companies as well (Amgen, Lilly, and Abbvie). Finally, I am a very active educator. I lecture to medical students, medicine residents, dermatology residents, and other physicians on all topics in dermatology, including the topics of acne and rosacea. I am constantly educating medical students, medicine residents, and most importantly dermatology residents in the clinical setting, with emphasis on the pathophysiology, diagnosis, and medical management of dermatologic conditions.

5. I have been retained by Lerner, David, Littenberg, Krumholz & Mentlik, LLP (“counsel”) to provide my opinions in the field of dermatology, the treatment of acne and rosacea as well as the treatment of certain symptoms common to acne and rosacea. I have read and understood U.S. Patent No. 8,603,506 (“the ‘506 Patent”) (Exh. 1001), its predecessors (Exhs. 1016, 1020, 1026, 1036), and all other references discussed in this declaration. I am being compensated for my time in an amount consistent with my customary consulting fee and my compensation is not contingent on my opinion or the outcome of this proceeding.

A Person of Ordinary Skill In The Art

6. I understand from counsel that patents such as the ‘506 Patent are neither addressed to experts nor to laymen; rather they are addressed to persons of ordinary skill in the relevant art at the time that the invention was made, which I

have been told by counsel to assume is April 5, 2001. I also understand from counsel that factors relevant to the level of skill in the art include, without limitation: the educational level of the inventor, the types of problems encountered in the relevant area, 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. In my opinion, considering these factors, a person of ordinary skill in the art would be a licensed, board-certified, and practicing dermatologist. And when I give my opinions herein, unless stated otherwise, it is my opinion of what such a person of ordinary skill in the art would know or do at the time.

7. I note first that the claims in question, which I understand to be claims 1, 7, 8, 14, 15, and 20 of the '506 Patent (Exh. 1001 col.31 l.60 to col.32 l.65) are directed to methods of treating an extremely common symptom of rosacea, a condition treated virtually every day by practicing dermatologists at even the most entry level. Treating skin conditions is the province of medical doctors in the U.S. As such, I would not consider those without formal medical training to be persons of ordinary skill. That said, as discussed below, treatment here involves administering a well-known active agent (doxycycline), in a well-established way (orally), for treating conditions and symptoms that were well-known by April 5, 2001 to be treated in that fashion (papules and pustules of

rosacea). Furthermore, the relevant doses of the active agent were all already FDA approved and commercially available. Accordingly, while the claims in question are clearly directed to dermatologists, I would not consider this technology to be sophisticated, particularly relative to other forms of dermatological medical treatments or research.

8. In reaching my conclusion, I have also considered the type of problems addressed by the '506 Patent, and prior art solutions to these types of problems. In my opinion they all involve balancing the need for treatment with a pharmaceutically active agent and the need to avoid exposing the patient to possible side effects and/or unintended consequences from the proposed treatment. This is a problem that is faced by every treating physician, every time they prescribe any medication, or decide not to do so. And the solutions, that of deciding to prescribe anything, deciding what to prescribe, how much to prescribe, and for how long, are well established and within the sound discretion of treating dermatologists.

9. While some general practitioners (such as pediatricians, internal medicine physicians, and family medicine physicians) do treat acne and rosacea, they typically do so in a limited fashion, using select common therapies (often advertised ones), and with adherence to the standard of care. They generally do not have expertise in the pathophysiology of acne or rosacea, the variety of clinical

presentations, or the array of treatment options. They are not likely to use off-label therapies or manage challenging or refractory cases. Patients who fail first-line and perhaps second-line therapies are referred to dermatologists for management. Accordingly, while I believe a person of ordinary skill in the art must at least be a medical doctor, I also believe that the '506 Patent is directed more specifically to medical doctors formally trained in dermatology and board-certified in this specialty.

10. Finally, I have been told by counsel that Robert A. Ashley, who is listed as the inventor of the '506 Patent, has a master's degree from Oxford in biochemistry and no specific degrees in medicine. (Exh. 1052.) This is a lower level of formal education than I would have expected in the field of treating acne and rosacea and/or their specific symptoms, which is certainly a medical condition requiring a medical education.

11. Considering all of this, I think that a person of ordinary skill in the art in April of 2001 would be a licensed, board-certified, and practicing dermatologist, likely with as little as one year of experience in treating patients in a hospital, clinical, and/or private setting. Such a dermatologist would, by virtue of their relatively recent graduation from medical school and residency, likely be better educated in current research and trends at the time and less dominated by observations and practices learned by practicing physicians with more prolonged

personal experience. But I would still expect more experienced dermatologists to understand the current research and trends. I consider myself to be a person of at least ordinary skill in this art. Moreover, because of my work experience and my supervision of residents and medical students, and my review of the relevant literature from the relevant time period (prior to April 5, 2001), I believe that I am well situated to understand what a person of ordinary skill in the art would have known and understood at the relevant time.

Definitions

12. The '506 Patent defines "rosacea" as merely a form of acne. (Exh. 1001 col.4 ll.31-41 ("[f]or the purpose of this specification, acne includes all known types of acne. Some types of acne include, for example, acne vulgaris . . . and acne rosacea.").) Moreover, while the claims use the word "rosacea," the specification uses the term "acne rosacea," a term that is generally no longer used in dermatology. (*Id.* col.4 l.41; Exh. 1034, at 144 ("The disease [rosacea] was originally called acne rosacea, a misleading term that unfortunately persists.").) Acne, and therefore the individual conditions subsumed by that term, in turn, is defined as "a disorder of the skin characterized by papules, pustules, cysts, nodules, comedones, and other blemishes or skin lesions." (Exh. 1001 col.4 ll.24-26.)

13. While this is clearly what the ‘506 Patent says, I find this to be an inaccurate characterization and I believe a dermatologist of ordinary skill in the art would as well. In my opinion, a dermatologist of ordinary skill in the art would not lump things like acne vulgaris and rosacea together. They are similar in that they are both skin conditions and both include inflammatory papules and pustules, but species like acne vulgaris (common acne) and rosacea have totally different pathophysiologies as well as different clinical presentations, including but not limited to: body sites affected (acne vulgaris generally involves the face, chest, shoulders, and back; rosacea is generally mid-facial), disease incidence (acne vulgaris generally starts in adolescence; rosacea generally starts in adults), associated symptoms (acne vulgaris can be associated with bone and joint inflammation; rosacea is often associated with ocular inflammation), etc. The ‘506 Patent does correctly note that rosacea can be characterized by the “permanent dilation of blood vessels (telangiectasias) [sic].” (*Id.* col.4 ll.41-43.) This is not something that characterizes common acne at all. In contrast, while the ‘506 Patent suggests that all of the conditions it lumps together under the acne umbrella are characterized by comedones, a dermatologist of ordinary skill in the art knows that comedones are not a symptom of rosacea. And this is the only symptom for which treatment is actually discussed. In truth, the two conditions are far more different than they are similar.

14. As an aside, I am aware that another patent to the same inventor with a similar specification actually claims treating telangiectasias of various origins, including rosacea. (Exh. 1026, U.S. Patent No. 7,014,858.) However, I am not aware of any evidence that antibiotics, at any dose level, are actually useful to this end; the patent offers none. And now, 15 years or so after the first application leading to the '506 Patent was filed, I know of no work that confirms that this treatment is effective. The current standard of care for treating telangiectasias is surgical ablation, typically via specific lasers (Exh. 1044, at 280). While Exh. 1044 is not prior art, it was published before the issuance of the '858 patent on March 31, 2006. There is no drug treatment of any kind that I know of that treats telangiectasias. I believe that a dermatologist of ordinary skill in the art would find the suggestion that low dose antibiotics could treat telangiectasias to be non-credible. Furthermore, it demonstrates a lack of understanding of rosacea.

15. In fact, the '506 Patent barely mentions rosacea, doing so only twice: once when identifying it, along with 29 other conditions, as species of "acne" and once when explaining that rosacea was characterized by erythema and telangiectasia. (Exh. 1001 col.4 ll.41-43.) The '506 Patent never expressly explained that treating even these two symptoms of rosacea was its goal, let alone treating the other symptoms allegedly common to all of the various forms of acne described. Indeed, there is almost as little discussion of papules and pustules as

there is of rosacea. Papules and pustules are merely described as one of several things that allegedly characterize acne in general (*id.* col.4 l.26) and as one of the inflammatory lesions allegedly treated in treating acne vulgaris (*id.* col.19 ll.55-56, col.20 l.17, col.20 ll.25-32). Nothing describes treating papules and pustules generally, or treating papules and pustules of rosacea. In fact, the only symptom specifically addressed is comedones (*id.* col.3 l.57, col.4 ll.44-47, col.7 ll.1-16), which, as noted previously, is not a symptom of rosacea at all. And it provided no data showing that it is possible to treat rosacea or any of its symptoms.

16. Nothing in the disclosure of the '506 Patent would have told a dermatologist of ordinary skill in the art to use a specific dose of a specific antibiotic for treating rosacea or its papules and pustules. Many different antibiotic and indeed nonantibiotic compounds are described in the '506 Patent (*id.* col.4 l.58 to col.5 l.28, col.7 l.37 to col.8 l.25, Exs.1-36, col.20 l.45 to col.31 l.58) and many different, and as discussed below, often contradictory, doses are described in the '506 (*see id.* col.5 l.35 to col.6 l.43). Never is a dose of any particular drug described as being useful for treating rosacea, let alone its papules and pustules.

17. Without the benefit of the claims, there is next to nothing in the specification to suggest that a goal of the inventor was the treatment of papules and pustules of rosacea or how, specifically, that was to be accomplished. Given that rosacea was a clear afterthought, named in an outdated manner, identified virtually

not at all, not described or exemplified in connection with any specific treatment or symptom, and discussed by symptoms that either do not exist (comedones), or actually cannot be treated by antibiotics (telangiectasias), I believe that the ‘506 Patent did not have a clear disclosure capable of teaching a dermatologist of ordinary skill in the art how to treat the papules and pustules of rosacea, much less by the use of low dose doxycycline as claimed.

18. Note that in contrast to the ‘506 Patent, when I speak of acne and when the papers generally cited herein discuss acne, I mean, and I understand the authors of these papers to mean, the treatment of common acne or “acne vulgaris.” This will be the case unless I, or the authors, specifically state otherwise or the context makes it clear that the term is not being used generically.

19. Neither the term “papule” nor the term “pustule” appears to be specifically defined in the ‘506 Patent. However, the patent does seem to acknowledge that pustules are implicated in the “more inflammatory types of acne.” (*Id.* col.1 ll.37-41.) “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.” (Exh. 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” (*Id.* at 31.) “The inflammatory lesions [of acne] vary from small papules with an inflammatory areola to pustules to large tender fluctuant nodules and cysts All these lesions show an inflammatory infiltrate in the dermis,” (*Id.* at 669.) “The predominant lesions [in rosacea] are papules and pustules.” (*Id.* at 680; *see also* Exh. 1046, at 852, 958; Exh. 1047, at 1023, 1175.) Papules and pustules are extremely common to both acne 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.

20. Their term “antibiotic” and the phrase “having substantially no antibiotic activity,” like the term “acne,” are not found in the claims. Nonetheless the concept they embody is reflected in the doses recited in the claims and are, in my opinion, in need of discussion and clarification. The ‘506 Patent teaches the administration of an antibiotic drug — a drug known to have the potential to kill microbes, but in an amount which is allegedly ineffective for that purpose. Specifically, the methods “comprises administering systemically to the human a tetracycline compound in an amount that is effective to treat acne but has substantially no antibiotic activity (i.e. substantially no antimicrobial activity)” (Exh. 1001 col.3 ll.46-50.) The ‘506 Patent further explains that the

amount of the antibiotic is the minimum amount necessary to treat acne, but is “such that it does not significantly prevent the growth of microbes, e.g. bacteria.” (*Id.* col.5 ll.33-35.)

21. Of course whether any particular amount of any particular antibiotic drug provides substantially no antimicrobial activity will vary significantly, at a minimum, with the drug, the microbe, and the patient. In my opinion, systemically administering orally a 40mg dose, indeed even a 20mg dose, of doxycycline, will have antibiotic activity. It surely will alter the flora of the digestive tract by killing bacteria, if even temporarily. And the prolonged administration of such doses, even if sub-therapeutic for its intended purpose, will necessarily retard bacterial growth at least in the digestive tract.

22. Even the labels for PERIOSTAT and ORACEA, both 40mg doses of doxycycline administered orally, acknowledge potential side effects linked directly to the destruction of bacteria. ORACEA for example identifies the possibility of *Clostridium difficile*-associated diarrhea, the overgrowth of non-susceptible microorganisms, and the possibility of bacterial resistance developing. (Exh. 1043, at 1000 Warnings/Precautions.) PERIOSTAT’s label states that therapy may result in overgrowth of non-susceptible microorganism and increased incidence of vaginal *Candidiasis*. (Exh. 1042, at 945 Precautions.) All of these conditions result from the destruction of native microbes allowing the uncontrolled growth of

others. Thus 40 mg doses of doxycycline are admittedly sufficient to “significantly prevent the growth of microbes, e.g. bacteria.” (Exh.1001 col.5 ll.33-35.)

23. It is difficult enough to reconcile the concepts of antibiotic and allegedly “subantibiotic” amounts of drugs otherwise known to be antibiotics as advocated in the ‘506 Patent. That difficulty is amplified, however, by the ‘506 Patent’s internally contradictory description of antibiotic and nonantibiotic dose. In the context of doxycycline, for example, the ‘506 Patent states that “antibiotic doses” include 50, 75, and 100mg/day. (*Id.* col.5 ll.43-44.) The ‘506 Patent 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.) But 80% of a 100mg/day dose is 80mg. Is this an antibiotic or a subantibiotic dose? 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. (*See id.* col.5 ll.54-58.) But just two paragraphs earlier, the same specification states that 50mg, which falls in this 30 to 60mg range, is an antibiotic dose. So, according to the ‘506 Patent, is 50mg an antibiotic dose or a dose too low for significant antibiotic effect?

24. Consequently, in discussing various aspects of the ‘506 Patent, I intentionally use the term “allegedly subantimicrobial.” This is not a term of the claims, but it is reflected in the doses recited as the rationale for administering a

dose that is below 50mg of doxycycline. I use this term here in view of the difficulty in understanding the concept of an antimicrobial or nonantimicrobial dose created by the '506 Patent.

Off-Label Use

25. A doctor may prescribe an FDA-approved medication for any use, including so-called “off-label uses.” These are uses other than those found in the FDA-approved prescribing information. Gabapentin, for example, is FDA approved for the treatment of epilepsy and shingles. However, it has several off-label uses for pain and other conditions. (Exh. 1055, at 559.) Aspirin is another well-known example. Aspirin has long been known for the treatment of headaches, inflammation, and fever. However, aspirin products are now often used once a day as antiplatelet aggregation drugs in cardiac patients. Moreover, while aspirin is often given at 500mg or more up to six times a day for fever, for example, it is generally prescribed at a much lower level of 81mg once per day for antiplatelet aggregation.

26. Similarly, the tetracycline medications are themselves an example of off-label use. The tetracyclines in general, and doxycycline specifically, are well known by dermatologists to have a plethora of off-label uses, including but not limited to the following conditions: pyoderma gangrenosum (Exh. 1057, at 23-24), Sweet's syndrome (Exh. 1058, at 584-85), sarcoidosis, foreign body granulomas

(Exh. 1059, at 985), and numerous autoimmune bullous disorders, such as bullous pemphigoid (Exh. 1060, at 670-72; Exh. 1061, at 305-06; Exh. 1062, at 74-76; Exh. 1063, at 753-56, pemphigus vulgaris (Exh. 1065, at 998-99), cicatricial pemphigoid (Exh. 1066, at 254-55), and linear IgA bullous disorders (Exh. 1065, at 998-99).

27. In fact, even PERIOSTAT can have off-label use, as was acknowledged by the authors of a study looking into using PERIOSTAT (apparently named “Dermostat” in the study) to treat inflammatory conditions: “[p]eriostat was approved by the FDA in 1998, and it could currently be used for its anti-inflammatory benefits with excellent results.” (Exh. 1015, at 2.) I see this as mere confirmation that PERIOSTAT was available for off-label use and that doctors were free to use it, and indeed it appears they were doing so.

The Known Use Of Tetracyclines To Treat Papules And Pustules Of Rosacea

28. The systemic use of the tetracycline family of medications in the treatment of inflammatory acne and rosacea goes back at least about 50 years. Indeed, to my knowledge, the earliest documentation of the use of tetracyclines to treat rosacea dates back to 1966, when Sneddon IB noted in the *British Journal of Dermatology* that, “There is no doubt that tetracycline controls not only pustulation, which one could accept might be of bacterial origin, but the liability to flushing and the permanent dilatation of the capillaries also clear in favourable

cases.” (Exh. 1006, at 651.) “The mechanism of its beneficial action [tetracycline] is as yet unknown, but the observation that it controls not only pustulation but erythema suggests that it is not entirely an antibacterial or antiodemodectic effect.” (*Id.* at 652.) Furthermore, Sneddon notes, “[m]any of the state of dermatological textbooks published in the last two years mention tetracycline as a significant agent in treatment [of rosacea], and this must reflect the attitude of dermatologists as a whole, but there has been no statistical support for this opinion. Perhaps statistics are unnecessary when the treatment is so good that it obviously works.” (*Id.* at 649.) This would suggest to one of ordinary skill in the art that tetracyclines were already in wide use for treating rosacea as far back as the 1960s. In Sneddon’s study, tetracycline administration was successful in controlling rosacea in 87% of patients studied. (*Id.* at 651-52.) Sneddon did not expressly disclose oral antibiotics. However, he disclosed that patients were given a month’s supply of tetracycline or an indistinguishable placebo. Coupled with the prevalence of oral dosing, I believe a dermatologist of ordinary skill in the art would read Sneddon as disclosing administering oral antibiotics.

29. Later studies corroborated Sneddon’s findings. A randomized double-blind controlled trial in 1971 demonstrated a benefit of tetracyclines in the treatment of papules and pustules of rosacea. (Exh. 1007, at 1050-51.) Controlled trials in 1980 (Exh. 1008, at 444) and 1983 (Exh. 1009, at 64) similarly showed

improvement of inflammatory rosacea with administration of oxytetracycline, another early member of the tetracycline family (Exh. 1054, at 21). While the term “acne rosacea” is not used specifically in Sneddon’s study nor the related studies listed above, the fact that these studies are investigating “papules and pustules of rosacea” implies to me that a dermatologist of ordinary skill in the art would interpret these studies as investigating inflammatory rosacea, which was historically termed “acne rosacea”.

30. The disclosure of the ‘506 Patent clearly contemplates the use of tetracyclines, but the claims of the ‘506 Patent are specific to doxycycline. But, well before the filing of the ‘506 Patent, dermatologists would have tended to favor doxycycline over other earlier used members of the tetracycline family. “Although first-generation tetracycline remains useful, the second-generation tetracyclines in the form of minocycline and doxycycline hyclate, and, most recently, doxycycline monohydrate, offer a number of advantages over tetracycline.” (Exh. 1067, at 415.) “The newer tetracyclines have markedly increased bioavailability, greatly improved absorption in the presence of foods, and a broader range of antibacterial activity. The increased bioavailability allows for once-daily administration in the treatment of acne and a twice-daily regimen for soft tissue infections and chlamydia.” (*Id.*) Fasting is not required when taking doxycycline. However, tetracycline absorption is significantly influenced by food and dairy products. (*See*

id. at 412.) The relative side effect profile, the ability to dose less drug and less frequently, and the greater flexibility of dosing in terms of administering with or without food leading to better compliance (*See id.* at 414), as well as the recognition amongst dermatologists of the efficacy of doxycycline in acne, would have made doxycycline preferable to tetracycline in the mind of treating dermatologists well before the '506 Patent was filed.

31. An early report of doxycycline in the treatment of cutaneous rosacea (earlier reports exist for ocular rosacea) was the 1997 study by Torresani that showed that doxycycline doses ranging from 100-200mg/day improved the erythema, telangiectasia, papules and pustules of rosacea in 17 patients. (Exh. 1010, at 942-45.) In particular, the number of papules and pustules decreased from 20-30 lesions to <5 on average. (*Id.* Figs.3, 4.) Interestingly, while finding doxycycline to be effective, Torresani found a second agent, clarithromycin, to be even more potentially attractive. (*Id.* at 945.) Torresani does not expressly disclose oral antibiotics but the length of the study, frequency of dosing, and the prevalence of oral dosing, I believe a dermatologist of ordinary skill in the art would read Torresani as disclosing administering oral antibiotics.

32. In August 2000, JB Bikowski published a case report documenting successful treatment of two patients with inflammatory rosacea with monotherapy of doxycycline monohydrate. (Exh. 1011.) Note, in particular, the “nodules”

mentioned and shown in Figure 3. (*See id.* at 150.) This is a typical illustration of a deep inflammatory papule/pustule. While the paper is not totally clear on this point, the reference to “systemic antibiotic therapy” would be understood by a dermatologist of ordinary skill in the art as a reference to oral administration. Oral antibiotics are expressly mentioned on page 149, and the patients were dosed at home with follow-ups in the office. One patient was initially treated with 100mg/day to obtain clearance, then maintained on the same dose. The second patient was initially treated with 50mg/day to obtain clearance, then maintained on 50mg every other day. (*Id.*) Both patients remained clear in long-term follow-up. Taking into account that the half-life of the doxycycline is 18 hours, then the expected dose at the end of one day would be less than half of the initial dose given. (*See* Exh. 1042, at 954 (“Doxycycline is eliminated with a half-life of approximately 18 hours by renal and fecal excretion of unchanged drug.”).) Thus, by April 5, 2001 it was known that even in relatively low doses, doxycycline could be used to successfully treat the papules and pustules of rosacea.

**The Role Of Inflammation In Papules And Pustules
And the Role of Tetracyclines as Anti-inflammatory Agents**

33. It is well documented that the pathogenesis of papules and pustules of rosacea is intimately tied to the immune system and that inflammation is an essential component and the final common denominator of papule and pustule formation. In rosacea, there “is erythema and telangiectasia making up the vascular

component, and on the other papules and pustules which constitute the inflammatory aspect.” (Exh. 1035, at 36). Additionally, in rosacea, “[b]acteriological studies of these pustules [of inflammatory rosacea] reveal nothing of interest.” (Exh. 1034, at 145.)

34. Importantly, the tetracycline family of medications was known to have numerous effects on inflammatory conditions and pathways Exh. 1017, at 111-14; Exh. 1018, at 533; Exh. 1019, at 52-53; Exh. 1021, at 520-21; Exh. 1022, at 1311-13; Exh. 1023, at 1166-67; Exh. 1024, at 14015-019; Exh. 1025, at 260-62; Exh. 1027, at 15; Exh. 1028, at 690-91; 1029, at 668-69; Exh. 1030, at 444-45; Exh. 1031, at 311-12; Exh. 1032, at 178-79.) Some of these mechanisms were also explicitly demonstrated to be addressed by doxycycline. (Exh. 1023, at 1166-67; Exh. 1024, at 14015-019; Exh. 1025, at 260-62; Exh. 1030, at 444-45; Exh. 1031, at 311-12; Exh. 1032, at 178-79.)

35. Of particular relevance to the issue of treating papules and pustules is the fact that the tetracycline family has been shown to directly impact overall white blood cell chemotaxis, and in particular the chemotaxis of polymorphonuclear (PMN) white blood cells (also known as neutrophils). (Exh. 1019, at 52-54.) White blood cells, and in particular neutrophils, predominantly comprise the inflammatory infiltrate of the papules and pustules of rosacea. (Exh. 1034, at 147.) Therefore, impeding the white blood cells’ ability to track to these sites would

decrease the quantity of the white blood cells in papules and pustules and thus result in direct improvement of the papules and pustules of rosacea.

36. The tetracycline family has also been shown to accelerate neutrophil apoptosis, which limits the ability of white blood cells to damage surrounding tissues and thus prevents amplification of inflammation. (Exh. 1033, at 97.) And doxycycline has also been shown to decrease the ability of PMNs to phagocytose, which results in a decreased release of pro-inflammatory mediators (Exh. 1031, at 311-13) and has been shown to be a potent anti-oxidant, which results in decreased inflammation by absorbing reactive oxidation species. (Exh. 1032, at 178-79.) Affecting these properties would decrease the inflammation occurring in the papules and pustules.

37. Although it was clearly known that tetracycline medications, including doxycycline, could positively impact the pathways involved in the inflammation that comprises papules and pustules, it would be wrong to assume that the connection to treating the papules and pustules of rosacea with tetracycline medications, including doxycycline, was not already being independently established. Indeed, more than a decade before the earliest relevant application leading to the '506 Patent was filed, those of ordinary skill in the art had already begun to attribute doxycycline's usefulness in treating rosacea to properties other than its antibiotic benefits and in particular were pointing to its anti-inflammatory

properties. (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, dermatitis, herpetiformis, and pyoderma gangrenosum, which are *not* believed to have a microbial etiology.”) (emphasis in original.); Exh. 1010, at 945 (“The therapeutic activity of tetracyclines seems to be related to their anti-inflammatory efficacy.”).)

38. Golub explained that tetracycline antibiotics, which had long been advocated as useful adjuncts in periodontal therapy, can inhibit mammalian collagenase and collagen breakdown by a mechanism independent of its antimicrobial efficacy. (See Exh. 1048, at 321-22; *see also* Exh. 1013 p.1 ll.10-16 (“The inflammatory response contributes, for example, to the pathological changes in a number of acute and chronic processes involving diverse organs and tissues such as the lungs, bone, heart, joints, skin and periodontium, etc.”) (emphasis added); p.5 ll. 11-12 (“Certain tetracyclines have been shown to suppress matrix metalloproteinases independently of tetracycline antibiotic activity.”).) According to Golub “[t]he current study was carried out to determine whether a newer, semi-synthetic tetracycline, doxycycline, could be administered to humans in a low dose regimen (20 or 30 mg capsules, rather than the 50 or 100 mg capsules which are commercially available) which would effectively inhibit collagenase activity in the *gingival* tissue as well as in crevicular fluid.” (Exh. 1048, at 322 (emphasis in

original).) “The subjects were instructed to take one capsule in the morning and one at night, but not at mealtimes.” (*Id.*)

39. In seeking to explain why the authors felt that low dose doxycycline could be effective in treating these periodontal conditions, they also cited to the known link between tetracyclines and inflammation in treating, among other things, rosacea. (*Id.* at 325 (“Recently, novel properties of these drugs have been discovered which help explain their clinical effectiveness and may also expand their future applications *beyond* their current use as antimicrobials.” (*Id.* (emphasis in original).)) “As one example, tetracyclines now appear to possess anti-inflammatory properties when administered to patients with certain skin diseases, diseases such as rosacea . . . which are *not* believed to have a microbial etiology.” (*Id.* (emphasis in original).) The authors then described several mechanisms linked to inflammation, which appeared to be involved in and were common to both periodontal disease and rosacea. Specifically, Golub noted that tetracyclines have an ability to inhibit mammalian collagenase and other matrix metalloproteinase activities, which may also contribute to the anti-inflammatory efficacy of these drugs. (*See id.* at 325-26.) It is the effect on these same pathways in periodontal disease that prompted the study. (*See id.* (“In the current study, a low dose regimen of doxycycline appeared to substantially reduce the collagenolytic activity in the

fluid of the periodontal pocket (GCF) and in the gingiva of humans with adult periodontitis.”.)

40. The knowledge of all of the features and mechanisms of inflammation in papules and pustules as well as other inflammatory conditions, doxycycline’s role in mitigating them, and additionally the link to treating inflammatory rosacea, would each suggest to a dermatologist of ordinary skill that it is the anti-inflammatory properties of tetracyclines, and not their antimicrobial properties, that result in the observed improvement in papules and pustules.

41. Clear corroborative support for the inflammatory role in rosacea comes from the benefit that intralesional, oral, and even topical corticosteroids play, particularly in severe cases of acne and rosacea. Corticosteroids have no effect on infectious pathogens; in fact, their use is contraindicated in the setting of infection. Yet, intralesional corticosteroids will reliably dissolve the papules of pustules of rosacea. In severe cases, oral corticosteroids are warranted to quickly suppress inflammation. (Exh. 1064.)

42. It is not just that these compounds were known to be anti-inflammatory — they would have been expected to have efficacy at low doses. Doxycycline’s anti-inflammatory properties were known to occur in a dose-dependent manner, with concentrations just above 0µg/mL having effect. (Exh. 1031, at 312; Exh. 1032, at 178-79.) That does not mean that one would

expect virtually any dose to be clinically effective. But the fact that one does not need some threshold dose to realize a biological effect suggests that it is possible to employ lower doses with a reasonable expectation of finding a suitable effective dose for a patient. Moreover, at the time, PERIOSTAT was already FDA approved (Exh. 1053) and commercially available (Exh. 1042). Its known efficacy in treating periodontal disease, another inflammatory condition, using doses of doxycycline that were allegedly sub-antimicrobial — 40mg/day would be additional affirmation. While a connection between PERIOSTAT and inflammatory skin lesions might have been surprising in the dental community, or to the inventor, a dermatologist, in light of what was published prior to April 2001, would have viewed this information as mere confirmation of what was already known. Indeed, by April 5, 2001 it was well known that doxycycline could be used to successfully treat the papules and pustules of rosacea. In fact, there were disclosures of using PERIOSTAT to treat inflammatory acne. (*See* Exh. 1015.)

43. In summary, as of April 5, 2001, a dermatologist of ordinary skill in the art would have known that:

- a. published studies demonstrated the benefit of the tetracycline family of medications, including doxycycline, in the treatment of the papules and pustules in rosacea;

- b. doxycycline had advantages over other tetracyclines including the ability to administer lower doses less frequently and reduced food effect;
- c. the pathogenesis of the papules and pustules of rosacea was known to be primarily inflammatory in nature, not bacterial;
- d. the anti-inflammatory effects of doxycycline begin at concentrations of just above 0 µg/mL and increase in a dose-dependent manner; and
- e. a 40mg dose of doxycycline was effective in treating inflammatory conditions.

Multiple Rationales For Reducing the Dose of Doxycycline

44. Thus, I believe that a person of ordinary skill in the art at the relevant time would reasonably expect that administration of low dose doxycycline to improve, and thus treat, the papules and pustules of acne and rosacea. Moreover, because its anti-inflammatory properties exist at doses just above 0µg/mL, and its commercial use at allegedly sub-antimicrobial doses to treat other inflammatory conditions, a person with this knowledge would expect administration of any meaningful dose of doxycycline to improve the papules and pustules of rosacea and at some level, there would be observable clinical improvement.

45. Not only would this knowledge provide a reasonable expectation of success, it would provide motivation for dermatologists to use low dose

doxycycline. Dermatologists would not automatically use antibiotic doses of a drug to address nonbacterial based conditions when, as here, there was a clear rationale to do otherwise.

46. However, other reasons exist, any one of which provides a valid justification, for using lower doses. The chance that by switching from tetracycline to doxycycline would lower the dose and aid in compliance was justification for switching drugs in the past. (Exh. 1067, at 414 (“The doxycyclines and minocycline have an advantage over tetracycline because of their higher degree of lipophilicity/absorption. A lower dosage regimen than with tetracycline is therefore possible, providing for greater patient compliance.”).) This motivation would be present here as well — lowering the dose could aid in compliance. Moreover, lower doses of active ingredients could be less expensive. A lower dose of active ingredient could result in smaller tablet or capsule size, which would require not only less active ingredient but also less additive materials to create, and thus be less expensive. A lower dose of active ingredient could also result in more tablets or capsules being produced – one could get twice as many tablets or capsules using 20mg active ingredient versus 40mg active ingredient. Indeed, some of these same reasons previously motivated a move from other tetracyclines to doxycyclines in treating acne. (*See, e.g.*, Exh.1067, at 413 (“The simpler dosage regimen of these two compounds compared with tetracycline (twice daily rather than four times a

day) and lowered dose (200 mg instead of 1000 mg) may enhance patient compliance.”.) As someone with a background in business and health care economics, especially in light of ever-rising health care costs, it’s imperative to always consider how to reduce cost while maintaining health benefits.

47. Thus, it is not overstating things to say that one would generally seek to lower a dose whenever possible. Here, there were very good reasons to do so.

48. But efficacy in treating inflammation is not the only issue a treating physician must consider, and not the only reason they would seek to reduce the dose used wherever possible. It is generally understood by medical professionals that there are risks that come with treating virtually any patient, for virtually any condition, with virtually any pharmacologically active agent. This is certainly true for antibiotics. Indeed, there are well-known potential adverse effects of antimicrobial doses of tetracyclines, including doxycycline. (Exh. 1037, at 124; Exh. 1038, at 75; Exh. 1039, at 1226-28; Exh. 1041, at 728-29; Exh. 1050, 3:58-62; Exh. 1048, at 328; Exh. 1051, at 943.) The use of a lower dose was particularly attractive here where the condition being treated was chronic and could require a long-term exposure to an antibiotic drug. That very logic played into the decision to use low doses of antibiotics to treat periodontal disease. (Exh. 1048, at 328; Exh. 1050 col.3 ll.45-64 (both discussing possible reduction in exposure to side effects and forestalling creation of drug resistant microorganisms despite long

term treatment).) Rosacea, like periodontal disease, is often chronic, requiring prolonged treatment. (Exh. 1034, at 144 (“Rosacea is a chronic skin disorder . . .”).) Thus, concerns over the disadvantages of long term exposure to antibiotic levels of doxycycline would be the same for rosacea as for periodontal disease.

49. All doctors balance the possible good coming from administering a particular dose of a particular drug against the possibility of side effects or other unintended consequences of doing so. Lowering the dose is generally expected to reduce the level of exposure and the possibility of side effects. Accordingly, reducing the dose of a drug is therefore always desirable. In this situation, where one would allegedly not be taking advantage of the antibiotic properties of doxycycline, and where it was reasonably expected that anti-inflammatory effective levels would be lower than those needed for antibiotic activity, a dermatologist of ordinary skill would be further motivated to use low dose doxycycline in treating the papules and pustules of rosacea. (Exh. 1048, at 328 (“specifically formulated low-dose doxycycline capsules may yield the same clinical efficacy [in treating periodontal disease] without inducing the well-known side-effects . . . of long term antibiotic usage.”); Exh. 1050, 3:45-49, 3:57-64, 4:29-32 (discussing use of allegedly sub-antimicrobial doses of tetracyclines to avoid side effects of antibiotic levels).)

50. And there would be one other consideration on the mind of a treating dermatologist in this instance. Rosacea can be a source of both physical and emotional discomfort. (Exh. 1006, at 649.) However, it is not life threatening. If left untreated, it will only impact a patient's quality of life to a certain extent, which is variable from patient to patient. Utilizing lower doses in an effort to find a low, yet effective dose would offer the possibility of lower risks of side effects while not causing patients any harm — indeed, it might avoid harm. Balancing 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.

51. This is not a unique approach in dermatology. Indeed, this is exactly what is done, for example, with blood pressure medications in patients with hypertension. Anti-hypertensive medications are started at low doses so as to obtain benefit (lower blood pressure) and limit risk (hypotension). If the low doses are ineffective at lowering blood pressure adequately, the medication can be titrated up incrementally to obtain the goal blood pressure while avoiding the risk of excessively lowering the blood pressure.

52. In some other diseases, it may be more appropriate to start at higher doses of medication to obtain rapid benefit and then titrate down to the lowest dose

necessary to maintain benefit. In patients with certain systemic inflammatory diseases, high dose immunosuppression with a medication like prednisone is initiated to quickly suppress the inflammation. The medication is then tapered slowly over time to the lowest dose necessary to maintain control. It might be reasonable to employ this same approach with the tetracycline family of medications, including doxycycline, if higher doses of doxycycline could result in a more rapid improvement in the papules and pustules of acne and rosacea and if that were particularly important for a particular patient.

53. A dermatologist of ordinary skill in the art with the knowledge as I have outlined herein, all of which was published at the time, would have a reasonable expectation that administration of low doses of doxycycline would result in at least some benefit in the papules and pustules of rosacea, in at least some patients, and would be the safest starting dose to administer. If a low dose did not work, the dose could be increased until an effective dose was reached or a decision was made to try some other treatment. This would minimize the risks of antibiotic side effects from the very start while finding an effective dose. And with PERIOSTAT being both FDA approved (Exh. 1053) and commercially available (Exh. 1042), low dose (20mg and 40mg/day) doxycycline was immediately at hand.

PERIOSTAT

54. PERIOSTAT, and the research leading to its marketing, provides a particularly apt analogy for using low dose doxycycline in treating the papules and pustules of rosacea. As noted earlier, the role of tetracyclines as an anti-inflammatory had been recognized in rosacea. (Exh. 1048, at 325.) Researchers investigating the treatment of periodontal disease had also hypothesized “that specifically formulated low-dose doxycycline capsules may yield the same clinical efficacy without inducing the well-known side-effects . . . of long-term antibiotic usage.” (*Id.* at 328.) They did so in the context of reporting the results of a treatment regimen involving a twice daily administration of either 20 or 30 mg capsules of doxycycline for a total daily dose of 40 or 60 mg per day. (*Id.* at 322.) It is this same 20 mg dosing, twice a day, for the treatment of periodontal disease that was later approved as PERIOSTAT. (Exh. 1042.)

55. Indeed, scientists, including those at CollaGenex Pharmaceuticals, Inc., the predecessor-in-interest of the ‘506 Patent Owner, noted that subantimicrobial dose doxycycline (SDD) consisting of 20mg doxycycline hyclate had been approved as an adjunct for the treatment of adult periodontitis, and acknowledged that “[s]ubstantial evidence indicates that the adjunctive use of SDD provides a significant benefit to SRP due to its anticollagenase and

anti-inflammatory activities rather than to its antimicrobial activity.” (Exh. 1049 at 1466; *see also* U.S. Patent No. 4,666,897 describing administration of tetracyclines in an amount of between 20 to 80% of the normal antibiotic therapeutic dose (Exh. 1050, 3:45-49, 4:29-32., typically 100mg/day after day 1).)

56. U.S. Patent No. 4,666,897 also recognized that “[t]he present invention is intended for use as long-term (as well as short-term, or even episodic) therapy. The long-term administration of tetracyclines at antibiotically effective dose levels may have a negative effect on healthy flora, such as intestinal flora, and may also lead to the production of resistant organisms. These disadvantages are substantially reduced by the use of subantibiotic dosages.” (*Id.* 3:57-64.) Thus, the nonantibacterial nature of the condition, indeed its inflammatory nature, and the prospect of avoiding antibiotic level side effects while being able to dose less frequently than with other tetracyclines, all supported the use of 40mg/day of doxycycline.

57. Like periodontal disease, papules and pustules of rosacea are an inflammation-based phenomenon. Indeed, “[t]he inflammatory response contributes, for example, to the pathological changes in a number of acute and chronic processes involving diverse organs and tissues such as the lungs, bone, heart, joints, skin and periodontium, etc.” (Exh. 1013 p.1 ll.10-16.) In particular, examples of diseases in which inflammation, such as extracellular protein

degradation/destruction plays a prominent role include “skin diseases such as acne and psoriasis, lichenoid lesions, epidermolysis bullosa, aphthae (reactive oral ulcer), dental diseases such as periodontal diseases, peri-implantitis, jaw cysts and other periapical cysts, dental conditions which are the target of root canal treatment or endodontic treatment, related diseases, external and intrinsic root resorption, caries, etc.” (*Id.* p.5 ll.15-20.)

58. Accordingly, the need for providing antimicrobial effective doses does not exist in rosacea. Like periodontal disease, doxycycline was known to be effective in treating rosacea. And prior to Golub’s research, earlier dosing of doxycycline in periodontitis involved allegedly antibiotic level doses. (Exh. 1050, 4:29-32 (“doxycycline is typically utilized in a dosage of 100 mg every 12 hours during the first day of treatment followed by a maintenance dose of 100 mg daily”)) By reducing the amount of doxycycline administered, one would have a reasonable belief that they could reduce a patient’s exposure to the negative side effects of antibiotics and take advantage of the other possible advantages that come from reduced dosing discussed previously. Thus, the rationale for lower dose doxycycline for treating papules and pustules of rosacea is exactly the same as that already recognized in treating other inflammatory-based conditions, such as periodontal disease, which resulted in the development of and FDA approval of PERIOSTAT.

59. Even though PERIOSTAT is labeled for periodontal use, doctors are free to prescribe medications for “off-label uses.” And here, where the active substance in PERIOSTAT is merely a relatively smaller dose of a well-known active agent administered through a traditional route of administration, the labeled indication for PERIOSTAT would offer no dissuasion to dermatologists. (*See, e.g.*, 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.”).)

60. It is also my opinion that a dermatologist of ordinary skill in the art at the time would be aware of PERIOSTAT and the research leading to PERIOSTAT even though periodontitis is not typically treated by dermatologists. Anyone of ordinary skill in the art considering how best to treat papules and pustules of rosacea would look into, amongst other things, treatments which were known to be effective including tetracyclines, and most especially doxycycline. In particular, they would have looked into doxycycline’s use as an anti-inflammatory agent and the doses at which it was effective for inflammatory conditions. When they did so, at the time, they would have found an extensive array of publications explaining the discovery of the inflammatory nature of periodontal disease and its treatment with low dose doxycycline. Much of this art came from Dr. Golub and his group at the University of Stony Brook. A number of his articles have already been cited. (*See* Exh. 1048; *see also* Exhs. 1021, 1022, 1027, 1029, 1050.) The fact that

periodontal disease represents an analogous problem solved in an analogous way would have been apparent to a dermatologist of ordinary skill in the art and, as noted previously, would have provided a particularly apt model.

Bisphosphonates

61. I find it curious that claims 1, 8, and 15 also mention that the dose of doxycycline should be administered without a bisphosphonate. Bisphosphonates are a class of drugs given to treat calcification disorders like osteoporosis and Paget's disease. There was little mention of the rationale for this exclusion in my review of the '506 Patent. But, as none of the references I have reviewed and discussed herein suggest administering doxycycline, at any dose level, with a bisphosphonate, I think it fairly clear that those of ordinary skill in the art would prescribe and administer low dose doxycycline without ever suggesting the use of a bisphosphonate — just as the art has done. If the art teaches anything on this point, it teaches doxycycline mono-therapy.

Skin Flora

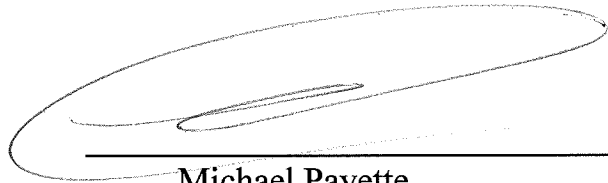
62. There is a similar recitation in the claims that in giving the dose of doxycycline, there will be no reduction in skin microflora during a six-month treatment. As I noted earlier, that does not mean that there would be substantially no impact on bacteria elsewhere in the body, such as in the digestive tract — I think that there would be. And there potentially could be other effects as well. But

assuming that the patent is correct on this issue, the same thing would have to be the case for patient's taking PERIOSTAT. Whether patients knew or did not know taking PERIOSTAT would not affect their skin microflora, or whether or not this had even been tested, the claimed result would have had to be the natural consequence of taking a particular dose of doxycycline for a particular period of time and would rarely be impacted by the indication for which the drug was used.

I hereby declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. § 1001).

Executed on: _____

8/11/15



Michael Payette

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