

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Ashley, Robert	Examiner:	Susan Tran
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For:	Methods of Treating Acne		

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Response to May 14, 2012 Office Action

Sir:

In Response to May 14, 2012 Office Action, Applicant respectfully requests the instant Amendment be entered.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

Dr. Reddy's Laboratories, Ltd., et al. v. Galderma Laboratories, Inc. IPR2015-_____ Exhibit 1070

Listing of the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

Claims 1-20 (Cancelled).

21. (Previously Presented) 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; and
 - (iii) results in no reduction of skin microflora during a six-month treatment, without administering a bisphosphonate compound.
22. (Previously Presented) The method according to Claim 21, wherein said doxycycline is doxycycline monohydrate.
23. (Previously Presented) The method according to Claim 22, wherein said doxycycline monohydrate is administered in an amount of 40 milligrams.
24. (Previously Presented) The method according to Claim 23, wherein said doxycycline monohydrate is administered by sustained release.
25. (Previously Presented) A method according to Claim 24, wherein said doxycycline monohydrate is administered once a day.
26. (Previously Presented) The method according to Claim 22, wherein said doxycycline monohydrate is administered in a dose of 20 mg twice a day.

27. (Previously Presented) The method according to Claim 21, wherein said doxycycline, or a pharmaceutically acceptable salt thereof, is administered in an amount which provides a serum concentration in the range of about 0.1 to about 0.8 µg/ml.

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

29. (Previously Presented) The method according to Claim 28, wherein said doxycycline is doxycycline monohydrate.

30. (Previously Presented) The method according to Claim 29, wherein said doxycycline monohydrate is administered in an amount of 40 milligrams.

31. (Previously Presented) The method according to Claim 30, wherein said doxycycline monohydrate is administered by sustained release.

32. (Previously Presented) A method according to Claim 31, wherein said doxycycline monohydrate is administered once a day.

33. (Previously Presented) The method according to Claim 29, wherein said doxycycline monohydrate is administered in a dose of 20 mg twice a day.

34. (Previously Presented) The method according to Claim 28, wherein said doxycycline, or a pharmaceutically acceptable salt thereof, is administered in an amount which provides a serum concentration in the range of about 0.1 to about 0.8 µg/ml.

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

36. (Previously Presented) The method according to Claim 35, wherein said doxycycline is doxycycline monohydrate.

37. (Previously Presented) The method according to Claim 36, wherein said doxycycline monohydrate is administered by sustained release.

38. (Previously Presented) A method according to Claim 37, wherein said doxycycline monohydrate is administered once a day.

39. (Previously Presented) The method according to Claim 36, wherein said doxycycline monohydrate is administered in a dose of 20 mg twice a day.

40. (Previously Presented) The method according to Claim 35, wherein said doxycycline, or a pharmaceutically acceptable salt thereof, is administered in an amount which provides a serum concentration in the range of about 0.1 to about 0.8 µg/ml.

REMARKS

Claims 1-20 were previously cancelled. Claims 21-40 were previously added. Thus, Claims 21-40 are pending.

The Claimed Invention

Pending Claims 21, 28 and 35 are independent. These claims recite a method for treating papules and pustules of rosacea by oral administration of doxycycline (or a salt thereof). Papules and pustules occur on skin in facial rosacea. The dose is expressed differently in each independent claim. The dose recited in Claim 21 is 10-80% of a 50 mg dose of doxycycline. The dose recited in Claim 28 is 40-80% of a 50 mg dose of doxycycline. The dose recited in Claim 35 is 40 mg. The claims recite that all these doses result in no reduction of skin microflora during a six-month treatment

Applicant takes this opportunity to elaborate on the disease of rosacea. There are four sub-types of rosacea. Rosacea patients can have any one, or occasionally more than one, of these sub-types. One sub-type affects the eyes and is called ocular rosacea. Another sub-type is characterized by papules and pustules, and is called herein facial rosacea.¹ Ocular rosacea and facial rosacea are distinct medical conditions.²

¹ The National Rosacea Society assembled a committee to develop a standard classification system of rosacea. Their report, authored by Wilkin et al., appeared in J. Am. Acad. Dermatol. 46, 584-587 (2002), and is attached as Exhibit A. This authoritative report identified four specific sub-types of rosacea. Subtype 2 is called "papulopustular rosacea," and is characterized by transient papules and/or pustules. Subtype 4 is called "ocular rosacea," and is characterized by ocular manifestations.

² (a) In addition to evidence provided in footnote 1, facial rosacea and ocular rosacea are treated by physicians in different specialties with different Board certifications, *i.e.*, dermatologists and ophthalmologists, respectively.

(b) Moreover, the agency that approves drugs in the United States, namely the Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration, evaluates drugs for facial rosacea and ocular rosacea in different divisions. Facial rosacea is evaluated in the Division of Dermatologic and Dental Products. Ocular rosacea is evaluated in the Division of Anti-Infection and Ophthalmologic Products. For the examiner's convenience, a 2006 chart of the organization of the CDER showing the separate divisions of Dermatologic and Dental Products and of Anti-Infection and Ophthalmologic Products is attached as Exhibit B.

In particular, papules and pustules are inflammatory lesions that occur only on **skin**. They do not occur in the eye. See, e.g., the following definitions from www.medterms.com.

"Papules: Small solid rounded bumps rising from the **skin** that are each usually less than 1 centimeter in diameter (less than 3/8 inch across). . . ."

"Pustule: A pustule is a small collection of pus in the top layer of **skin** (epidermis) or beneath it in the dermis. Pustules frequently form in sweat glands or hair follicles...."

See, also, www.nlm.nih.gov/medlineplus/encyclopedia.html.

"A papule is a **skin** lesion that is small, solid, and raised."

"Pustules are small, inflamed, pus-filled, blister-like lesions on the **skin** surface."

The definitions from the above websites are attached as Exhibit C.

Accordingly, it is clear that papules and pustules are features of facial rosacea, but not of ocular rosacea. Therefore, the claimed method, by its terms, requires the treatment of facial rosacea, but not of ocular rosacea. That is, there is no ocular component of rosacea in the pending claims since papules and pustules do not occur in the eye.

Obviousness Rejection under §103(a) in View of *Perricone* and *Pflugfelder*

The examiner rejects Claims 21, 23, 25-28, 30, 32-35 and 38-40 under §103(a) as allegedly being obvious over US 6,365,623 (hereinafter "*Perricone*") in view of US 6,455,583 (hereinafter "*Pflugfelder*"). (Office Action pages 2-3.)

In particular, the examiner alleges that *Perricone* teaches the treatment of pustules and papules with oral administration of an antibiotic compound. The examiner concedes that *Perricone* does **not** teach a specific amount of an antibiotic compound, does **not** teach doxycycline, and does **not** teach rosacea. In an attempt to overcome the deficiencies in *Perricone*, the examiner cites *Pflugfelder* for teaching "a method for treating conditions associated with rosacea... [comprising] orally administering a tetracycline compound in a sub-antimicrobial amount..."

The examiner alleges that it would have been obvious “to optimize the method of *Perricone* to administer antibiotic compound in a sub-antimicrobial amount in view of the teachings of *Pflugfelder*.” Applicant respectfully disagrees with the examiner’s analysis, as discussed below.

***Perricone* teaches treatment of skin with lipoic acid and antibiotics**

Perricone teaches that lipoic acid can be topically applied to the faces of persons with acne (col. 8, lines 6-10). In some embodiments, lipoic acid may be used “in combination with” antibiotic tetracycline to treat papules and pustules of acne (col. 8, lines 24-30).

As the examiner indicates, *Perricone* does not teach an exact amount of antibiotic tetracycline to be administered. However, *Perricone* does specifically instruct that an antibiotic amount be used in its treatment. In particular, *Perricone* states:

Lipoic acid may be added to an antibiotic preparation, or applied before, during, or after antibiotic treatment...[A]n advantage of using lipoic acid with antibiotics in cases where they might be efficacious is that a lower antibiotic dose or a shorter antibiotic regimen may be employed. (See col. 8, lines 27-32.) (Emphasis added.)

Perricone mentions the potential adverse effects of the use of antibiotic compounds, including tetracycline, clindamycin and erythromycin, and states that it may be advantageous to minimize antibiotic doses. However, *Perricone* does not state that any dose but an antibiotic dose is effective in treating acne. The method of *Perricone* requires an antibiotic dose. A minimum antibiotic dose is still an antibiotic dose.

To elaborate, as would be known to a skilled artisan, at a certain threshold dose, tetracycline exhibits antibiotic properties. Depending on various factors, including the severity of an ailment, a physician may prescribe tetracycline at a dose that is well above the antibiotic threshold dose, at a minimum antibiotic dose, or at a dose somewhere in between such doses. (For example, Exhibit H, attached, is a page from the www.pdrhealth.com showing that tetracycline is commonly prescribed from a dose of 1 to 2 grams per day.) Nonetheless, above a threshold dose, tetracycline will be an antibiotic dose.

In summary, *Perricone* teaches treating facial acne with the topical application of lipoic acid in combination with the oral administration of an antibiotic dose of tetracycline. Thus, there is no suggestion of treating acne (let alone treating the papules and pustules of rosacea) with a dose other than the commonly prescribed antibiotic dose of any tetracycline compound (let alone doxycycline). The method of *Perricone* requires an antibiotic dose.

In an attempt to overcome the deficiencies in *Perricone*, the examiner cites *Pflugfelder*. However, as discussed below, *Pflugfelder* cannot be properly combined with *Perricone* in a way that leads to the presently claimed method.

Pflugfelder teaches treatment of the eye for a disease of the eye

The examiner states that *Pflugfelder* teaches “a method for treating conditions *associated with* rosacea.” The condition that *Pflugfelder* teaches treating is an eye condition, i.e., meibomian gland disease. See the title and column 2, line 21 *et seq.*

According to *Pflugfelder*, meibomian gland disease is a “tear film and ocular surface disorder.” Symptoms include “blurred or filmy vision, burning or foreign body sensations in the eye, photophobia, and pain” and patients’ “meibomian glands can atrophy.” (See col. 1, lines 8-10 and 19-23.)

The treatment of a patient having meibomian gland disease is described in *Pflugfelder* as follows:

According to the subject invention, treatment of a patient having meibomian gland disease includes reducing or reversing irritation symptoms, delayed tear clearance, recurrent corneal epithelial erosion or aqueous tear deficiency. (Col. 3, lines 39-42.)

All of these manifestations of meibomian gland disease relate to the eye. That is, meibomian gland disease is an ailment that solely affects the eye. Accordingly, a person having ordinary skill in the art would understand *Pflugfelder* as disclosing the use of tetracyclines to treat the eye.

There is no disclosure or suggestion in *Pflugfelder* of treating any condition or symptom outside of the eye. There is no disclosure of treating any facial condition in *Pflugfelder*, let alone treating the papules and pustules of facial rosacea.

It is true, as noted by the examiner, that *Pflugfelder* discloses an *association* between meibomian gland disease and rosacea. There is, however, no discussion in *Pflugfelder* of the nature of the association. Moreover, the alleged “association” between meibomian gland disease and rosacea does not suggest a treatment for rosacea. Meibomian gland disease is **not** rosacea, and certainly not facial rosacea. Meibomian gland disease is a distinct clinical disorder.

Further, whenever *Pflugfelder* mentions rosacea, the focus is exclusively on meibomian gland which are, anatomically and functionally, organs of the eye.³ A skilled artisan would clearly understand, therefore, that the rosacea with which *Pflugfelder* reports

³ Meibomian glands are sebaceous glands that occur only on the rim of the eyelids, and are responsible for the supply to the eye of sebum, an oily substance that, *inter alia*, prevents evaporation of the eye's tear film. They do not appear anywhere in the body except on the rim of the eyelids, and have no function outside of the eye. A discussion and diagram showing the location of meibomian glands is shown on a page from Gray's Anatomy, which is attached as Exhibit D. (Emphasis added.)

meibomian gland disease is *somehow associated* is **ocular** rosacea. There is no suggestion that *Pflugfelder* contemplates treating facial rosacea.

The disclosures in *Pflugfelder* support this conclusion. For example, the phrase “meibomian gland disease associated with rosacea” is found twice in the “Detailed Description of the Invention” section of *Pflugfelder*. The first occurrence of the phrase is found in the paragraph bridging columns 3 and 4. There, a person having ordinary skill learns that the activity of gelatinase B “... is markedly increased in the tear fluid of patients with meibomian gland disease associated with rosacea,” and that the “... activity of gelatinase B appears to be inversely correlated with tear clearance.” A person having ordinary skill would conclude from these statements about the composition and clearance of tears that meibomian gland disease is associated with ocular rosacea.

In the next paragraph, *Pflugfelder* states explicitly that the rosacea contemplated is **ocular** rosacea. See column 4, lines 5-10, especially line 9, where *Pflugfelder* refers to certain factors “that have been found to be strongly correlated with the development of **ocular** rosacea in our studies.” (Emphasis added.).

Pflugfelder again uses the phrase “meibomian gland disease associated with rosacea” in the Detailed Description of the Invention section at column 4, line 17 *et seq.* There, *Pflugfelder* discloses treating meibomian gland disease associated with rosacea by topical administration of a tetracycline analogue in an ointment or in solution (e.g., “eye drops”). See column 4, line 17. A person having ordinary skill would understand a topical treatment of the eye as being for ocular symptoms.

That the phrase “meibomian gland disease associated with rosacea” refers to **ocular** rosacea is confirmed by the use of the same phrase in example 5 at column 8, line 55 *et seq.* of *Pflugfelder*. Example 5 discloses the treatment of eleven patients with “meibomian gland disease associated with rosacea.” The treatment included “... topical administration to the ocular surface or the eyelids” of oxytetracycline. See column 8, line 64. Table 2 at the top of

column 9 summarizes the results of the experiment in example 5 of *Pflugfelder*. The title of table 2 is “Patients with **Ocular** Rosacea Treated with Oxytetracycline Ointment 1.” (Emphasis added.)

A person having ordinary skill would understand that treatment of meibomian gland disease by topical administration “to the ocular surface or the eyelids” means treating the eye. Clearly, such treatment will not affect papules and pustules of facial rosacea. The unexplained association between meibomian gland disease and ocular rosacea reported in *Pflugfelder* is, therefore, not relevant to the teachings of *Perricone* which are directed to treating **facial** acne.

No reason to combine *Perricone* and *Pflugfelder*

The examiner summarizes the obviousness rejection over *Perricone* in view of *Pflugfelder* as follows:

[I]t would have been obvious to one of ordinary skill in the art... to optimize the method of *Perricone* to administer antibiotic compound in a sub-antimicrobial amount in view of the teaching of *Pflugfelder*. (See the sentence bridging pages 2 and 3 of the Office Action.)

The examiner proposes three reasons for combining the disclosure relating to treating facial acne in *Perricone* with the disclosure relating to treating meibomian gland disease in *Pflugfelder*. These reasons do not justify the combination.

As a first reason, the examiner alleges, “*Pflugfelder* teaches the use of an antibiotic compound for the treatment of rosacea related conditions known in the art.” (See the paragraph bridging pages 2 and 3 of the Office Action.)

However, as explained in detail above, *Pflugfelder* simply teaches treating an **ocular disorder**. There is no suggestion whatsoever in *Pflugfelder* to treat a skin condition. Whereas, *Perricone* simply teaches treatment of a **facial skin condition**. 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 much too unpredictable for such conjecture. Thus, a skilled artisan would have no reason to combine the two references.

As the second reason for combining the disclosures, the examiner states that *Pflugfelder* teaches that “long term administration of antibiotic compound in a sub-antimicrobial amount will minimize adverse side effects...” As the third reason, the examiner states that *Perricone* “teaches the desirability for administering antibiotic compounds in a lower dosage amount to eliminate adverse side effects...”

Applicant respectfully asserts that *Pflugfelder*’s teaching that a sub-antibiotic dose of a tetracycline compound is useful to treat ocular disorders is irrelevant to the method of *Perricone*. It is irrelevant for at least three reasons:

- i) *Perricone* teaches treating a different ailment than *Pflugfelder* (i.e., facial acne vis-à-vis meibomian gland disease);
- ii) *Perricone* teaches treating a different organ of the body than *Pflugfelder* (i.e., skin vis-à-vis the eye); and
- iii) *Perricone* specifically indicates that an antibiotic dose is necessary to treat facial skin acne.

Accordingly, although a skilled artisan may believe that a sub-antibiotic dose of tetracycline may lead to fewer side effects, the skilled artisan would have no reason to believe that such sub-antibiotic dose would be effective in the method of *Perricone* (let alone “optimize” treatment).

In summary, a skilled artisan would not combine a reference directed to treating facial acne with an antibiotic dose of tetracycline with a reference directed to treating an ocular disorder with sub-antibiotic doses. Accordingly, withdrawal of the obviousness rejection is respectfully requested.

Obviousness Rejection under §103(a) in View of Perricone, Pflugfelder and Sheth

The examiner rejects Claims 24, 25, 31, 32, 37 and 38 under §103(a) as allegedly being obvious over *Perricone*, *Pflugfelder*, and US 5,300,304 (hereinafter “*Sheth*”). (Office Action page 3.) These dependent claims recite sustained release of doxycycline and/or release over a 24 hour period. The examiner cites *Sheth* for allegedly teaching a once a day sustained release dosage of a tetracycline compound for treating acne.

Since the rejected dependent claims have a narrower scope than the independent claims, the dependent claims are patentable for at least the same reasons as the independent claims are patentable, as discussed above.

Obviousness Rejection under §103(a) in View of Perricone, Pflugfelder and Heesch

The examiner rejects Claims 22, 29 and 36 under §103(a) as allegedly being obvious over *Perricone*, *Pflugfelder*, and U.S. Patent Application Publication No. 2002/0165220 (hereinafter “*Heesch*”). (Office Action page 4.) These dependent claims recite a doxycycline monohydrate. The examiner cites *Heesch* for allegedly teaching that doxycycline hyclate has advantages over doxycycline (para. [0093] of *Heesch*).

Since the rejected dependent claims have a narrower scope than the independent claims, the dependent claims are patentable for at least the same reasons as the independent claims are patentable, as discussed above.

Secondary Considerations Further Support Patentability of the Present Claims

Applicant believes that the present claims are not *prima facie* obvious over the cited prior art alone or in combination for all the reasons above. Even if, for argument's sake, a proper *prima facie* obviousness rejection had been made out, it would be clearly rebutted by secondary considerations.

The use of antibiotic amounts of tetracyclines in treating rosacea has been known for more than sixteen years before the priority date asserted by the present application

The use of antibiotic amounts of tetracyclines in treating rosacea has been known since as early as the 1984 publication of Wong *et al.*, *J. Amer. Acad. Derm.* 11:1076-1081⁴ (hereinafter "*Wong*") (provided in the February 1, 2012 Information Disclosure Statement). The present application asserts a publication date of April 5, 2001. As mentioned above, the prior art does not disclose the method of administering a dose less than the commonly prescribed antibiotic dose of a tetracycline compound for treating acne in general, and acne rosacea in particular.

The previous assignee of the present application, CollaGenex Pharmaceuticals, Inc., launched the first tetracycline drug for rosacea designed to have a dose less than the commonly prescribed antibiotic dose of doxycycline in July of 2006. The drug, which is called Oracea®, is a 40 mg controlled release dose of doxycycline administered once a day, and is covered by the present claims.

It is significant that no one suggested such a drug in the prior art for more than sixteen years before applicant's priority application. It is also significant that no one developed such a drug for more than 21 years before CollaGenex launched Oracea®.

⁴ The use of antibiotic amounts of tetracyclines in treating rosacea has, in fact, been known much longer.

If it had been obvious to treat rosacea with a dose less than the commonly prescribed antibiotic dose of a tetracycline compound, surely someone would have done so in the more than 21 years between the publication of *Wong* and the launching of Oracea®. At least, someone would have suggested doing so in the sixteen years between the December 1984 publication date of *Wong* and the April 5, 2001 filing date of the priority date asserted by the present application. It is significant, therefore, that no one did.

Bikowski 2003

In addition, a physician, Joseph B. Bikowski, MD, published an article in 2003 entitled “Subantimicrobial Dose Doxycycline for Acne and Rosacea,” *SKINmed* 2, 234-245 (July-August 2003). The 2003 *Bikowski* article is attached as Exhibit E.

The article provides important evidence that, as of the April 5, 2001 priority date of the present application, the use of a dose less than the commonly prescribed antibiotic dose of a tetracycline for acne and rosacea was not known. Applicant, as a matter of full disclosure, informs the examiner that Dr. Bikowski was a consultant to the previous assignee, CollaGenex Pharmaceuticals, Inc.

The article begins by discussing the pathogenesis of acne and rosacea, and the therapies commonly used to treat these conditions. With regard to the mechanism of action of antimicrobials in acne, Dr. Bikowski states the following:

The multifactorial nature of acne ideally requires an agent with a variety of mechanisms, exerting an effect not only on the bacteria but also on the inflammatory host response induced by the bacteria.

See page 235, column 2, second paragraph (the page numbers are embedded in the text of the publisher’s notice at the lower right hand corner (odd-numbers) or left hand corner (even numbers) of the pages).

Accordingly, the state of the art in 2003 was the same as it was before the April 1, 2001 priority date of the present application. In particular, the state of the art in 2003 was that tetracyclines were used for a combination of antibiotic and non-antibiotic effects.

Dr. Bikowski summarizes prior art studies that were designed to measure the efficacy of tetracyclines to treat acne in Tables I and II. In all cases, an antibiotic dose was used.

Prior art studies involving the use of tetracyclines to treat rosacea are summarized in Table III of the *Bikowski* article. For all cases in which the dose was revealed, an antibiotic dose was used.

Dr. Bikowski recognizes the problem of bacterial resistance that may arise during long term treatment with antibiotic compounds. He then speculates as follows:

The exploitation of the anti-inflammatory properties of certain antibiotics **might be** sufficient to elicit a meaningful clinical response, and the administration of SDs (sub-antibacterial doses) **may** provide effective therapy without the risk of soliciting alterations in microbial susceptibility (emphasis added). See page 236, column 2, the last full paragraph.

Dr. Bikowski further reports that the first double-blind, placebo-controlled, long-term clinical trial for the use of a sub-antibiotic dose of doxycycline in acne was conducted by Skidmore and reported in an article in 2003. He then reports his own clinical trial for sub-antibiotic doses of doxycycline in adult rosacea. He reports that the clinical efficacy with sub-antibiotic doxycycline was very similar to results seen with antibiotic doses of tetracyclines.

The speculation in *Bikowski* regarding possible future use of non-antibiotic doses of tetracyclines, and the reports of first clinical trials in 2003 is significant. The *Bikowski* article constitutes further confirmation that the state of the art even after, and certainly before, the present invention was to use tetracyclines for their combination of antibiotic and

non-antibiotic effects on acne rosacea at antibiotic doses. The first disclosure of the use of CMTs or of doses less than commonly prescribed antibiotic doses of tetracyclines to treat acne rosacea was in provisional U.S. patent application serial no. 60/281,916 filed April 5, 2001, the priority date of which is asserted in the present application.

Commercial success of Oracea® further establishes unobviousness of the present claims

Patentability of the present claims is further supported by the significant commercial success of Oracea® since its launch in July of 2006.

A graph that illustrates the increasing number of prescriptions of Oracea® sold to the public since its launch on July 14, 2006 until December 15, 2007, attached as Exhibit F. The graph shows that sales increased from none to nearly 6000 per week over this period.

The successful acceptance of Oracea® by the public is further demonstrated by an article in the August, 2006 edition of *Dermatology Times* by a staff correspondent, Rochelle Nataloni. The *Nataloni* article is attached as Exhibit G.

In the article, Ms. Nataloni quoted Dr. James Q. Del Rosso, Clinical Associate Professor in the Department of Dermatology, University of Nevada School of Medicine (and consultant to the previous assignee of the present application, CollaGenex Pharmaceuticals, Inc.). Dr. Del Rosso stated that the treatment of rosacea "...has taken **a giant step forward** with the Food and Drug Administration's recent approval of Oracea (emphasis added)." See column 1, paragraph 1 of the *Nataloni* article.

Dr. Del Rosso explained why Oracea® constitutes "a giant step forward," and highlighted the unique nature of Oracea, by further stating the following:

Oracea's availability provides a convenient, effective and safe oral therapy option that works through anti-inflammatory activity and does not produce any antibiotic effects. Oracea is the only oral formulation available that can make that claim....

All of the other oral therapies that are used to treat rosacea ..., such as tetracycline, minocycline and other doxycycline formulations exert an antibiotic effect, so it's possible for antibiotic resistance to develop while patients are on those therapies...

A statement in a respected dermatological publication in 2006 that a method in accordance with the present claims is the only non-antibiotic oral therapy for acne, and is a "giant step forward" constitutes powerful evidence that the present claims are patentable.

For all the reasons given above, this application is now believed to be in condition for allowance. Notice to that effect at the examiner's earliest convenience is respectfully requested. If the examiner has any questions concerning this application, it is requested that the examiner contact applicant's undersigned representative at the telephone number provided below.

Respectfully submitted,

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