IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GALDERMA LABORATORIES, L.P.; NESTLÉ SKIN HEALTH S.A.; and TCD ROYALTY SUB, LLC,	:	
Plaintiffs,	:	
v.	:	C.A. No. 16-207-LPS
	:	**PUBLIC VERSION**
AMNEAL PHARMACEUTICALS, LLC and AMNEAL PHARMACEUTICALS CO. (I) PVT. LTD.,	:	
Defendants.	:	

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OPINION

August 27, 2018
Wilmington, Delaware

STARK, U.S. District Judge:

In March 2016, Plaintiffs Galderma Laboratories, L.P. ("Galderma"), Nestlé Skin Health S.A. ("NSH"), and TCD Royalty Sub, LLC ("TCD" and, with Galderma and NSH, "Galderma" or "Plaintiffs") filed suit against Defendants Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals Co. (I) Pvt. Ltd. (collectively, "Amneal" or "Defendants") under the Hatch-Waxman Act, 35 U.S.C. § 271(e). (*See* D.I. 1) Defendants seek to bring to market a generic version of Plaintiffs' Oracea® Capsules, a once-daily 40 milligram ("mg") administration of doxycycline for the treatment of the papules and pustules of acne rosacea. (D.I. 1 at ¶ 10) Plaintiffs allege infringement of U.S. Patent Nos. 8,206,740 ("Chang '740 patent"); 8,394,405 ("Chang '405 patent"); 8,470,364 ("Chang '364 patent"); 7,749,532 ("Chang '532 patent") (collectively, the "Chang patents"); 7,211,267 ("Ashley '267 patent"); 7,232,572 ("Ashley '572 patent"); 8,603,506 ("Ashley '506 patent"); and 9,241,946 ("Ashley '946 patent") (collectively, the "Ashley patents"). (*See* D.I. 1) The Chang and Ashley patents are generally directed to low-dose doxycycline formulations for the treatment of the papules and pustules of acne rosacea.

In February 2018, the Court held a five-day bench trial. (*See* D.I. 256, 258, 260-62 ("Tr."); D.I. 257 ("Sealed Tr. A"); D.I. 259 ("Sealed Tr. B")) Thereafter, the parties submitted a joint Statement of Uncontested Facts ("SUF") (D.I. 215 Ex. 1), proposed findings of fact (D.I. 245, 247, 266, 273), and post-trial briefing (D.I. 244, 246, 264, 265).

Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire record in this case and the applicable law, the Court concludes that: (1) Amneal infringes claim 1 of the Chang '740 patent, claims 1 and 3 of the Chang '405 patent, and claims 1 and 2 of the Chang '364 patent; (2) Amneal does not infringe claim 1 of the Chang '532 patent; (3) Galderma

is collaterally estopped from asserting infringement of claim 30 of the Ashley '267 patent and claims 14, 15, 23, 24, and 26 of the Ashley '572 patent; (4) Amneal infringes claims 3, 4, 5, 15, and 16 of the Ashley '506 patent and claims 13, 14, 15, and 16 of the Ashley '946 patent; (5) claim 30 of the Ashley '267 patent, claims 14, 15, 23, 24, and 26 of the Ashley '572 patent, claims 3, 4, 5, 15, and 16 of the Ashley '506 patent, and claims 13, 14, 15, and 16 of the Ashley '946 patent are not invalid for lack of enablement or written description or for obviousness; (6) claim 30 of the Ashley '267 patent, claim 15 of the Ashley '506 patent, and claim 13 of the Ashley '946 patent are not invalid as anticipated; and (7) claim 30 of the Ashley '267 patent and claims 14, 15, 23, 24, and 26 of the Ashley '572 patent are not invalid for indefiniteness.

The Court's findings of fact and conclusions of law are set forth in detail below.

FINDINGS OF FACT

This section contains the Court's findings of fact for issues raised by the parties during trial. Certain findings of fact are also provided in connection with the Court's conclusions of law.

I. The Parties

1. Plaintiff Galderma Laboratories, L.P. ("Galderma") is a privately-held partnership registered in the state of Texas, having a principal place of business at 14501 North Freeway, Fort Worth, Texas 76177. (SUF ¶ 1)

2. Plaintiff Nestlé Skin Health S.A. ("NSH") is a "societe anonyme" organized and existing under the laws of Switzerland, having a principal place of business at Avenue Gratta Paille 2, 1018 Lausanne, Switzerland. (SUF ¶ 2)

3. Plaintiff TCD Royalty Sub LLC ("TCD") is a limited liability company organized

and existing under the laws of the State of Delaware, having a principal place of business at 222 Delaware Avenue, Suite 1200, Wilmington, DE 19801. (SUF ¶ 3)

4. Defendant Amneal Pharmaceuticals LLC ("Amneal Pharma") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 400 Crossing Boulevard, Bridgewater, NJ 08807. (SUF ¶ 4)

5. Defendant Amneal Pharmaceuticals Co. (I) Pvt. Ltd. ("Amneal India") is an Indian corporation and a wholly-owned subsidiary and agent of Amneal Pharma, having a principal place of business at 882/1-871, Near Hotel Kankavati, Village Rajoda, Taluka Bavla, District Ahmedabad-382220, Gujarat, India. (SUF ¶ 5)

II. Rosacea and Its Treatment

6. Rosacea, or "acne rosacea," is a chronic inflammatory skin disorder that can cause pimple-like bumps known as "papules and pustules," which appear mainly in the center of the face. (Webster Tr. at 44-45[1])

7. As of 2000-2001, rosacea was treated by oral administration of antibiotics at antibacterial dosages (typically 100-200 mg of doxycycline per day) and administration of topical gels and creams. (Webster Tr. at 45-46; Zhanel Tr. at 145)

8. Prior to the launch of Oracea®, tetracylines were the most common oral treatment for rosacea. (Webster Tr. at 60; Zhanel Tr. at 145, 279)

9. Long-term use of tetracycline antibiotics can lead to significant undesirable side effects. (Webster Tr. at 48-49; Zhanel Tr. at 146-47)

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[1]Trial testimony from unsealed portions of the trial is cited as "([Witness last name] Tr. at [page number])." Testimony from sealed portions of the trial is cited as "([Witness last name] Sealed Tr. [A or B] at [page number])."

III. Oracea®

10. Plaintiff Galderma holds New Drug Application ("NDA") No. 50-805 on Oracea® capsules ("Oracea®"), which was approved by the U.S. Food and Drug Administration ("FDA") on May 26, 2006. (SUF ¶ 57)

11. Plaintiff Galderma markets Oracea® in the United States. (SUF ¶ 58)

12. The active ingredient in Oracea® is doxycycline. (SUF ¶ 59)

13. Oracea® is a capsule dosage form for oral administration. (SUF ¶ 60)

14. Oracea® is an oral pharmaceutical composition of doxycycline indicated for once-daily use for the treatment of inflammatory lesions (papules and pustules) of rosacea in adult patients. (SUF ¶¶ 61-63)

15. Oracea® is a hard gelatin capsule filled with two types of doxycycline beads, 30 mg immediate-release ("IR") beads and 10 mg delayed-release ("DR") beads. (SUF ¶ 64)

16. Oracea®'s 10 mg doxycycline DR beads are coated with an enteric polymer. (SUF ¶ 65)

17. Oracea® contains one or more pharmaceutical excipients. (SUF ¶ 66)

18. Oracea® is approved by the FDA for the treatment of only the inflammatory lesions (papules and pustules) of rosacea in adult patients. (PTX-516 at GAL-ORACEA-0011389-90)

19. Oracea®, when administered once-daily, is administered in an amount that is effective to treat the papules and pustules of rosacea. (Webster Tr. at 51; PTX-516 at GAL-ORACEA-0011394)

20. Oracea®, when administered once-daily, will give steady state blood levels of

doxycycline of a minimum of 0.1 μg/ml and a maximum of 1.0 μg/ml. (Rudnic Sealed Tr. B at B-77-78; PTX-516 at GAL-ORACEA-0011393)

21. The low dose of doxycycline in Oracea® is not an amount that would be useful to treat infections, but, surprisingly, is effective in treating the papules and pustules of rosacea. (Webster Tr. at 61; PTX-240 at 0001-03)

IV. Amneal's ANDA Product

22. Amneal submitted Abbreviated New Drug Application ("ANDA") No. 203278 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act ("FFDCA") seeking FDA approval for the commercial manufacture, use, and sale of a generic version of Oracea® ("Amneal's ANDA product") before the expiration of the patents-in-suit. (SUF ¶ 70)

23. ANDA No. 203278 describes a manufacturing process for the production of Amneal's ANDA product. (SUF ¶ 71)

24. The active ingredient in Amneal's ANDA product is doxycycline monohydrate, an antibiotic tetracycline compound. (SUF ¶ 73)

25. Amneal represents that its ANDA product is bioequivalent to Oracea®. (SUF ¶ 75)

26. Amneal's ANDA product will contain the package insert approved by the FDA ("Amneal's Label"). (SUF ¶¶ 72, 78)

27. Amneal's ANDA product, when used in accordance with Amneal's Label, will be administered orally to humans in a dosage of one 40 mg capsule once-daily for the treatment of inflammatory lesions (papules and pustules) of rosacea. (SUF ¶¶ 74, 77; PTX-100 at Amneal-Doxy2016-00434868)

28. Amneal's ANDA product contains pharmaceutically acceptable excipients. (SUF ¶ 81)

29. Amneal's ANDA product does not contain a bisphosphonate compound, nor does Amneal's Label require or instruct patients and physicians that it be administered with a bisphosphonate compound. (PTX-100 at Amneal-Doxy2016-00434885-886)

30. Amneal's ANDA product is indicated "for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients." (PTX-100 at Amneal-Doxy2016-00434868) Amneal is not seeking any other indication and will not market its ANDA product for any other use. (Edwards Sealed Tr. B at B-55)

31. Amneal's ANDA Product, when administered once-daily, will be administered in an amount that provides a serum concentration in the range of about 0.1 to 0.8 μg/ml. (Webster Tr. at 67-68; PTX-100 at Amneal-Doxy2016-00434887)

V. The Patents-in-Suit

A. The Chang Patents

32. The Chang patents describe "pharmaceutical composition[s] of doxycycline that contain[] an immediate release (IR) component of the drug and a delayed release (DR) component of the drug, which are combined into one dosage unit for once-daily dosing." (*E.g.*, PTX-004 at 2:46-50)

i. The Chang '740 Patent

33. U.S. Patent Application No. 12/155,676, from which the Chang '740 patent issued, was filed on June 6, 2008. (SUF ¶ 30) The Chang '740 patent claims priority to U.S. Provisional Patent Application No. 60/460,963, filed on April 7, 2003, and U.S. Provisional

Patent Application No. 60/547,964, filed on February 26, 2004. (SUF ¶ 31) The Chang '740 patent issued on June 26, 2012, naming Richard Rong-Kun Chang, Arash Raoufinia, and Niraj Shah as inventors, and listing Supernus Pharmaceuticals, Inc. as assignee. (SUF ¶ 32) The Chang '740 patent is set to expire on December 24, 2025. (SUF ¶ 33) Plaintiff TCD is the current owner of the Chang '740 patent. (SUF ¶ 34)

34. Plaintiffs assert claim 1 of the Chang '740 patent against Defendants. The asserted claim is reproduced below:

> 1. An oral pharmaceutical composition of doxycycline, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 μg/m1 and a maximum of 1.0 μg/ml, the composition consisting of (i) an immediate release (IR) portion comprising 30 mg doxycycline; (ii) a delayed release (DR) portion comprising 10 mg doxycycline; and optionally, (iii) one or more pharmaceutically acceptable excipients.

(PTX-004 at 11:57-64)

ii. The Chang '405 Patent

35. U.S. Patent Application No. 12/926,932, from which the Chang '405 patent issued, was filed on December 17, 2010. (SUF ¶ 35) The Chang '405 patent claims priority to U.S. Provisional Patent Application No. 60/460,963, filed on April 7, 2003, and U.S. Provisional Patent Application No. 60/547,964, filed on February 26, 2004. (SUF ¶ 36) The Chang '405 patent issued on March 12, 2013, naming Richard Rong-Kun Chang, Arash Raoufinia, and Niraj Shah as inventors, and listing Supernus Pharmaceuticals, Inc. as assignee. (SUF ¶ 37) The Chang '405 patent is set to expire on April 7, 2024. (SUF ¶ 38) Plaintiff TCD is the current owner of the Chang '405 patent. (SUF ¶ 39)

36. Plaintiffs assert claims 1 and 3 of the Chang '405 patent against Defendants.

Claim 1 recites:

> 1. An oral pharmaceutical composition comprising about 40 mg total doxycycline, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 μg/m1 and a maximum of 1.0 μg/m1, wherein the composition consists of 70 to 80 percent of the doxycycline formulated as an immediate release (IR) formulation and 20 to 30 percent of the doxycycline formulated as a delayed release (DR) formulation.

(PTX-005 at 12:1-9)

37. Claim 3 depends from claim 2. Claim 2 recites: "The composition of claim 1, which at a once-daily dosage will give steady state blood levels of the doxycycline of between 0.3 μg/m1 to 0.8 μg/m1." (PTX-005 at 12:10-12) Claim 3 recites: "The composition of claim 2, which at a once-daily dosage will give blood levels of the doxycycline of between 0.3 μg/m1 to 0.8 μg/m1." (PTX-005 at 12:13-14)

iii. The Chang '364 Patent

38. U.S. Patent Application No. 12/926,933, from which the Chang '364 patent issued, was filed on December 17, 2010. (SUF ¶ 45) The Chang '364 patent claims priority to U.S. Provisional Patent Application No. 60/460,963, filed on April 7, 2003, and U.S. Provisional Patent Application No. 60/547,964, filed on February 26, 2004. (SUF ¶ 46) The Chang '364 patent issued on June 25, 2013, naming Richard Rong-Kun Chang, Arash Raoufinia, and Niraj Shah as inventors, and listing Supernus Pharmaceuticals, Inc. as assignee. (SUF ¶ 47) The Chang '364 patent is set to expire on April 7, 2024. (SUF ¶ 48) Plaintiff TCD is the current owner of the Chang '364 patent. (SUF ¶ 49)

39. Plaintiffs assert claims 1 and 2 against Defendants. The asserted claims are reproduced below:

> 1. An oral pharmaceutical composition consisting of (i) an immediate release formulation (IR) comprising about 30 mg doxycycline; a delayed release formulation (DR) comprising about 10 mg doxycycline; and optionally, (iii) one or more pharmaceutically acceptable excipients.
>
> 2. An oral pharmaceutical composition comprising doxycycline, which at a once-daily dosage will give blood levels of the doxycycline of a minimum of 0.1 μg/m1 and a maximum of 1.0 μg/m1, the composition consisting of (i) an immediate release formulation (IR) comprising about 30 mg doxycycline; as a delayed release formulation (DR) comprising about 10 mg doxycycline; and optionally, (iii) one or more pharmaceutically acceptable excipients.

(PTX-007 at 12:1-14)

iv. The Chang ’532 Patent

40. U.S. Patent Application No. 10/819,620, from which the Chang ’532 patent issued, was filed on April 7, 2004. (SUF ¶ 26) The Chang ’532 patent issued on July 6, 2010, naming Richard Rong-Kun Chang, Arash Raoufinia, and Niraj Shah as inventors, and listing Supernus Pharmaceuticals, Inc. as assignee. (SUF ¶ 27) The Chang ’532 patent is set to expire on December 19, 2027. (SUF ¶ 28) Plaintiff TCD is the current owner of the Chang ’532 patent. (SUF ¶ 29)

41. Plaintiffs assert claim 1 of the Chang ’532 patent against Defendants. The asserted claim is reproduced below:

> 1. An oral pharmaceutical composition of doxycycline, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 μg/m1 and a maximum of 1.0 μg/ml, the composition consisting of (i) an immediate release (IR) portion comprising a drug, wherein the drug consists of about 30 mg doxycycline; (ii) a delayed release (DR) portion comprising a drug, wherein the drug consists of about 10 mg doxycycline, in which the DR portion is in the form of pellets coated with at least

> one enteric polymer; and (iii) one or more pharmaceutically acceptable excipients.

(PTX-003 at 11:64-12:6)

B. The Ashley Patents

42. The asserted claims of the Ashley patents generally cover methods of treating acne or rosacea by oral administration of a low daily dose doxycycline. (Webster Tr. at 61; Elder Tr. at 366)

i. The Ashley '267 Patent

43. U.S. Patent Application No. 10/117,709, from which the Ashley '267 patent issued, was filed on April 5, 2002. (SUF ¶ 6) The Ashley '267 patent claims priority to U.S. Provisional Patent Application No. 60/281,916, filed on April 5, 2001, and U.S. Provisional Patent Application No. 60/325,489, filed on September 26, 2001. (SUF ¶ 7) The Ashley '267 patent issued on May 1, 2007, naming Robert A. Ashley as inventor, and listing CollaGenex Pharmaceuticals, Inc. ("CollaGenex") as assignee. (SUF ¶ 8) The Ashley '267 patent is set to expire on April 5, 2022. (SUF ¶ 9) Plaintiff NSH is the current owner of the Ashley '267 patent. (SUF ¶ 10)

44. Plaintiffs assert claim 30 of the Ashley '267 patent against Defendants. The asserted claim is reproduced below:

> 30. A method according to claim 26, wherein the subantibacterial amount is an amount that results in no reduction of skin microflora during a six-month treatment.

(PTX-001 at 34:51-52)

ii. The Ashley ’572 Patent

45. U.S. Patent Application No. 11/061,866, from which the Ashley ’572 patent issued, was filed on February 18, 2005. (SUF ¶ 11) The Ashley ’572 patent claims priority to U.S. Provisional Patent Application No. 60/281,916, filed on April 5, 2001, and U.S. Provisional Patent Application No. 60/325,489, filed on September 26, 2001. (SUF ¶ 12) The Ashley ’572 patent issued on June 19, 2007, naming Robert A. Ashley as inventor, and listing CollaGenex Pharmaceuticals, Inc. as assignee. (SUF ¶ 13) The Ashley ’572 patent is set to expire on April 5, 2022. (SUF ¶ 14) Plaintiff NSH is the current owner of the Ashley ’572 patent. (SUF ¶ 15)

46. Plaintiffs assert claims 14, 15, 23, 24, and 26 of the Ashley ’572 patent against Defendants. The asserted claims depend indirectly from claim 1. Claim 1 recites:

> 1. A method for treating papules and pustules of rosacea in a human in need thereof comprising administering orally to said human a tetracycline compound, or a pharmaceutically acceptable salt thereof, in an amount that is effective to treat the papules and pustules of rosacea, but has substantially no antibiotic activity, said amount being 10-80% of the antibiotic amount, wherein the tetracycline compound is an antibiotic tetracycline compound or a pharmaceutically acceptable salt thereof administered in an amount that results in no reduction of skin microflora during a six-month treatment, without administering a bisphosphonate compound.

(PTX-002 at 32:22-34)

47. Claim 14 depends from 12, as does claim 15 indirectly. Claim 12 recites: “A method according to claim 1, wherein said tetracycline compound is doxycycline or a pharmaceutically acceptable salt thereof.” (PTX-002 at 33:5-7) Claims 14 and 15 recite:

> 14. A method according to claim 12, wherein said doxycycline or pharmaceutically acceptable salt thereof is administered in an amount of 40 milligrams.

> 15. A method according to claim 14, wherein said doxycycline or pharmaceutically acceptable salt thereof is administered by sustained release.

(PTX-002 at 33:10-15)

48. Claims 23 and 24 depend from claim 20. Claim 20 recites:

> 20. A method for treating papules and pustules of rosacea in a human in need thereof comprising administering orally to said human a hydrate of doxycycline in an amount that is effective to treat the papules and pustules of rosacea, but has substantially no antibiotic activity, said amount being 10-80% of the antibiotic amount, wherein the hydrate of doxycycline is administered in an amount that results in no reduction of skin microflora during a six-month treatment, said method not comprising administering a bisphosphonate compound.

(PTX-008 at 34:1-11)

49. Claims 23, 24, and 26 are reproduced below:

> 23. A method according to claim 20, wherein said hydrate of doxycycline is administered in an amount of 40 milligrams.
>
> 24. A method according to claim 20, wherein said hydrate of doxycycline is administered by sustained release.
>
> 26. A method according to claim 23, wherein said hydrate of doxycycline is administered once a day.

(PTX-002 at 34:18-27)

iii. The Ashley '506 patent

50. U.S. Patent Application No. 13/277,789, from which the Ashley '506 patent issued, was filed on October 20, 2011. (SUF ¶ 16) The Ashley '506 patent claims priority to U.S. Provisional Patent Application No. 60/281,916, filed on April 5, 2001, and U.S. Provisional Patent Application No. 60/325,489, filed on September 26, 2001. (SUF ¶ 17) The Ashley '506

patent issued on October 20, 2011, naming Robert A. Ashley as inventor, and listing Galderma Laboratories, Inc. as assignee. (SUF ¶ 18) The Ashley '506 patent is set to expire on April 5, 2022. (SUF ¶ 19) Plaintiff NSH is the current owner of the Ashley '506 patent. (SUF ¶ 20)

51. Plaintiffs assert claims 3, 4, 5, 15, and 16 of the Ashley '506 patent against Defendants. Claims 3, 4, and 5 depend indirectly from claim 1. Claim 1 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 (iii) results in no reduction of skin microflora during a six-month treatment, without administering a bisphosphonate compound.

(PTX-008 at 31:61-32:3)

52. Claim 3 depends from claim 2, as do claims 4 and 5 indirectly. Claim 2 recites: "The method according to claim 1, wherein said doxycycline is doxycycline monohydrate." (PTX-008 at 32:4-5) Claims 3, 4, and 5 are reproduced below:

> 3. The method according to claim 2, wherein said doxycycline monohydrate is administered in an amount of 40 milligrams.
>
> 4. The method according to claim 3, wherein said doxycycline monohydrate is administered by sustained release.
>
> 5. A method according to claim 4, wherein said doxycycline monohydrate is administered once a day.

(PTX-008 at 32:6-12)

53. Claim 16 depends from claim 15. Claims 15 and 16 are reproduced below:

> 15. A method for treating papules and pustules of rosacea in a human in need thereof, the method comprising administering orally to said human doxycycline, or a pharmaceutically acceptable salt

> thereof, in an amount of 40 mg per day, wherein the amount results in no reduction of skin microflora during a six-month treatment, without administering a bisphosphonate compound.
>
> 16. The method according to claim 15, wherein said doxycycline is doxycycline monohydrate.

(PTX-008 at 32:46-54)

iv. The Ashley '946 Patent

54. U.S. Patent Application No. 14/753,544, from which the Ashley '946 patent issued, was filed on June 29, 2015. (SUF ¶ 21) The Ashley '946 patent claims priority to U.S. Provisional Patent Application No. 60/281,916, filed on April 5, 2001, and U.S. Provisional Patent Application No. 60/325,489, filed on September 26, 2001. (SUF ¶ 22) The Ashley '946 patent issued on January 26, 2016, naming Robert A. Ashley as inventor, and listing Galderma Laboratories, Inc. as assignee. (SUF ¶ 23) The Ashley '946 patent is set to expire on April 5, 2022. (SUF ¶ 24) Plaintiff NSH is the current owner of the Ashley '946 patent. (SUF ¶ 25)

55. Plaintiffs assert claims 13, 14, 15, and 16 of the Ashley '946 patent against Defendants. The asserted claims are reproduced below:

> 13. A method for treating acne in a human in need thereof, the method comprising administering orally to said human doxycycline, or a pharmaceutically acceptable salt thereof, in an amount of 40 mg per day, wherein the amount results in no reduction of skin microflora during a six-month treatment, without administering a bisphosphonate compound, 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.
>
> 14. The method according to claim 13, wherein said doxycycline is doxycycline monohydrate.
>
> 15. The method according to claim 14, wherein said

doxycycline monohydrate is administered by sustained release.

16. A method according to claim 15, wherein said doxycycline monohydrate is administered once a day.

(PTX-010 at 32:51-67)

VI. Witnesses

A. Fact Witnesses

56. Dr. Lawrence Feldman testified by deposition. Dr. Feldman is a physician who specializes in dermatology, including the treatment of patients with rosacea. (Feldman Tr. at 376-80)

57. Mr. Robert Ashley testified by deposition. Mr. Ashley is a named inventor of the Ashley patents. (Ashley Tr. at 653)

58. Mr. Richard Rong-Kun Chang testified by deposition. Mr. Chang is a named inventor of the Chang patents. (Chang Tr. at 686)

59. Dr. Robert Skidmore testified by deposition. Dr. Skidmore is the lead author of the paper Robert Skidmore, *Effects of Subantimicrobial-Dose Doxycycline in the Treatment of Moderate Acne*, 139 Archives Dermatology 459 (2003). (PTX-288) ("*Skidmore*")

60. Mr. Jatin Gajjar testified by deposition. Mr. Gajjar is the Executive Vice President and head of Indian research and development at Amneal. (Gajjar Sealed Tr. A at A-22)

61. Ms. Candis Edwards testified by deposition. Ms. Edwards is the Senior Vice President of Regulatory Affairs at Amneal and is responsible for Amneal's NDA submissions, labeling, and bioequivalence. (Edwards Sealed Tr. B at B-48, B-50)

B. Galderma's Experts

62. Dr. Guy Webster, one of Plaintiffs' experts on infringement of the Ashley patents, received a bachelor's degree, Ph.D. degree, and M.D. degree from the University of Pennsylvania and completed his dermatology training at New York University. (Webster Tr. at 40, 44) Dr. Webster is a practicing dermatologist and member of the American Acne and Rosacea Foundation. (Webster Tr. at 41-42) Dr. Webster was recognized as an expert in clinical dermatology and microbiology associated with the skin. (Webster Tr. at 43)

63. Dr. George Zhanel, another of Plaintiffs' experts on infringement of the Ashley patents, received a Doctor of Clinical Pharmacy degree from the University of Minnesota and a Ph.D. degree in Medical Microbiology from the University of Manitoba in Winnipeg, Canada. (Zhanel Tr. at 138, 141-42) Dr. Zhanel is a professor of medical technology and infectious disease at the University of Manitoba and a research director of the Canadian Antimicrobial Resistance Alliance. (Zhanel Tr. at 137-38) Dr. Zhanel was recognized as an expert in clinical microbiology and antimicrobial stewardship in dermatology. (Zhanel Tr. at 141)

64. Dr. Edward Rudnic, Plaintiffs' expert on infringement of the Chang patents, received a bachelor's degree in Pharmacy, an M.A. degree in Science in Pharmaceutics, and a Ph.D. degree in Pharmaceutical Sciences from the University of Rhode Island. (Rudnic Tr. at 296, 302) Dr. Rudnic is the Chief Technology Officer at Dispersol Technologies and is an adjunct professor at the University of Maryland College of Pharmacy and University of Rhode Island College of Pharmacy. (Rudnic Tr. at 296, 299) Dr. Rudnic was recognized as an expert in the field of pharmaceutical formulation and drug development. (Rudnic Tr. at 302)

65. Dr. Henry Grabowski, Plaintiffs' expert on commercial success, received a

bachelor's degree from Lehigh University and M.A. and Ph.D. degrees in Economics from Princeton University. (Grabowski Tr. at 843, 845) Dr. Grabowski is the Director of the Duke University program in Pharmaceuticals and Health Economics. (Grabowski Tr. at 843) Dr. Grabowski was recognized as an expert in pharmaceutical industrial economics, including determining whether a pharmaceutical product has achieved commercial success. (Grabowski Tr. at 844)

C. Amneal's Experts

66. Dr. Edmund Elder, Amneal's expert on infringement of the Chang patents and validity of the Ashley patents, received a bachelor's degree in Pharmacy and a Ph.D. degree in Pharmaceutical Sciences from the Medical University of South Carolina. (Elder Tr. at 315, 318) Dr. Elder is the Director of the Zeeh Pharmaceutical Experiment Station at the University of Wisconsin-Madison. (Elder Tr. at 314) Dr. Elder was recognized as an expert in pharmaceutical drug development and formulations. (Elder Tr. at 317)

67. Dr. Barry Kreiswirth, one of Amneal's experts on infringement and validity of the Ashley patents, received a Ph.D. degree from New York University. (Kreiswirth Tr. at 458, 460) Dr. Kreiswirth is the director of the Public Health Research Institute affiliated with Rutgers University. (Kreiswirth Tr. at 457-58) Dr. Kreiswirth was recognized as an expert in clinical microbiology. (Kreiswirth Tr. at 460)

68. Dr. Monte Meltzer, another of Amneal's experts on infringement and validity of the Ashley patents,[2] received an M.D. degree from Georgetown University School of Medicine

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[2]At trial, the Court ruled that Dr. Meltzer was precluded from offering an opinion about whether Amneal's ANDA product infringes the Ashley patents. (*See* Tr. at 454, 577-80) Plaintiffs move to strike portions of Dr. Meltzer's testimony that, they contend, are inconsistent

and completed postgraduate training at Massachusetts General Hospital and a dermatology residency at Walter Reed Army Medical Center. (Meltzer Tr. at 572, 578-79, 599) Dr. Meltzer is the Director of Dermatology Services at the Union Memorial Hospital in Baltimore, MD and an Attending Physician in the Dermatology Residency Program at the University of Maryland Medical Center in Baltimore, MD. (Meltzer Tr. at 572) Dr. Meltzer was recognized as an expert in clinical dermatology. (Meltzer Tr. at 573)

VII. Person of Ordinary Skill in the Art

A. Chang Patents

69. A person of ordinary skill in the art ("POSA") in the field of the Chang patents as of 2002-2003 is someone with education and experience in drug delivery and formulation. Education and experience levels may vary, with some POSAs holding a bachelor's degree and having many years of experience and others holding higher degrees but having less work experience. A POSA would have knowledge and skill relating to the use, function, and formulation of pharmaceutical excipients; knowledge and training regarding the equipment, processes, and techniques used to analyze and test formulation materials; and an understanding of pharmacokinetic principles and how they relate to drug development. (Rudnic Tr. at 304)

B. Ashley Patents

70. A POSA in the field of the Ashley patents as of 2000-2001 is someone who holds an M.D. or Ph.D. in dermatology, microbiology, or a related discipline and has three to five years of research or clinical experience, or someone who holds a bachelor's degree in a field related to

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with the Court's ruling. (D.I. 244 at 11 n.3) The Court hereby grants Plaintiffs' motion to the extent it STRIKES the testimony at Meltzer Tr. at 584:1-18, 592:2-9, 592:17-21, 593:3-594:7.

pharmacy or pharmacology and has several years of practical experience relating to dermatologic or related conditions. (Webster Tr. at 63; Zhanel Tr. at 142-43; Elder Tr. at 327; Kreiswirth Tr. at 460-61; Meltzer Tr. at 573-74)

VIII. Facts Relating to Infringement of the Chang Patents

A. Prosecution History

71. The patent application that eventually issued as the Chang '532 patent was first filed as App. No. 10/819,620 (the "'620 application") on April 7, 2004, with 48 claims. (PTX-013.0001, .0028-32)

72. The applicant cancelled the original 48 claims and replaced them with newly-added claims 49-80 in a preliminary amendment. (PTX-013.380-85) New independent claim 49 read:

> (New) An oral pharmaceutical composition comprising a pharmaceutically effective amount of doxycycline, which at a once daily dosage will give steady state blood levels of doxycycline of a minimum of about 0.1 μg/ml and a maximum of about 1.0 μg/ml, the composition ***comprising*** an immediate release (IR) portion comprising about 30 mg doxycycline and a delayed release (DR) portion comprising about 10 mg doxycycline.

(PTX-013.0381) (emphasis added)

73. The Examiner issued a Non-Final Rejection, rejecting the claims as obvious in view of prior art that disclosed an oral antibiotic composition "comprised of at least two portions, including an immediate release portion and a delayed release portion" intended to be administered once-daily. (PTX-13.435)

74. The applicant then amended the claims, changing "comprising" to "consisting essentially of." (PTX-13.447)

75. The Examiner issued a Final Rejection of these claims, noting the phrase "consisting essentially of" did not fully overcome the obviousness rejection. (PTX-013.458-61)

76. The applicant again amended claim 49 to read:

> An oral pharmaceutical composition of doxycycline, which at a once daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 ug/ml and a maximum of 1.0 ug/ml, the composition ***consisting of*** (i) an immediate release (IR) portion comprising a drug, wherein the drug consists of about 30 mg doxycycline; (ii) a delayed release (DR) portion comprising a drug, wherein the drug consists of about 10 mg doxycycline, in which the DR portion is in the form of pellets coated with an least one enteric polymer; and (iii) one or more pharmaceutically acceptable excipients.

(PTX-013.0537) (emphasis added)

77. The Examiner accepted this claim language and issued the patent. (PTX-13.553-55)

78. When the Chang patents were later challenged in *inter partes* review ("IPR"), Dr. Rudnic opined that the DR portion of Chang results in "no substantial release of doxycycline in the acidic stomach environment." (DTX-241 ¶ 176)

B. Doctrine of Equivalents

1. Amneal's ANDA Product

79. Amneal represents that it believes its ANDA product is bioequivalent to Oracea®. (SUF ¶ 75)

80. Amneal's Label relies on the results of a pharmacokinetic study of Oracea®, which were reported in the Oracea® NDA and on its product labeling. (Rudnic Sealed Tr. B at B-74-75)

81. Amneal designed its ANDA product based on legal advice from attorneys. (Edwards Sealed Tr. B at B-49-50; Gajjar Sealed Tr. A at A-25-26)

82. Amneal's ANDA product is formulated to be administered orally. (SUF ¶ 74)

83. Amneal's ANDA product will be administered as a 40 mg dosage of doxycycline taken once-daily. (Rudnic Sealed Tr. B at B-59)

84. Amneal's ANDA product is [redacted] containing [redacted] (PTX-331 at Amneal-Doxy2016-00010320)

85. [redacted] are made by [redacted] (PTX-331 at Amneal-Doxy2016-00010402-403; Rudnic Sealed Tr. B at B-59-63; Gajjar Sealed Tr. A at A-22-24)

86. [redacted] of Amneal's ANDA product are manufactured using [redacted], resulting in [redacted]. (PTX-331 at Amneal-Doxy2016-00010392; Rudnic Sealed Tr. B at B-61-63)

87. [redacted] Amneal's [redacted] is designed so that, [redacted]. (PTX-331 at Amneal-Doxy2016-00010320;

Rudnic Sealed Tr. B at B-142)

88. [redacted]. (PTX-331 at Amneal-Doxy2016-00010404; Rudnic Sealed Tr. B at B-79-80; Elder Sealed Tr. B at B-184)

89. [redacted] of Amneal's ANDA product does not [redacted] (Rudnic Sealed Tr. B at B-79-80; Elder Sealed Tr. B at B-188; PTX-331 at Amneal-Doxy2016-00010392, -426)

90. [redacted] in Amneal's ANDA product is [redacted]. (SUF ¶ 79)

91. "Immediate release" does not mean that all of the drug is released instantaneously. (Rudnic Sealed Tr. B at B-107) Rather, an "immediate" release formulation can take 30 minutes to an hour or more to release. (Rudnic Sealed Tr. B at B-110-14)

2. Dissolution Data

92. Oracea®'s dissolution data shows that 30 mg of doxycycline is released in the first 30 minutes, followed by "no appreciable change" in the amount of doxycycline released until the two-hour mark. (Rudnic Sealed Tr. B at B-170-71) At the two-hour mark, the pH of the body environment in which the medicine is found switches to a buffer, and the 10 mg DR portion of Oracea® is released. (Elder Sealed Tr. B at B-195; Rudnic Sealed Tr. B at B-171; PTX-045 at Amneal-Doxy2016-00309561)

93. The *in vitro* dissolution data for Amneal's ANDA product shows that [redacted], Amneal's ANDA product releases [redacted]. (PTX-054 at Amneal-Doxy2016-00313476; Rudnic Sealed Tr. B at B-70-72, B-172 (agreeing Amneal's ANDA

product releases [redacted]); Elder Sealed Tr. B at B-194; Gajjar Sealed Tr. A at A-34) From [redacted], Amneal's ANDA product releases [redacted]. (Rudnic Sealed Tr. B at B-172; Elder Sealed Tr. B at B-195 (stating [redacted] is released from Amneal's product" [redacted])) By [redacted], Amneal's ANDA product releases [redacted]. (Rudnic Sealed Tr. B at B-172) At [redacted] the [redacted] of Amneal's product releases. (Elder Sealed Tr. B at B-195; Rudnic Sealed Tr. B at B-172-73)

94. The dissolution data measures the total release of doxycycline but does not indicate where the released doxycycline has come from within the dosage form. (Elder Sealed Tr. B at B-190)

95. Plaintiffs did not test [redacted] of Amneal's ANDA product to determine when release of the [redacted] occurred. (Rudnic Sealed Tr. B at B-171-72)

96. Amneal did not test [redacted] of its product's dissolution or provide scientific studies showing [redacted] of Amneal's [redacted] dissolves i[redacted]. (Elder Sealed Tr. B at B-214-15, B-227-28)

97. Amneal chose [redacted] for [redacted] because [redacted] (PTX-331 at Amneal-Doxy2016-00010400)

98. Amneal's ANDA describes quality controls for [redacted], preparation of [redacted], and [redacted]. (PTX-331 at Amneal-Doxy2016-00010553-556)

3. Sheth

99. In the IPRs, Dr. Rudnic submitted declarations in support of the nonobviousness of the challenged Chang patents over U.S. Patent No. 5,348,748 ("Sheth"), in combination with the Ashley '932 publication. (*E.g.*, DTX-241 at 84; DTX-0271)

100. The formulation disclosed in Sheth contains a "secondary loading portion" that is coated with "a blend of pH-sensitive polymer and water-soluble polymer." (Rudnic Sealed Tr. B at B-135; *see also* DTX-241 ¶ 172)

101. The Sheth formulation's water-soluble polymer can be HPMC, which is known as a "pore former." (DTX-241 ¶ 175; Elder Sealed Tr. B at B-186-87)

102. Dr. Rudnic argued during the IPRs that the HPMC coating of Sheth "immediately dissolve[d] to create 'pores' or 'channels' through which drug can slowly diffuse out in a slow, ***sustained release*** fashion beginning promptly after administration," while the DR portion claimed in the Chang patents "delayed release (*i.e.*, preventing release until a later time) to ***all*** of the drug contained in that portion." (DTX-241 ¶¶ 175, 181) (emphasis in original)

103. Dr. Rudnic also argued that the Sheth coating "was intentionally designed to be 'leaky' in the stomach," while "the Chang [patents] expressly state[] that for the 'DR portion' described and claimed therein, 'there is ***no substantial release*** of doxycycline in the acidic stomach environment . . . ." (DTX-241 ¶ 176) (emphasis in original)

104. Dr. Rudnic stated that the time it took for the HPMC to wet and dissolve to form pores before any drug could release was a "lag" but "would not be considered a 'delay.'" (DTX-271 at 13)

105. The Patent Trial and Appeal Board ("PTAB") found that the secondary loading

portion of Sheth was not a "delayed release" portion within the meaning of the Chang patents because it releases drug immediately following oral administration. (DTX-0232 at Amneal-Doxy2016-00437460-461)

106. The blended polymer film coat surrounding the secondary loading portion of Sheth is [redacted]. (Rudnic Sealed Tr. B at B-140)

107. The secondary loading portion of Sheth does not have another drug portion or any other layer on top of its blended polymer coating. (Rudnic Sealed Tr. B at B-91-92; Elder Sealed Tr. B at B-219-20) Thus, following oral administration, the polymer coating of Sheth is immediately subject to gastric fluid. (Rudnic Sealed Tr. B at B-91; Elder Sealed Tr. B at B-221-22)

4. The Chang '532 Patent

108. The Chang '532 patent has an additional limitation that the 10 mg DR portion be "in the form of pellets coated with at least one enteric polymer." (PTX-003 at 13:6-7)

109. The [redacted] in Amneal's ANDA product and [redacted] in Amneal's ANDA Product are [redacted] (Rudnic Sealed Tr. B at B-97; *see also* PTX-331 at Amneal-Doxy2016-00010320)

110. The Chang '532 patent defines "enteric materials" as "polymers that are substantially insoluble in the acidic environment of the stomach, but are predominantly soluble in intestinal fluids at specific pHs." (PTX-003 at 7:15-18) The Chang '532 specification also states that "[w]ith the enteric coated pellets, there is no substantial release of doxycycline in the acidic stomach environment of approximately below pH 4.5." (PTX-003 at 7:47-49)

111. The [redacted] of Amneal's ANDA product that is [redacted]. (Elder Sealed Tr. B at B-199)

112. Amneal's [redacted] releases [redacted]. (Elder Sealed Tr. B at B-204)

IX. Facts Relating to Infringement of the Ashley Patents

A. Collateral Estoppel

113. In *Research Foundation of State University New York v. Mylan Pharmaceuticals Inc.*, 809 F. Supp. 2d 296 (D. Del 2011) ("*Mylan*"), the Court determined that Mylan's ANDA product, a 40 mg once-daily dose of doxycycline, did not infringe the Ashley '267 or '572 patents ("Ashley I patents"). (DTX-201 at 22-27)

114. In *Galderma Laboratories Inc. v. Amneal Pharmaceuticals*, *LLC*, 921 F. Supp. 2d 278 (D. Del. 2012) ("*Amneal I*"), the Court held that Plaintiffs were collaterally estopped from asserting that Amneal's previous ANDA product infringed the Ashley I patents based on the Court's finding of non-infringement in *Mylan*.

115. Galderma expressly stated to the Court that the clarified claim constructions it sought (and obtained) in this case do not change the scope of the claims. (*See* D.I. 85 at 32, 33, 35)

B. Doctrine of Equivalents

116. In *Mylan*, the Court made a finding of fact that Oracea® and Mylan's ANDA product, both 40 mg once-daily dosages of doxycycline, were administered in an amount that results in no reduction of skin microflora during a six-month treatment. (DTX-201 ¶¶ 32, 77)

117. The Court was not asked, however, to construe or analyze infringement of the skin

microflora limitation in *Mylan*. (DTX-201 at 22-27)

118. Approximately 100,000,000,000 bacterial cells inhabit the human body. (Zhanel Tr. at 222)

119. Bacteria exist all over normal skin, and the types of bacteria on the skin can vary dramatically based on their location. (Zhanel Tr. at 22-23)

120. The sampling site one chooses to examine "is a major determinant of the microbial composition" one obtains. (Webster Tr. at 126; *see also* DTX-638 at 2)

121. Doxycycline is a potent and broad-spectrum antimicrobial agent, meaning it affects a large number of organisms. (Zhanel Tr. at 224)

122. When administered orally, doxycycline is absorbed into the bloodstream and travels wherever blood goes in the body, including all areas of the skin. (Zhanel Tr. at 224-25)

1. Amneal's ANDA Product

123. Amneal's ANDA Product is to be administered as a 40 mg capsule of doxycycline once-daily. (PTX-100 at Amneal-Doxy2016-00434868)

124. Amneal has not conducted its own clinical microbiology studies of its ANDA product, but instead relies on clinical microbiology studies submitted to the FDA in connection with the Oracea® NDA because Amneal has represented that its ANDA product is bioequivalent to Oracea® (in the fed and fasted states). (Zhanel Tr. at 158; Edwards Sealed Tr. B at B-49, B-51-52)

125. Amneal's Label states: "*In vivo* microbiological studies utilizing a similar drug exposure for up to 18 months demonstrated no detectable long term effects on bacterial flora of the oral cavity, skin, intestinal tract and vagina." (PTX-100 at Amneal-Doxy2016-00434890)

126. This statement was approved by the FDA for inclusion in the Oracea® Label following the FDA's review of, among others, *Skidmore*. (Zhanel Tr. at 177-78)

2. *Skidmore*/Example 38

127. The purpose of the *Skidmore* study, which was funded by CollaGenex, was to determine the effects of a six-month treatment of a 40 mg daily doxycycline dosage (20 mg twice-daily) on skin microflora. (PTX-288 at PTX-288 at GLD0083628, -630; Zhanel Tr. at 165) 128. Patients in the *Skidmore* study received either (1) 20 mg of doxycycline hyclate twice-daily or (2) placebo. (PTX-288 at GLD0083629)

129. Samples of the skin surface were taken by swabbing the glabella, an area on the center of the forehead between the brows, at baseline, two months, four months, and six months. (PTX-288 at GLD0083630; Webster Tr. at 121, 720; Zhanel Tr. at 168-69)

130. Each sample was measured to determine the total number of anaerobic and facultative bacteria, reported as total microbial colony counts. (PTX-288 at GLD0083630)

131. Figure 3 reports that there was no statistically significant difference in total microbial colony count for each target organism from baseline to six months. (PTX-288 at GLD008361-362; Zhanel Tr. at 165-66; Webster Tr. at 78-80)

132. Each sample was also measured to determine the total number of isolates resistant to at least 4 μg/ml doxycycline, as well as the minimum inhibitory concentration (MIC) values for those bacteria, identified by genus and species. (PTX-288 at GLD0083630; Zhanel Tr. at 173-75)

133. Four μg/ml is the clinical breakpoint for doxycycline. (Zhanel Tr. at 167) Organisms with a MIC less than 4 μg/ml are susceptible to doxycycline, while those with a MIC

more than 4 μg/ml are resistant to doxycycline. (Zhanel Tr. at 167)

134. Figure 3 reports that there was no increase in the number of bacteria resistant to 4 μg/ml, and there was no increase in MIC values for bacteria resistant to 4 μg/ml doxycycline. (DTX-288 at GLD008361-362; Zhanel Tr. at 167)

135. There were also no strong correlations between resistance to doxycycline and resistance to any of the other five antibiotics tested, and no difference between the correlation coefficients for cross-resistance in the doxycycline 6-month samples and either the placebo 6-month samples or the doxycycline baseline samples. (PTX-288 at GLD0083631-632; Zhanel Tr. at 167)

136. The findings of *Skidmore* demonstrate that 20 mg twice-daily doxycycline results in no change in the composition of the normal skin flora and does not result in the emergence of doxycycline-resistant organisms. (PTX-288 at GLD008361; Zhanel Tr. at 165-67; Webster Tr. at 78-80)

137. It is possible for an organism to have a MIC less than 4 μg/ml. (Zhanel Tr. at 269-70; Kreiswirth Tr. at 518-89) Testing at 4 μg/ml would not capture changes in resistance below 4 μg/ml. (Kreiswirth Tr. at 518-19)

138. The microbiology and clinical efficacy testing described in *Skidmore* is also described in Ashley Example 38. (*E.g.*, PTX-001 at 20:4-21:17)

139. Example 38 reports that a six-month treatment with a 40 mg daily dose of doxycycline (20 mg twice-daily) "resulted in no reduction of skin microflora . . . nor an increase in resistance counts when compared with placebo." (*E.g.*, PTX-001 at 21:7-9)

140. Example 38 does not specify on which part of the body sampling occurred but

specifies that subjects have "moderate facial acne." (*E.g.*, PTX-001 at 20:21)

141. Example 38 is the strongest intrinsic evidence of what the applicant intended to convey by the term "results in no reduction of skin microflora during a six-month treatment." (PTX-378 at 0007)

142. Amneal's Label relies on the results of *Skidmore*. (PTX-100 at Amneal-Doxy2016-00434890)

143. Sampling the sebaceous facial skin was the standard method as of 2001 for studying the effects on skin microflora of acne or rosacea drugs compared to placebo. (Webster Tr. at 80-82; Zhanel Tr. at 168-69)

144. Amneal's experts agreed that it would be "impractical" and "prohibitively expensive" to assay the entire skin surface to study the effects of doxycycline on skin microflora. (Meltzer Tr. at 620; Kreiswirth Tr. at 546)

145. Dr. Meltzer testified that sampling 20 regions of the body by swabbing, scraping, and performing punch biopsies would not be sufficient to prove there was no reduction in skin microflora. (Meltzer Tr. at 615-20)

146. Dr. Kreiswirth testified that it would be "reasonable" to sample at least three regions of the skin, but did not know how many samples would be needed to prove no reduction in skin microflora and did not know of any study conducted prior to 2001 utilizing the procedures he proposed. (Kreiswirth Tr. at 547-49)

147. Amneal has not presented any study contradicting the methodology or results of the *Skidmore* study. (Webster Tr. at 84, 121; Zhanel Tr. at 283; Kreiswirth Tr. at 536-37; Edwards Tr. at B-57-58)

148. Amneal has not presented any evidence that changing the sampling location of the *Skidmore* study would have led to different results or conclusions. (Webster Tr. at 121; Zhanel Tr. at 283)

3. Indirect Infringement

149. Amneal's Label instructs patients, and directs doctors to instruct patients, to take one 40 mg oral capsule of Amneal's ANDA product once-daily for the treatment of inflammatory lesions (papules and pustules) of rosacea. (*See* PTX-100 at Amneal-Doxy2016-00434868)

150. Amneal's ANDA product is indicated "for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients." (PTX-100 at Amneal-Doxy2016-00434868) Amneal is not seeking any other indication and will not market its ANDA product for any other use. (Edwards Sealed Tr. B at B-55)

X. Facts Relating to Validity of the Ashley Patents

A. Enablement and Written Description

151. The Ashley patents state that a patient's blood level should be above a therapeutic floor of 0.1 µg/ml and below a sub-antibiotic ceiling of 1.0 µg/ml. (*E.g.*, PTX-002 at 6:52-62)

152. The Ashley patents state that "[i]n an especially preferred embodiment, doxycycline hyclate is administered at a 20 milligram dose twice daily. Such a formulation is sold for the treatment of periodontal disease by CollaGenex Pharmaceuticals, Inc. of Newtown, Pa. under the trademark Periostat®." (*E.g.*, PTX-008 at 5:59-63)

153. The Periostat® Label and Periostat® Approval Package would allow a POSA to readily ascertain information about the single-dose and steady-state pharmacokinetic properties of Periostat® (including Cmax, Tmax, and half-life) in various modes of administration. (*See*

PTX-519 at Amneal-Doxy2016-00023434; PTX-518 at Amneal-Doxy2016-00290255, -281, -320, -334-47)

154. The Periostat® Approval Package would also tell a POSA that 40 mg IR doxycycline administered once-daily would achieve a maximum steady-state blood level of 0.834 μg/ml. (PTX-518 at Amneal-Doxy2016-00290343-347)

155. As of 2000-2001, a POSA would have known doxycycline absorbs primarily in the upper gastrointestinal ("GI") tract, and does not absorb well in the colon or lower GI tract. (*See* PTX-518; Rudnic Tr. at 780-81)

156. The Ashley patents disclose administration of 40 mg doxycycline by "sustained release," which the Ashley patents define as delivering drug "to achieve a certain level of the drug over a particular period of time." (*E.g.*, PTX-008 at 9:7-10)

157. The Ashley patents incorporate by reference the patent application, "Controlled Delivery of Tetracycline and Tetracycline Derivatives," filed on April 5, 2001, and assigned to CollaGenex (the "Ashley '854 application"). (*E.g.*, PTX-008 at 9:11-19)

158. The Ashley '854 application describes "methods of delivering tetracycline compounds by sustained release." (PTX-008 at 9:11-12)

159. The Ashley '854 application discloses a preferred embodiment of a controlled release composition where "the controlled-release composition is entrapped in the upper portion of the gastrointestinal tract, for example, in the stomach or duodenum." (DTX-206 at 16:9-14)

160. The Ashley '854 application explains such compositions are "typically manufactured by utilizing controlled-release agents of a larger particle size, as known in art," and "[i]t is preferred that at least 50%, more preferably greater than 80%, of the tetracycline in the

composition be released in the upper [gastrointestinal] tract." (DTX-206 at 16:11-14)

161. There were at least 19 patents and patent applications covering gastroretentive technologies as of 2001. (Rudnic Tr. at 785-86; PTX-125; PTX-126; PTX-197; PTX-198; PTX-199; PTX-200; PTX-201; PTX-202; PTX-203; PTX-204; PTX-205; PTX-206; PTX-207; PTX-208; PTX-209; PTX-210; PTX-211; PTX-212; PTX-215)

162. The literature as of 2000-2001 described the use of tetracyclines, including doxycycline, in gastroretentive technologies. (Rudnic Tr. at 790)

163. U.S. Patent No. 6,120,803 ("the '803 patent"), issued on September 19, 2000, disclosed a once-daily gastroretentive controlled release dosage "adapted to deliver in the stomach, as a single dose and over a prolonged time period," intended to sustain release for up to 24 hours. (Rudnic Tr. at 790; PTX-208 at 6-8) The '803 patent identified doxycycline as an "agent[] for which the invention is particularly useful." (PTX-208 at 19)

164. WO 00/38650 ("WO '650") was published on July 6, 2000. (Rudnic Tr. at 791; PTX-212) WO '650 detailed a formulation with a swellable layer "adapted to swell in the stomach to facilitate retention of the dosage form in the stomach over a prolonged period of time." (Rudnic Tr. at 791; PTX-212 at 8) WO '650 identified doxycycline as a specific compound for which the disclosed formulations could be used. (Rudnic Tr. at 791; PTX-212 at 42)

165. U.S. Patent No. 6,207,197 (the "'197 patent"), issued on March 27, 2001, described gastroretentive controlled release microspheres that release drug in the stomach for a prolonged period of time. (Rudnic Tr. at 791-92; PTX-209 at 4-5) The '197 patent described the microspheres as useful for once-daily dosing and identified doxycycline as a compound for

which the formulations could be used. (Rudnic Tr. at 791-92; PTX-209 at 9)

166. The ’803 patent, WO ’650 application, and ’197 patent were available to a POSA as of 2001. (Rudnic Tr. at 792; PTX-208; PTX-212; PTX-209)

167. Gastroretentive compositions, which swell and stay in the stomach, would have been known to a POSA as of 2000-2001. (Rudnic Tr. at 784)

168. The Ashley patents do not provide working examples of a once-daily or SR formulation. (Elder Tr. at 328)

169. The exact absorption window of doxycycline was not known as of 2001. (Elder Tr. at 333-34)

170. In the late 1990s, CollaGenex hired Faulding Pharmaceuticals to conduct a non-public study to determine doxycycline’s absorption window and create a once-daily 40 mg doxycycline product. (Elder Tr. at 335-36; DTX-565 at 1)

171. While Faulding was successful in discovering doxycycline’s absorption window, its attempts at formulating a once-daily doxycycline dosage were not successful. (Elder Tr. at 336-37; DTX-0565; DTX-201 at 21)

172. CollaGenex then hired Shire Laboratories to “conduct a feasibility study” of once-daily 40 mg doxycycline formulations. (Ashley Tr. at 672-73; DTX-593 at 1)

173. Shire developed and patented a once-daily 40 mg doxycycline formulation. (Chang Tr. at 686)

174. Dr. Chang testified that no once-daily doxycycline formulations existed before he developed one while working at Shire. (Chang Tr. at 686)

175. In *Mylan*, the Court found “CollaGenex had no meaningful idea what composition

might achieve a once-daily doxycycline product without antibiotic effect or if it was even possible to do so because CollaGenex lacked formulation expertise." (DTX-201 at 20)

176. In *Mylan*, the Court found that "[i]t was unexpected that a therapeutic, controlled-release, once-daily dosage form which provided steady state plasma concentrations of doxycycline of a minimum of 0.1 μg/ml and a maximum of 1.0 μg/ml could be achieved." (DTX-201 at 21)

177. While prosecuting the Chang patents, the applicant told the PTO that as of 2003, "the art did not provide guidance for a ***single*** immediate release pharmaceutical dosage form that would deliver 25 mg to 40 mg doxycycline and still achieve subantimicrobial effect." (PTX-17 at 285) (emphasis in original)

178. Dr. Rudnic opined during the Chang IPRs that a POSA would "view the combination of the Ashley [specification] and the Ashley '854 application as articulating a mere ***wish*** for a low-dose once-daily doxycycline formulation, without guidance on how to obtain one, or any demonstration that Mr. Ashley had obtained such a formulation or knew how to do so." (DTX-241 ¶ 94) (emphasis in original)

179. Dr. Rudnic also argued that the Ashley '854 application "does not disclose or teach ***any*** actual formulation that at once-daily dosage will give steady state blood levels" within the required therapeutic window. (DTX-241 ¶ 94) (emphasis in original)

180. Dr. Rudnic further stated that "a skilled artisan would have to engage in excessive trial-and-error experimentation . . . to determine, which, if any, of the numerous hypothetical formulations within the broad scope of the Ashley references might actually work to meet the goals of the Chang '740 patent inventors – a once-daily doxycycline formulation that . . . would

effectively treat inflammatory conditions like rosacea while remaining below blood levels linked to antibacterial side effects." (DTX-241 ¶ 128)

181. In *Amneal I*, Amneal submitted a "Statement of Contested Facts" to the Court, indicating what it intended to litigate at trial. (PTX-129)

182. In that submission, Amneal stated that the claims of the Ashley patents, including the claims reciting administration "once a day" and by "sustained release," are enabled. (*E.g.*, PTX-129 ¶¶ 102, 124) Amneal stated that the Ashley patents expressly disclose "once-daily" and "sustained release" administration of 40 mg doxycycline that achieves the desired blood levels of the invention; the Periostat® Label and Periostat® Approval Package would provide a POSA with substantial information, including that 40 mg IR doxycycline administered once-daily would achieve a maximum steady-state blood level of 0.834 μg/ml; and the Ashley patents incorporate by reference the Ashley '854 application, which describes formulation approaches for achieving "once-daily" dosing and "sustained release" with low dose doxycycline. (*E.g.*, PTX-129 ¶¶ 156, 159, 160, 121-22, 180, 191, 234-35, 536, 542-43)

183. The Ashley '854 application contains a hand-drawn figure of potential release profiles of "instantaneous release," "sustained release," and "delayed release" doxycycline. (DTX-206 at 23)

184. When shown the figure, Mr. Ashley testified his "understanding of [the drawing] would be that these are just hypothetical, wholly hypothetical, profiles of release." (Ashley Tr. at 657) Mr. Ashley added he "really ha[d] no understanding of what [the controlled release agents described in the Ashley '854 application] would mean." (Ashley Tr. at 655)

185. Mr. Ashley also testified that "there's really no guidance, meaningful guidance, in

[the Ashley ' 854 application], and I had no idea at the time how one might achieve" a controlled release formulation. (Ashley Tr. at 654-55)

186. During the Chang IPRs, Dr. Rudnic stated that the Ashley '932 publication "does not present a single example of an actual formulation that was developed or even contemplated by Mr. Ashley." (DTX-241 ¶ 95)

187. Mr. Ashley is not a formulator and viewed his invention as being "the notion of a flat or relatively flat release profile or relatively flat pharmaco-serum profile." (Ashley Tr. at 654-55)

B. Anticipation and Obviousness

188. Periostat® is an oral antibiotic tetracycline compound that provides a 40 mg daily dose of doxycycline. (PTX-008 at 5:59-63; Feldman Tr. at 387-88)

189. The Ashley patents identify Periostat® as "an especially preferred embodiment" of the inventions. (*E.g.*, PTX-008 at 5:59-63)

190. Dr. Feldman suffers from rosacea, including the papules and pustules of rosacea. (Feldman Tr. at 388)

191. In October 1998 or 1999, Dr. Feldman attended a dermatology conference in Las Vegas, Nevada where he learned about "new[ ] ideas" for the treatment of rosacea, including the use of Periostat®. (Feldman Tr. at 383, 385)

192. While taking Periostat® for gingivitis, Dr. Feldman's rosacea improved. (Feldman Tr. at 387, 389)

193. In January 2000, Dr. Feldman contacted CollaGenex and requested "professional courtesy samples of Periostat" to continue his use. (Feldman Tr. at 413-14)

194. CollaGenex provided Dr. Feldman with 300-400 professional courtesy samples of Periostat®. (Feldman Tr. at 413-14)

195. In late January or early February 2000, Dr. Feldman used the professional courtesy samples of Periostat® to treat his rosacea and experienced a reduction in his pustules. (Feldman Tr. at 388-89)

196. On February 19, 2000, Dr. Feldman diagnosed a patient as suffering from rosacea, including rosacea pustules, and gave his patient a three-month prescription for Periostat® and one three-month refill. (Feldman Tr. at 400-01)

197. Dr. Feldman prescribed "Periostat 20 milligrams B.I.D. [twice daily] due to its anti-inflammatory effect with decreased risk of side effects." (Feldman Tr. at 401-02)

198. Dr. Feldman's personal use of Periostat® led him to anticipate that Periostat® would improve his patient's condition. (Feldman Tr. at 403, 406-08)

199. In 2004, Dr. Feldman saw his patient again, at which time he did not notice anything about her rosacea, and the patient did not say anything about her rosacea. (Feldman Tr. at 412)

200. Dr. Feldman was free to discuss his own personal use of Periostat® to treat rosacea. (Meltzer Tr. at 601-02)

201. Dr. Feldman's patient was free to discuss her use of Periostat® to treat rosacea. (Meltzer Tr. at 601-02)

202. Dr. Feldman stored the patient record in a secure locked storage facility. (Feldman Tr. at 391, 395-96, 432)

203. Amneal has not identified Dr. Feldman's patient or produced any testimony from

Dr. Feldman's patient.

204. Amneal has not produced the Periostat® prescription Dr. Feldman wrote for his patient.

205. Prior to February 19, 2000, Dr. Feldman was not personally aware of anyone who had prescribed Periostat® for the treatment of rosacea. (Feldman Tr. at 437)

206. Prior to *Mylan*, Dr. Feldman had never disclosed his patient's record to anyone else. (Feldman Tr. at 426-27, 432)

207. Dr. Feldman never published, publicly presented, or in any other way made public his prescribing of Periostat® to his patient, or his own personal use of Periostat®. (Feldman Tr. at 427-28, 437)

208. Dr. Feldman never (1) attempted to sell the idea of using Periostat® to treat rosacea, (2) informed CollaGenex that Periostat® could be used to treat rosacea, or (3) considered submitting a patent application for the use of Periostat® to treat rosacea. (Feldman Tr. at 427-28; *see also* DTX-0201 at 307 ¶ 152)

209. The Court made the same factual findings in *Mylan*. (DTX-201 at 11-12)

210. Amneal has not presented any evidence relating to obviousness or anticipation beyond what was presented to the Court in *Mylan*. (Tr. at 951-52)

LEGAL STANDARDS

I. Infringement

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). Courts employ a two-step analysis in making an infringement determination. *See*

Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed. Cir. 1995). First, a court must construe the asserted claims. *See id.* Next, the trier of fact must compare the properly-construed claims to the accused infringing product. *See id.* If an accused product does not infringe an independent claim, it also does not infringe any claim depending from that independent claim. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Id.* at 1552.

The patent owner has the burden of proving infringement by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988). A patent owner may prove infringement under two theories: literal infringement or the doctrine of equivalents. Literal infringement occurs where "every limitation in a patent claim is found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995). Infringement under the doctrine of equivalents occurs where the accused product embodies every element of a claim either literally or by an equivalent. *See id.* This doctrine "allows the patentee to claim insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 733 (2002).

A patentee may be prevented from invoking the doctrine of equivalents by prosecution history estoppel. *See id.* at 734-36. Applicability of prosecution history estoppel is a question of law. *See Panduit Corp. v. HellermannTyton Corp.*, 451 F.3d 819, 826 (Fed. Cir. 2006).

II. Presumption of Validity

An issued patent is presumed to be valid. *See* 35 U.S.C. § 282. Therefore, to invalidate a

patent, a party must carry its burden of proof by "clear and convincing evidence." *See Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). Clear and convincing evidence is evidence that "proves in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] highly probable." *Intel Corp. v. ITC*, 946 F.2d 821, 830 (Fed. Cir. 1991) (internal quotation marks omitted; first alteration in original). A defendant's burden to prove invalidity based on prior art (e.g., anticipation or obviousness) is "especially difficult when the prior art [on which it relies] was before the PTO examiner during prosecution of the application." *Hewlett-Packard Co. v. Bausch & Lamb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990).

III. Enablement

"Enablement is a question of law based on underlying factual findings." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012). "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Id*. (internal quotation marks omitted). "Enablement serves the dual function in the patent system of ensuring adequate disclosure of the claimed invention and of preventing claims broader than the disclosed invention." *Id.* at 1380-81. "Thus, a patentee chooses broad claim language at the peril of losing any claim that cannot be enabled across its full scope of coverage." *Id.* at 1381. "The scope of the claims must be less than or equal to the scope of the enablement to ensure that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims." *Id*. (internal quotation marks omitted).

"Whether undue experimentation is needed is not a single, simple factual determination,

but rather is a conclusion reached by weighing many factual considerations." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Id.* Although "a specification need not disclose what is well known in the art," "[t]ossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). A patent "cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification." *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010).

IV. Written Description

Paragraph 1 of 35 U.S.C. § 112[3] states in pertinent part:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

The statute sets out separate requirements for written description and enablement. *See Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1344 (Fed. Cir. 2010) (holding that written description and enablement requirements are separate). Yet these requirements "often rise and

[3]The Court will use the version of 35 U.S.C. § 112(a) in effect prior to passage of the Leahy–Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 300-01 (2011). The pre-AIA version of § 112(a) applies to all patents with an effective filing date of on or before March 16, 2013, which includes the asserted patents. *See Solvay S.A. v. Honeywell Int'l Inc.*, 742 F.3d 998, 1000 n.1 (Fed. Cir. 2014). The post-AIA version of this portion of the statute (§ 112(a)) is identical to the pre-AIA version.

fall together." *Id.* at 1352.

Whether a specification satisfies the written description requirement is a question of fact. *See GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 744 F.3d 725, 729 (Fed. Cir. 2014); *see also Alcon, Inc. v. Teva Pharms. USA, Inc.,* 664 F. Supp. 2d 443, 468 (D. Del. 2009) ("Satisfaction of the written description requirement is a fact-based inquiry, depending on 'the nature of the claimed invention and the knowledge of one skilled in the art at the time an invention is made and a patent application is filed.'") (quoting *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008)).

To comply with the written description requirement, a patent's specification "must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Ariad*, 598 F.3d at 1351 (internal alterations and quotation marks omitted). "[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date. . . . [T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.* "[T]he written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." *Id.* at 1352. However, "a description that merely renders the invention obvious does not satisfy the requirement." *Id.*

V. Anticipation

A claim is anticipated under 35 U.S.C. § 102(a) or (b) if:

(a) the invention was known or used by others in this country, or

> patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States . . . .

35 U.S.C. § 102.[4] A patent claim is anticipated if each and every limitation is found, either expressly or inherently, in a single prior art reference. *See Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Such disclosure can be explicit or inherent in the prior art. *See Cont'l Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). Mere disclosure of each and every limitation of a claim, however, is not enough for anticipation. "An anticipating reference must enable that which it is asserted to anticipate." *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1345 (Fed. Cir. 2008). Furthermore, a single prior art reference must also disclose the limitations as arranged in the claim. *See Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) ("[U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102."). Whether a claim is anticipated is a question of fact. *See Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006).

VI. Obviousness

A patent may not issue "if the differences between the claimed invention and the prior art

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[4]The Court will use the pre-AIA version of 35 U.S.C. § 102, which applies in this case. *See Solvay*, 742 F.3d at 1000 n.1.

are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a). Obviousness is a question of law based on underlying factual findings concerning: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of non-obviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (internal citation and quotation marks omitted); *see also Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."). While an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415, 419 (2007).

The use of hindsight is not permitted when determining whether a claim would have been obvious to one having ordinary skill in the art. *See id*. at 421 (cautioning against "the distortion caused by hindsight bias" and obviousness "arguments reliant upon *ex post* reasoning"). To protect against the improper use of hindsight when assessing obviousness, the Court is required to consider objective (or "secondary") considerations of non-obviousness, such as commercial

success, failure of others, unexpected results, and long-felt but unmet need. *See, e.g.*, *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Objective considerations "may often be the most probative and cogent evidence in the record" relating to obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

VII. Indefiniteness

A patent claim is indefinite if, "viewed in light of the specification and prosecution history, [it fails to] inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014). A claim may be indefinite if the patent does not convey with reasonable certainty how to measure a claimed feature. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015). But "[i]f such an understanding of how to measure the claimed [feature] was within the scope of knowledge possessed by one of ordinary skill in the art, there is no requirement for the specification to identify a particular measurement technique." *Ethicon Endo–Surgery, Inc. v. Covidien, Inc.*, 796 F.3d 1312, 1319 (Fed. Cir. 2015).

DISCUSSION

I. Infringement of the Chang Patents

Galderma asserts that Amneal's ANDA product infringes claim 1 of the Chang '532 patent, claim 1 of the Chang '740 patent, claims 1 and 3 of the Chang '405 patent, and claims 1 and 2 of the Chang '364 patent (the "asserted claims of the Chang patents") under the doctrine of equivalents.[5] (D.I. 273 ¶ 36) Amneal counters that Galderma is precluded from asserting its

[5]Prior to trial, the Court struck Galderma's literal infringement contentions regarding the Chang patents. (*See* D.I. 203)

doctrine of equivalents infringement theory and that, in any event, Amneal's ANDA product does not infringe the Chang patents. As explained below, the Court concludes Galderma is not precluded from alleging infringement of the Chang patents under the doctrine of equivalents. Furthermore, Galderma has proven, by a preponderance of the evidence, that Amneal's ANDA product infringes all of the asserted claims of the Chang patents under the doctrine of equivalents, other than claim 1 of the Chang '532 patent.

A. Galderma Is Not Precluded from Asserting Infringement Under the Doctrine of Equivalents

Amneal contends that Galderma cannot assert infringement under the doctrine of equivalents because: (1) Galderma's theory would vitiate the claims, (2) Galderma surrendered equivalents to the 10 mg DR portion during prosecution, and (3) Galderma disclaimed in prosecution formulations that release in the stomach. The Court disagrees.

1. Galderma's theory does not vitiate any claim limitation

Amneal contends that Galderma's doctrine of equivalents theory is improper because it vitiates the claim requirement of "delayed release," which the Court construed to mean "release of a drug at a time other than immediately following oral administration." (PTX-378 at 0010) Amneal, starting from the premise that [redacted] releases "immediately following oral administration," argues that Galderma's infringement theory "impermissibly extend[s] the scope of equivalents to cover the exact antithesis of the claim term." (D.I. 246 at 5) The Court disagrees. Galderma has demonstrated that Amneal's [redacted], in combination with its [redacted], is equivalent to a 10 mg DR portion. *See generally DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1018-19 (Fed. Cir. 2006) ("A holding that the doctrine of

equivalents cannot be applied to an accused device because it 'vitiates' a claim limitation is nothing more than a conclusion that the evidence is such that no reasonable jury could conclude that an element of an accused device is equivalent to an element called for in the claim, or that the theory of equivalence to support the conclusion of infringement otherwise lacks legal sufficiency."). As explained throughout this Opinion, the [redacted] does not release immediately after oral administration.[6] There is no vitiation of the claim element.

2. Prosecution history estoppel does not apply

Amneal contends that the applicants' actions in response to an obviousness rejection also preclude Galderma from asserting infringement under the doctrine of equivalents. (*See* D.I. 246 at 5) Prosecution history estoppel limits the doctrine of equivalents. *See Glaxo Wellcome, Inc. v. Impax Labs., Inc.*, 356 F.3d 1348, 1351 (Fed. Cir. 2004). There is a presumption that a narrowing amendment made for a reason of patentability surrenders the entire territory between the original claim limitation and the amended claim limitation. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1365 (Fed. Cir. 2003); *Cross Med. Prods. v. Medtronic Sofamar Danek, Inc.*, 480 F.3d 1335, 1341 (Fed. Cir. 2003). To rebut this presumption, "the patentee must demonstrate that the alleged equivalent would have been unforeseeable at the time of the narrowing amendment, that the rationale underlying the narrowing amendment bore no more than a tangential relation to the equivalent in question, or

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[6]Although the Court was not asked to construe "immediate release," both parties pointed to the definition of the term in the Chang patents, which is: "a dosage form that is intended to release substantially all of the active ingredient on administration with no enhanced, delayed or extended release effect." (*See, e.g.*, Sealed Tr. A at A-12; D.I. 273 ¶ 19) In the Court's view, for the reasons explained throughout this Opinion, the [redacted] of Amneal's ANDA product, which includes [redacted], is ***not*** intended to release on administration. Instead, its release is delayed.

that there was some other reason suggesting that the patentee could not reasonably have been expected to have described the alleged equivalent." *Festo*, 344 F.3d at 1368. An amendment cannot reasonably be viewed as surrendering a particular equivalent if the rationale underlying the amendment bears no more than a tangential relation to the equivalent. *See Festo Corp.*, 535 U.S. at 740-41. Thus, "[i]n determining whether an estoppel arose, and the scope of the estoppel, the analysis focuses on the claims as originally filed, the amendments made, and the reasons therefor." *Funai Elec. Co. v. Daewoo Elecs. Corp.*, 616 F.3d 1357, 1368 (Fed. Cir. 2010).

The original application for the Chang '532 patent had 48 claims, which were cancelled in a preliminary amendment and replaced with newly-added claims 49-80. (PTX-013.0028-32, .380-81) The new claims recited compositions "comprising" 30 mg IR and 10 mg DR portions of doxycycline. (PTX-013.381) The Examiner issued a Non-Final Rejection of the claims as obvious in view of prior art that disclosed once-daily compositions comprising "at least two portions," including IR and DR. (PTX-013.435) The applicant amended the claims, changing "comprising" to "consisting essentially of." (PTX-013.447) The Examiner then issued a Final Rejection of the claims. (PTX-013.458-61) In response, the patentee amended the claims to change "consisting essentially of" to "consisting of" 30 mg IR and 10 mg DR portions. (*See* PTX-013.537) The Examiner then issued the patent. (PTX-013.553-55)

While Amneal contends this amendment means the patentee surrendered embodiments with SR or other non-DR portions, the Court disagrees. As the Court noted in its claim construction opinion, "[t]here is no argument or discussion accompanying the amendment that provides additional insight" into the applicant's reasons for making the amendment that would support finding the applicant had disclaimed compositions with an IR portion and multiple types

of DR portions. (PTX-378.0013) Therefore, the Court agrees with Galderma that the record does not demonstrate a clear disavowal of subject matter. (*See also* D.I. 265 at 9) (contending applicant amended claims in order to "exclude a high antibacterial dosage amount from the scope of the claims") Thus, the Court is not persuaded that the "consisting of" amendment was made for the purposes of patentability such that it compels a conclusion of prosecution history estoppel.

3. Galderma did not disclaim particular DR formulations

Amneal also contends Galderma is estopped from asserting doctrine of equivalents infringement based on statements Dr. Rudnic made during the Chang IPRs. (*See* D.I. 264 at 6) "[S]tatements made by a patent owner during an IPR proceeding can be . . . relied upon to support a finding of prosecution disclaimer." *Aylus Networks, Inc. v. Apple Inc.*, 856 F.3d 1353, 1361 (Fed. Cir. 2017). However, to support a finding of disclaimer, "any such statements must be both clear and unmistakable." *Id.* (internal quotation marks omitted). Dr. Rudnic's statements do not meet that standard.

During the Chang IPRs, Dr. Rudnic opined that the DR portion claimed in Chang results in "no substantial release of doxycycline in the acidic stomach environment." (DTX-241 ¶ 176) This, Amneal argues, should preclude Galderma from asserting doctrine of equivalents infringement for DR portions that ***do*** release a substantial amount of doxycycline in the stomach environment. (D.I. 246 at 6)

But, again, Amneal has failed to show a clear disavowal of claim scope. *See Cordis Corp. v. Medtronic Ave, Inc.*, 511 F.3d 1157, 1177 (Fed. Cir. 2008). As the Court previously found – like the PTAB had before it – while Dr. Rudnic distinguished the secondary loading

portion of Sheth from the DR portion claimed in Chang, his statements did not clearly limit the scope of the claims to DR portions having no substantial release of doxycycline below pH 4.5. (*See* PTX-378.0010-11; DTX-0232 at Amneal-Doxy2016-00437454-455) Accordingly, the Court is not persuaded prosecution history estoppel applies.

B. Amneal Infringes Under the Doctrine of Equivalents

Galderma contends that Amneal's [redacted], in combination with its [redacted], is equivalent to the 10 mg DR portion of doxycycline claimed in Chang. "What constitutes equivalency must be determined against the context of the patent, the prior art, and the particular circumstances of the case." *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 609 (1950). "Consideration must be given to the purpose for which an ingredient is used in a patent, the qualities it has when combined with the other ingredients, and the function which it is intended to perform." *Id.* The analysis must consider "the role played by each element in the context of the specific patent claim." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 40 (1997). "An important factor is whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was." *Graver Tank*, 339 U.S. at 609.

The Supreme Court has set out two frameworks for evaluating equivalency: (1) the function-way-result test, which asks whether an alleged equivalent performs substantially the same function in substantially the same way to obtain the same result; and (2) the substantial differences test, which asks whether the substitute element plays a role substantially different from the claimed element. *See Warner-Jenkinson*, 520 U.S. at 40; *Graver Tank*, 339 U.S. at 608-09. The Federal Circuit has noted that "the substantial differences test may be more suitable than

[the function-way-result test] for determining equivalence in the chemical arts." *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858, 869 (Fed. Cir. 2017).

The Court agrees with both sides that the result here is the same regardless of the test used. (*See* D.I. 244 at 7; D.I. 246 at 7, 12) Under both tests, the Court finds that Galderma has proven, by a preponderance of the evidence, that Amneal's ANDA product infringes the asserted claims of the Chang patents, except for the asserted claim of the Chang '532 patent.

Galderma contends that the [redacted], in combination with the [redacted], is insubstantially different from the 10 mg DR portion claimed in Chang. Galderma focuses on whether Amneal's [redacted] is a DR portion within the meaning the Court has given to "delayed release" – that is, "release of a drug at a time other than immediately following oral administration." (D.I. 130) In Galderma's view, Amneal "intentionally engineered" its [redacted]. (*See* Rudnic Sealed Tr. B at B-82-84; Sealed Tr. A at A-7 (opening statement)) The [redacted] and [redacted] combine, Galderma argues, to act as "barriers" [redacted]. (*See* Rudnic Sealed Tr. B at B-82-84) That combined insulating effect and resulting "delay," Galderma contends, means the [redacted] does not release until at a time "other than immediately following oral administration," making it a DR portion within the Court's construction of that term. (*See* Rudnic Sealed Tr. B at B-81) It follows, Galderma argues, that Amneal's product contains [redacted] that is insubstantially different from the 10 mg DR portion claimed in Chang. (*See* Rudnic Sealed Tr. B

at B-81-88)

Amneal sees its product very differently. In Amneal's view, its [redacted] is not [redacted], but rather is [redacted] that is quite distinct from the DR portion claimed in Chang. To highlight the difference between [redacted], Amneal relies on the IPR testimony of Galderma's expert, Dr. Rudnic. During the Chang IPRs, Dr. Rudnic distinguished the DR portion claimed in Chang, which Dr. Rudnic argued "delayed [the] release . . . [of] ***all*** of the drug contained in that portion," from the secondary loading portion disclosed in Sheth, which Dr. Rudnic argued was surrounded by a blended pH-sensitive and water-soluble polymer that "immediately" formed pores, allowing drug to dissolve out "in a slow, sustained release fashion beginning promptly after administration." (DTX-241 ¶¶ 172, 175, 181) (emphasis in original) According to Dr. Rudnic in the IPRs, the time it took the blended polymer of Sheth to form pores and begin releasing drug was not a "delay." (*See* DTX-271 at 13) The PTAB agreed, finding that Sheth did not contain a DR portion within the meaning of the Chang patents. (*See* DTX-0232 at Amneal-Doxy2016-00437460-461) Amneal also emphasizes that "immediate release" does not require instantaneous release, but instead depends on whether the drug is available for wetting, dissolution, and release right after oral administration. (*See* Rudnic Sealed Tr. B at B-113-14) (agreeing "[t]ime is irrelevant" to whether portion is IR) Here, [redacted] It follows, Amneal argues – and, in Amneal's view, Plaintiffs' expert, Dr. Rudnic, agrees – that Amneal's [redacted]

[redacted] (*See* Elder Sealed Tr. B at B-186, B-196)

Under the function-way-result test, Galderma contends that the function of Amneal's [redacted], in combination with the [redacted], is to delay release of [redacted] until a time other than immediately following oral administration. (*See* Rudnic Sealed Tr. B at B-85) The way it does so is [redacted]. (*See* Rudnic Sealed Tr. B at B-85, B-92-93) The result, according to Galderma, is [redacted]. (*See* Rudnic Sealed Tr. B at B-70-72)

Amneal, however, views the purpose of its [redacted] to be [redacted], but not to [redacted]. (*See* Elder Sealed Tr. B at B-186) Amneal also rejects the notion that its [redacted] and [redacted] have an insulating effect [redacted], arguing instead that its [redacted] works to [redacted]. (*See* Elder Sealed Tr. B at B-193) To that end, Amneal argues that neither [redacted] nor [redacted] delays release of a drug. (*See* Elder Sealed Tr. B at B-184-85; Rudnic Sealed Tr. B at B-79-80) Because neither component alone delays the release of [redacted], Amneal argues, [redacted] (*See* Elder Sealed Tr. B at B-185) Finally, Amneal argues that its ANDA product results in [redacted]

[redacted]. (*See* Rudnic Sealed Tr. B at B-170-72)

Each side makes persuasive arguments in its favor and highlights shortcomings in the other's theories. Galderma has shown that [redacted]. (*See* Rudnic Sealed Tr. B at B-82-84) Further, as Plaintiffs persuasively argue, nothing in the Court's construction of "delayed release" requires that the delay be caused by an enteric coating or other "technology." (*See* D.I. 130)[7] For its part, Amneal points to strong evidence that neither its [redacted] nor its [redacted], on its own, cause a delay in the release of drug. Relatedly, Amneal has shown that accepting Galderma's theory risks implying that every IR formulation can be considered to have a DR portion, since the innermost molecule of drug in any IR formulation will not release until some significant time – here, for doxycycline, 30 minutes or more – after oral administration. (*See* Tr. at 964-65)

To prevail at trial, a party is not required to make a showing wholly unblemished by flaws, inconsistencies, and doubts. Instead, the Court, when sitting as factfinder, is called upon to make a determination based on the evidence presented, applying the appropriate burden of proof, even when there is strong evidence on both sides of the dispute. Doing so here, the Court

[7](*But see* DTX-241 at 16 n.2) (Rudnic IPR Declaration stating: "unless otherwise noted, I will use the term 'SR' to refer to technologies that modify release by controlling the rate of drug release")

concludes that Galderma has proven infringement by a preponderance of the evidence.[8]

Nothing in the Court's construction of "delayed release" limits the way in which that delay is created. (*See* D.I. 130) Thus, it does not matter whether the delay is caused by an enteric coating or some other barrier, so long as release does not occur until "a time other than immediately following oral administration." (D.I. 130) It is undisputed that Amneal's ANDA product is manufactured [redacted]. (*See* FF ¶ 85) Because of that [redacted] Amneal's [redacted], meaning that release [redacted] is delayed until sometime well after "immediately following oral administration." (*See* Rudnic Sealed Tr. B at B-153) The Court agrees with Galderma that [redacted] means that Amneal's [redacted] is not available for release until a time other than immediately following oral administration, satisfying the Court's construction of "delayed release."

Amneal's arguments to the contrary are, ultimately, unavailing. While Amneal's argument that, under Galderma's theory, an otherwise purely IR formulation could be considered to have a DR portion (that is, the innermost molecules of the IR portion) is clever, it does not justify judgment for Amneal. Simply put, Amneal's hypothetical product is not before the Court. Here, [redacted], Amneal's ANDA product contains [redacted]

[8]This case illustrates the imperative of carefully applying the burden of proof – here, preponderance of the evidence – and holding the parties to it. In saying the Court is persuaded by Plaintiffs, the Court is saying that Plaintiffs are (at least) slightly more persuasive, given all the evidence the Court credits. The Court is not saying Galderma has entirely rebutted all of Amneal's critiques.

. (*See* FF ¶ 85)

In this way, the combination of that by itself would not "delay" release of with that also by itself would not "delay" release of results in "delaying" the release of . In this way, while it may seem an odd conclusion, Galderma has effectively proven that zero ( ) plus zero ( ) equals something greater than zero ( ).

Amneal's appeal to Sheth similarly lacks merit. Sheth's secondary loading portion did not have another drug portion layered on top of it. (*See* Rudnic Sealed Tr. B at B-91-92; Elder Sealed Tr. B at B-219-20) Thus, the film coating of Sheth was immediately exposed to gastric fluid and, hence, formed pores through which the drug could release promptly following oral administration. (*See* Rudnic Sealed Tr. B at B-91-92; Elder Sealed Tr. B at B-219-20) Here,

Additionally, even accepting that Amneal's is , the Court agrees with Galderma that are not mutually

exclusive. (*See* Rudnic Tr. at 181; Elder Tr. at 281-19; *see also* D.I. 380 at 86-87) Nothing in the Court's construction requires that there be no or substantially no release of drug for a period of time (such as the plateau in release exhibited in Oracea®'s dissolution data). Thus, the fact that Amneal's [redacted] does not mean it cannot also be [redacted].

Thus, while the Court agrees with Amneal that neither its [redacted] nor its [redacted] could, standing alone, be said to delay release [redacted], the Court is persuaded that, when viewing Amneal's product as a whole, [redacted] combine to delay the process of wetting, dissolution, and release of [redacted] until a time other than immediately following oral administration. Accordingly, the Court concludes that Galderma has proven, by a preponderance of the evidence, that Amneal's [redacted], in combination with its [redacted], is insubstantially different from the 10 mg DR portion claimed in Chang.

The Court's conclusion is the same under the function-way-result test. First, the Court agrees with Galderma that the purpose of Amneal's [redacted], in combination with [redacted], is to delay release of [redacted] until a time other than immediately following oral administration. While Amneal argues that the function of [redacted] is to [redacted], the Court, for the reasons discussed above, does not consider [redacted] to be mutually exclusive under the construction of delayed release in this case.

The Court further agrees with Galderma that Amneal's ANDA product delays release in the same way that the DR portion claimed in Chang does. As discussed above, the Court's construction of "delayed release" is agnostic as to how the delay is accomplished, be it by an

[redacted]. Hence, the fact that the delay here is caused by [redacted] is immaterial. During claim construction, the Court rejected Amneal's attempt to require that the delay be due to an enteric coating, finding no support for such a limitation in the specification or claims. (*See* D.I. 129 at 10) While Amneal makes a strong argument that neither its [redacted], when viewed in isolation, delays release, the Court, for the reasons discussed above, must consider how Amneal's ANDA product functions as a whole. When doing so, the Court agrees with Galderma that Amneal's [redacted] combined with the [redacted] function [redacted] and, thus, delay [redacted] from releasing until a time other than immediately following oral administration.

Finally, the Court agrees with Galderma that Amneal's [redacted], in combination with the [redacted], achieves the same result as the 10 mg DR portion claimed in Chang. While Amneal showed that its product's dissolution profile is [redacted], what is important to the claims is that Amneal's ANDA product releases [redacted] at a time other than immediately after oral administration. That result can be achieved in more than one way.

Again, Amneal's arguments to the contrary are unavailing. Amneal contends that "there is no basis to assume" that [redacted]. (Elder Sealed Tr. B at B-191-92) To that end, Dr. Elder opined that [redacted]

[redacted]. (*See* Elder Sealed Tr. B at B-192) There is no evidence beyond Dr. Elder's speculation to support such a conclusion. Dr. Rudnic credibly testified about [redacted]. (*See* Rudnic Sealed Tr. B at B-62-63, B-65, B-88) Such [redacted] results in the [redacted], as is reflected in Amneal's dissolution data. (*See* Rudnic Sealed Tr. B at B-88-89) Dr. Elder offered no study or other citation to substantiate his opinion, and Amneal did not perform any testing to prove [redacted]. (*See* Elder Sealed Tr. B at B-215) Further, Amneal's ANDA describes quality controls for making [redacted] that support a finding that Amneal's [redacted], and, hence, [redacted]. (*See* PTX-331 at Amneal-Doxy2016-00010553-556) Moreover, as Dr. Rudnic persuasively explained, a POSA would understand that [redacted]. (*See* Rudnic Sealed Tr. B at B-66-67; *see also id.* at B-63-64 ("Amneal did a fabulous job [with its product] . . . . [redacted]); Elder Tr. at B-215 (acknowledging he can point to no data supporting view that [redacted]))

Accordingly, the Court concludes that Amneal's [redacted], in combination with its [redacted], performs the same function in the same way to achieve the same result

as the 10 mg DR portion claimed in Chang. Therefore, again, Amneal's ANDA product satisfies the "delayed release" limitation of the Chang patents under the doctrine of equivalents.

C. Amneal's ANDA Product Does Not Infringe the Chang '532 Patent

Galderma alleges that Amneal's ANDA product infringes claim 1 of the Chang '532 patent. Claim 1 has an additional limitation missing from the asserted claims of the other Chang patents: the "the DR portion is in the form of pellets" and is "coated with at least one enteric polymer." (PTX-003 at 12:2-5) The Chang '532 patent defines "enteric materials" as "polymers that are substantially insoluble in the acidic environment of the stomach, but are predominately soluble in intestinal fluids at specific pHs." (PTX-003 at 7:15-18) The [redacted] and [redacted] of Amneal's ANDA product are [redacted] (*See* PTX-331 at Amneal-Doxy2016-00010319-320, -469, -551; Rudnic Sealed Tr. B at B-97) But the parties dispute whether Amneal's ANDA product contains a DR portion "coated with at least one enteric polymer" or an equivalent thereof.

Galderma contends that the [redacted] of Amneal's ANDA product, in combination with its [redacted], is insubstantially different from a 10 mg DR portion coated with an enteric polymer. Galderma notes that [redacted]. (*See* Rudnic Sealed Tr. B at B-98) As to the [redacted], Galderma contends that the combined effect of the [redacted] delay release until a time other than immediately following oral administration and, therefore, are insubstantially different from an enteric coated DR portion. (*See* Rudnic Sealed Tr. B at B-98) Under the function-way-result test, Galderma argues that the [redacted] function to [redacted]. (*See* Rudnic

Sealed Tr. B at B-99) The way it does so, Galderma contends, is by delaying release of the drug until a time other than immediately following oral administration, [redacted] (*See* Rudnic Sealed Tr. B at B-99) The result, according to Galderma, [redacted]. (*See* Rudnic Sealed Tr. B at B-99-100)

Amneal counters that its [redacted] is very different from a DR portion coated with an enteric polymer. Amneal points to the Chang '532 patent itself, which teaches that enteric coatings prevent release of drug in the stomach. [redacted] (*See* PTX-003 at 7:47-49; Elder Sealed Tr. B at B-204; Rudnic Sealed Tr. B at B-167) Moreover, Amneal observes, [redacted] (*See* PTX-003 at 7:47-53; Elder Sealed Tr. B at B-201-02) Under the function-way-result test, Amneal contends that its product does not infringe because its [redacted]. (*See* Elder Sealed Tr. B at B-204)

The Court agrees with Amneal. No persuasive evidence has been presented that a POSA would view any part of Amneal's product – [redacted] – as interchangeable with or otherwise insubstantially different from an enteric polymer. Galderma has not demonstrated that enteric polymers, which prevent release in the stomach, would be considered interchangeable with [redacted]. Nor has Galderma

offered evidence proving that Amneal's ANDA works in the same way as an enteric polymer to delay release. Instead, Amneal has shown that [redacted]

(*See* Elder Sealed Tr. B at B-201-04)

Therefore, Galderma has failed to prove that Amneal's ANDA product infringes claim 1 of the Chang '532 patent.

II. Infringement of the Ashley Patents

Galderma contends that Amneal's ANDA product infringes claim 30 of the Ashley '267 patent and claims 14, 15, 23, 24, and 26 of the Ashley '572 patent (the "asserted claims of the Ashley I patents"), as well as claims 3, 4, 5, 15, and 16 of the Ashley '506 patent and claims 13, 14, 15, and 16 of the Ashley '946 patent (the "asserted claims of the Ashley II patents"), "at least" under the doctrine of equivalents. Amneal responds that Galderma is collaterally estopped from asserting the Ashley I patents and, anyway, Amneal's ANDA product does not infringe any of the asserted claims of the Ashley patents, literally or under the doctrine of equivalents.

As explained below, the Court agrees with Amneal that Galderma is collaterally estopped from asserting the Ashley I patents. With respect to the Ashley II patents, Galderma has proven by a preponderance of the evidence that Amneal's ANDA product infringes the asserted claims under the doctrine of equivalents.

A. Galderma Is Collaterally Estopped from Asserting the Ashley I Patents

Each of the asserted claims of the Ashley I patents requires administration of a "sub-antibacterial amount" of doxycycline or an amount that causes "substantially no antibiotic activity" (the "sub-antibiotic" limitations). (*E.g.*, PTX-001 at 34:46-48; PTX-002 at 32:25-27)

Amneal contends that Galderma is collaterally estopped from asserting the Ashley I patents based on the Court's finding in *Mylan* that 40 mg doxycycline administered once-daily does not meet the "sub-antibacterial amount" limitation of the Ashley I patents. *See Mylan*, 809 F. Supp. 2d at 317. Galderma disagrees, arguing that the instant case does not present the "identical" issue as *Mylan*. In Galderma's view, the issue of doctrine of equivalents infringement was never litigated in *Mylan* and should be considered separate from literal infringement for purposes of collateral estoppel.

A party asserting collateral estoppel must prove: (1) the previous determination was necessary to the decision, (2) the identical issue was previously litigated, (3) the issue was actually decided on the merits and the decision was final and valid, and (4) the party being precluded from re-litigating the issue was adequately represented in the previous action. *See Jean Alexander Cosmetics, Inc. v. L'Oreal USA Inc.*, 458 F.3d 244, 249 (3d Cir. 2006); *Novartis Pharms. Corp. v. Abbott Labs.*, 375 F.3d 1328, 1333 (Fed. Cir. 2004).

Three of the four elements are not in dispute. Galderma does not argue that the Court's previous finding of non-infringement of the Ashley I patents was not necessary to the decision in *Mylan*, which Galderma concedes was final and valid. (*See* D.I. 244 at 19-20) Nor does Galderma argue that it was not adequately represented in *Mylan*, where it was represented by the same counsel as it is in the present case. (*See* D.I. 244 at 19-20) The parties' disagreement is over whether Galderma's doctrine of equivalents infringement theory presents the "identical issue" that was previously litigated and decided on the merits in *Mylan*. The Court concludes that it does.

In *Mylan*, the Court decided that a 40 mg once-daily administration of doxycycline ***does***

significantly inhibit the growth of microorganisms and, therefore, fails to meet the sub-antibacterial limitation of the Ashley I patents. *See Mylan*, 809 F. Supp. 2d at 317-22. Here, Amneal's ANDA product undisputedly involves once-daily administration of 40 mg doxycycline. (*See* PTX-100 at Amneal-Doxy2016-0043868; Edwards Tr. at B-48) Thus, as in *Amneal I* – where the Court held Galderma was collaterally estopped from asserting the Ashley I patents against Amneal – "in order to prevail against Amneal on its claim for infringement of the Ashley patents, Galderma would have to prevail on the 'identical issue' it previously litigated – and lost – in the Mylan Action." *Amneal I*, 921 F. Supp. 2d at 281. Galderma is not permitted to do so.

Galderma's response is that, for purposes of collateral estoppel, the "issue" of doctrine of equivalents infringement, which Galderma did not raise at trial in *Mylan*, is a separate "issue" from literal infringement. (*See* D.I. 244 at 19-20) The Court disagrees. Doctrine of equivalents infringement is one theory of infringement, not a distinct issue itself. *See generally Dana v. E.S. Originals, Inc.*, 342 F.3d 1320, 1324 (Fed. Cir. 2003) (finding "no error in the district court's conclusion that the defendants had ample opportunity and incentive to litigate the ***issues of infringement*** and validity") (emphasis added). This is consistent with the view that invalidity, too, is a single issue for purposes of collateral estoppel, regardless of how many different theories are presented as a basis for invalidating a patent. *See Evonik Degussa GmbH v. Materia Inc.*, 53 F. Supp. 3d 778, 794 (D. Del. 2014) (treating "validity as a single issue is appropriate where a party seeks to assert an additional theory in support of its challenge"); *Astrazeneca UK Ltd. v. Watson Labs., Inc. (NV)*, 905 F. Supp. 2d 596, 602-03 (D. Del. 2012) (accepting view that validity is single issue and citing case support for this position). Having decided to pursue only one theory of infringement in *Mylan*, Galderma is bound by the consequences of that choice –

namely, that collateral estoppel bars litigants from raising separate arguments in support of the same issue in a later case, where the other prerequisites for application of collateral estoppel are met.

The fact that the Court clarified its construction of the sub-antibiotic limitation does not change this conclusion. As Galderma represented to the Court numerous times in seeking the clarified construction, the Court's clarified construction of the sub-antibacterial limitation does not change the scope of the claims. (*See* D.I. 85 at 32 ("[W]e're not seeking a new construction."), 33, 35 ("We're not seeking to modify [the construction from *Mylan*] in any way.")) Thus, the clarified construction does not provide a basis for Galderma to avoid the estoppel effects of the Court's finding of non-infringement of the Ashley I patents in *Mylan*.[9] *See Molinaro v. Fannon/Courier Corp.*, 745 F.2d 651, 655 (Fed. Cir. 1984) ("[W]here a determination of the scope of patent claims was made in a prior case . . . the determined scope cannot be changed.").

Collateral estoppel applies even if Galderma here presented new evidence that was not before the Court in *Mylan*. The Court decided the issue of infringement in *Mylan* following a trial at which Galderma had a full and fair opportunity to present any evidence of infringement it wished. Any new evidence Galderma offers now in support of its doctrine of equivalents

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[9]In a footnote, Galderma argues that it has proven "Amneal literally infringes the 'sub-antibacterial amount' terms as construed by the Court in this case." (D.I. 244 at 20 n.7) To the extent Galderma is contending it should not be estopped from asserting literal infringement based on the Court's clarified construction of the sub-antibacterial amount term, the Court disagrees. As discussed above, the Court's clarified claim construction did not change the scope of the sub-antibacterial limitation – just as Galderma repeatedly insisted to the Court it would not. (*See* D.I. 85 at 32-33, 35) Thus, Galderma has no basis to assert that it is not collaterally estopped from asserting literal infringement of the Ashley I patents, which was undisputedly at issue in *Mylan*. *See* 809 F. Supp. 2d at 317.

infringement theory was neither controlling nor otherwise essential to the Court's finding of non-infringement in *Mylan*. *See Apeldyn Corp. v. Sony Corp.*, 87 F. Supp. 3d 681, 692 (D. Del. 2015) (explaining new evidence "cannot be used to avoid collateral estoppel unless the facts are 'controlling' or 'essential to [the] judgment'") (quoting *Raytech Corp. v. White*, 54 F.3d 187, 193 (3d Cir. 1995)).

The Court is mindful of Galderma's warning that considering infringement to be a single issue will inevitably lead to the waste of judicial resources. The Court's ruling arguably incentivizes patentees to raise both literal and doctrine of equivalents infringement in all cases, so as to avoid losing on one and later being estopped from pressing the other. But the approach Galderma urges risks incentivizing parties to withhold infringement theories in order to ensure a "second-bite at the infringement apple" in the event of a finding of non-infringement.[10] Galderma's approach upends the finality of judgements that collateral estoppel aims to preserve and would require parties to relitigate infringement of the same products covered by the same patents when the issue of infringement has already been decided – a decidedly wasteful use of judicial resources. *See Taylor v. Sturgell*, 553 U.S. 880, 892 (2008) (explaining collateral estoppel "protect[s] against the expense and vexation attending multiple lawsuits, [and] conserv[es] judicial resources") (internal quotation marks omitted); *Parklane Hosiery Co., Inc. v. Shore*, 439 U.S. 322, 326 (1979) (explaining collateral estoppel prevents litigants from being required to relitigate identical issues with same parties).

Thus, the Court finds Galderma is collaterally estopped from asserting infringement of the

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[10]*See also* D.I. 53 at 51-54 (addressing parties' competing arguments in context of motion to dismiss).

Ashley I patents, literally or under the doctrine of equivalents.

B. Infringement of the Ashley II Patents

Galderma alleges Amneal's ANDA product infringes the asserted claims of the Ashley II patents "at least" under the doctrine of equivalents. The only limitation in dispute is "wherein the amount [of doxycycline] results in no reduction of skin microflora during a six-month treatment" (the "skin microflora limitation"). (*E.g.*, PTX-010 at 32:55-56) The Court construed this term to mean an amount that "results in no reduction of skin microflora vis-à-vis a placebo control during a six-month treatment, with microbiological sampling at baseline and month six." (PTX-378 at 0006) While Galderma has not proven Amneal's ANDA product literally meets this limitation, Galderma has proven, by a preponderance of the evidence, that Amneal's ANDA product infringes the asserted claims of the Ashley II patents under the doctrine of equivalents.

1. Galderma has not proven Amneal's ANDA product literally infringes the Ashley II patents

Galderma urges the Court to find Amneal's ANDA product, a once-daily 40 mg dosage of doxycycline, literally meets the skin microflora limitation based on the *Skidmore* study and Amneal's Label. Amneal counters that these are insufficient bases to establish literal infringement, particularly *Skidmore*, which sampled only the sebaceous skin of the forehead. The Court agrees with Amneal.

Skidmore does not prove that Amneal's ANDA product literally meets the skin microflora limitation. Nothing in the Court's construction of the skin microflora limitation limits the claim to the bacteria found on a particular part of the body. (*See* Webster Tr. at 124) (agreeing claims are not limited to bacteria found on face) Hence, it applies to microflora across the entire human

body. At least hundreds of millions of bacterial cells exist all over normal skin, and there is great diversity in the types of bacteria found on the skin, even in areas close to one another. (*See* Zhanel Tr. at 222) Accordingly, it may be impossible to prove that absolutely no microflora in any part of the body is inhibited by administration of 40 mg doxycycline once-daily. It is enough here, however, to conclude that *Skidmore*, which reports on one area of the body (*see* Webster Tr. at 121; Zhanel Tr. at 168), is insufficient to prove "no reduction of skin microflora vis-à-vis a placebo" in all parts of the body and, thus, does not prove literal infringement.

Amneal's Label also does not prove literal infringement. Amneal's Label states: "*In vivo* microbiological studies utilizing a similar drug exposure for up to 18 months demonstrated no detectable long-term effects on bacterial flora of the . . . skin . . . ." (PTX-100 at Amneal-Doxy2016-00434890) As Amneal notes, this statement does not address the effects of Amneal's ANDA product on skin microflora in the immediate, short-term, or medium-term (i.e., from baseline to six-months). Accordingly, the Label simply does not address all time frames, including the relevant time frame (0-6 months), for determining whether there has been a reduction in skin microflora.

This conclusion holds despite the Court's previous statement that administration of Oracea® and Mylan's ANDA product, both 40 mg daily dosages of doxycycline, "results in no reduction of skin microflora during a six-month treatment." (DTX-201 ¶¶ 32, 77) In *Mylan*, the Court was not asked either to construe or analyze the skin microflora limitation – a fact Galderma makes a point of noting (*see* D.I. 244 at 11) ("Importantly, the Ashley II patents were not at issue in the prior *Mylan* or *Amneal I* Actions . . . .") – and, of course, was not tasked with deciding whether Amneal's ANDA product meets the skin microflora limitation. Having now

had the benefit of trial and argument addressing the skin microflora limitation, the Court concludes, based on the record before it and under the Court's construction of the skin microflora limitation, that Galderma has not proven that administration of Amneal's ANDA product would literally meet the skin microflora limitation.

2. Amneal infringes the Ashley II patents under the doctrine of equivalents

While Galderma's evidence was not sufficient to prove Amneal's ANDA product literally infringes, Galderma has proven, by a preponderance of the evidence, that Amneal's ANDA product infringes the asserted claims of the Ashley II patents under the doctrine of equivalents.

The Court agrees with Galderma that the results of the *Skidmore* study demonstrate that Amneal's ANDA product will be administered in an amount that results in essentially no reduction in skin microflora over a six-month period. As Plaintiffs' expert, Dr. Zhanel explained, *Skidmore* (the results of which were reported in the Ashley patents as Example 38) was a double-blind, randomized, placebo-controlled trial that sampled the skin microflora of patients with moderate acne before and after a six-month treatment of 40 mg doxycycline daily. (*See* PTX-288 at GLD0083629; Zhanel Tr. at 165) *Skidmore* found that, as compared to the placebo, 40 mg doxycycline daily had no effect on the skin microflora, caused no change in the composition of the normal skin flora, and did not result in the emergence of doxycycline-resistant organisms. (*See* PTX-288 at GLD0083631-632; Zhanel Tr. at 165-66; Webster Tr. at 78-80) More specifically, *Skidmore* showed that 40 mg of doxycycline daily results in no statistically significant change in the total microbial colony counts for each species sampled, including *P. acnes*; no increase in the number of bacteria resistant to 4 μg/ml doxycycline; and no increase in

MIC values for isolates resistant to 4 μg/ml doxycycline. (*See* DTX-288 at GLD008361-362; Zhanel Tr. at 165-67) These findings prove that administration of 20 mg twice-daily doxycycline (or 40 mg once-daily) (*see* Webster Tr. at 80) results in, at most, a negligible reduction of skin microflora during a six-month treatment.

Amneal's Label confirms this conclusion. As discussed above, Amneal's Label states: "*In vivo* microbiological studies utilizing a similar drug exposure for up to 18 months demonstrated no detectable long-term effects on bacterial flora of the . . . skin . . . ." (PTX-100 at Amneal-Doxy2016-00434890) This excerpt (as it relates to skin) was approved by the FDA for inclusion in Oracea®'s Label based on the results of the *Skidmore* study. (*See* Webster Tr. at 71-72; Zhanel Tr. at 157) Thus, the FDA has accepted the finding that a once-daily 40 mg dose of doxycycline is equivalent to the 20 mg twice-daily administration tested in *Skidmore*. (*See* Webster Tr. at 80) Amneal's Label contains the same statement as Galderma's, showing that Amneal's ANDA product will be administered in an amount that results in no detectable long-term effects on skin microflora.

Amneal's arguments to the contrary fail to persuade the Court. Amneal contends that microbiological sampling of at least three or four representative areas of the body would be necessary to prove infringement. However, as the Court previously found, *Skidmore* is the strongest intrinsic evidence of what the patentee intended to convey with the skin microflora limitation. (*See* D.I. 129 at 6) Testimony at trial also confirmed that, as of 2000-2001, a POSA would have considered swabbing the glabella, the methodology employed in *Skidmore*, to be the standard method for studying the effect of doxycycline on skin microflora. (*See* Zhanel Tr. at 168 (explaining why sebaceous facial skin is ideal for testing bacteria associated with acne);

Webster Tr. at 80-82 (explaining logic behind sampling forehead, where *P. acnes* lives, because *P. acnes* "is the bug to which the inflammation in acne is directed")) As Drs. Kreiswirth and Meltzer conceded – and as is supported by common sense – sampling the entire skin surface for skin microflora would be impractical and cost-prohibitive. (*See* Kreiswirth Tr. at 546 ("I mean, sampling all areas of your skin, first of all, would be expensive and probably not necessary to sample all areas of your skin"); Meltzer Tr. at 620 ("It's impractical, I agree with you, to assay the entire skin surface."))

Moreover, Amneal's experts could not agree on how many locations would need to be sampled or the types of sampling methods that would be required to prove infringement. (*Compare* Kreiswirth Tr. at 548 (stating that sampling three, four, or five regions of skin is required) *with* Meltzer Tr. at 615-21 (suggesting that samples from even 20 regions of body would not be sufficient to prove infringement)) Nor could Dr. Kreiswirth point to any study available as of 2001 that utilized the procedures he proposes. (*See* Kreiswirth Tr. at 549) Amneal likewise did not present any studying contradicting the findings of *Skidmore* or calling into question the methodology *Skidmore* used. (*See* Edwards Tr. at B-57-58 (conceding she was unaware of any study contradicting *Skidmore*'s findings); Kreiswirth Tr. at 536 (agreeing *Skidmore* is only study to have addressed question of effects of 40 mg doxycycline daily on skin); *see also* Webster Tr. at 121 ("Nothing has come out to contradict [Skidmore]. It stands."))

Amneal's various hypotheticals about bacteria that may be inhibited at less than 4 µg/ml, but that would not appear in the results of *Skidmore*, do not contradict the Court's conclusion as to doctrine of equivalents infringement. As Dr. Zhanel testified, 4 µg/ml is the clinical breakpoint for determining resistance to doxycycline, and, while Dr. Zhanel testified that it

would not be ***impossible*** to test for resistence less than 4 μg/ml, the Court is persuaded that any reduction in microflora that would go undetected by *Skidmore* would be *de minimis*. (*See* Zhanel Tr. at 167, 174-75, 270-72) (explaining resistence testing procedures used in *Skidmore* and that organisms are not resistant to doxycycline if MIC is less than 4 μg/ml)

Thus, based on the record in this case, the Court concludes that Galderma has proven, by a preponderance of the evidence, that the administration of Amneal's ANDA product meets the skin microflora limitation under the doctrine of equivalents.

C. Galderma Has Proven Amneal Indirectly Infringes the Ashley II Patents

Galderma has also proven that Amneal's efforts to persuade doctors and patients to use Amneal's ANDA product in a manner consistent with Amneal's Label make Amneal liable for indirectly infringing the asserted claims of the Ashley II patents, by both inducing and contributing to direct infringement by third parties. "To prove induced infringement, the patentee must show direct infringement, and that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *Toshiba Corp. v. Imation Corp*., 681 F.3d 1358, 1363 (Fed. Cir. 2012) (internal quotations omitted). "[I]nduced infringement under § 271(b) requires knowledge that the induced acts constitute patent infringement." *Global–Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 766 (2011). To prove contributory infringement, the patent owner must demonstrate: (1) an offer to sell, a sale, or an import; (2) of a component or material for use in a patented process constituting a material part of the invention; (3) knowledge by the defendant that the component is especially made or especially adapted for use in an infringement of such patents; and (4) the component is not a staple or article suitable for substantial non-infringing use. *See Fujitsu Ltd. v. Netgear Inc*., 620

F.3d 1321, 1326 (Fed. Cir. 2010) (citing 35 U.S.C. § 271(c)).

As discussed above, Galderma has proven that administration of Amneal's ANDA product directly infringes the Ashley II patents under the doctrine of equivalents. Amneal's Label instructs patients to take, and directs doctors to administer, Amneal's ANDA product once-daily by mouth for the treatment of only inflammatory lesions. (*See* PTX-100 at Amneal-Doxy2016-00434868) Accordingly, Amneal's Label will "inevitably lead some consumers to practice" the use of 40 mg daily doxycycline for the treatment of the papules and pustules of rosacea. *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010); *see also Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 926 (Fed. Cir. 2011) ("We have long held that the sale of a product specifically labeled for use in a patented method constitutes inducement to infringe that patent, and usually is also contributory infringement."). Amneal's Label further establishes that Amneal has the specific intent to induce infringement of the asserted claims of the Ashley II patents. *See AstraZeneca*, 633 F.3d at 1060 ("The pertinent question is whether the proposed label instructs the users to perform the patented method. If so, the proposed label may provide evidence of [the generic's] affirmative intent to induce infringement."). Amneal offered no argument to the contrary. (*See* D.I. 264 at 25 n.17) (arguing only that Galderma has failed to prove direct infringement) Nor is there any evidence or argument that Amneal's ANDA product will have a substantial non-infringing use. *See Eli Lilly*, 435 F. App'x at 927 (holding that "unauthorized activity does not avoid infringement by a product that is authorized to be sold solely for the infringing use").

Accordingly, Galderma has proven that if Amneal were to market its ANDA product, Amneal would both induce and contribute to infringement of the asserted claims of the Ashley II

patents.

III. Validity of the Ashley Patents

Amneal contends that: (1) all of the asserted claims of the Ashley patents are invalid for lack of enablement; (2) all of the asserted claims of the Ashley patents are invalid for lack of written description; (3) claim 30 of the Ashley '267 patent, claim 15 of the Ashley '506 patent, and claim 13 of the Ashley '946 patent are invalid as anticipated by Dr. Feldman's and/or his patient's use of Periostat® to treat rosacea; (4) claims 3, 4, 5, and 16 of the Ashley '506 patent, claims 14, 15, and 16 of the Ashley '946 patent, and all of the asserted claims of the Ashley '572 patent are obvious in view of Dr. Feldman and/or his patient's use of Periostat®; and (5) the asserted claims of the Ashley I patents are indefinite in view of the "sub-antibacterial amount" terms.

As explained below, Amneal has failed to meet its burden to prove by clear and convincing evidence that any of the asserted claims are invalid.

A. Enablement

Amneal contends that all of the asserted claims of the Ashley patents are invalid because the patents fail to enable the use of SR or once-daily doxycycline formulations, as certain of the asserted dependent claims require.[11] The Court disagrees.

1. Scope of the claimed invention

"Under the doctrine of claim differentiation, dependent claims are presumed to be of

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[11]Dependent claims 15, 24, and 26 of the 'Ashley 572 patent; claims 4 and 5 of the Ashley '506 patent; and claims 15 and 16 of the Ashley '946 patent recite "sustained release" or "once a day" administrations of doxycycline. (*See* PTX-002 at 33:13-15, 34:21-22, 34:26-27; PTX-008 at 32:9-13; PTX-010 at 32:64-67)

narrower scope than the independent claims from which they depend." *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1242 (Fed. Cir. 2003). That is, "the presence of a dependent claim that adds a particular limitation raises a presumption that the limitation in question is not found in the independent claim." *Liebel–Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 910 (Fed. Cir. 2004); *see also Acumed LLC v. Stryker Corp.*, 483 F.3d 800, 806 (Fed. Cir. 2007).

Amneal contends that because certain dependent claims of the Ashley patents recite SR and once-daily formulations of doxycycline, the independent claims also encompass SR and once-daily formulations, and such formulations are part of the full scope the patents must enable. According to Amneal, "claims are not enabled . . . when a POSA can use only one embodiment out of many claimed." (D.I. 264 at 17-18) (citing, among others, *MagSil*, 687 F.3d at 1380; *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011); *Alcon Research, Ltd. v. Apotex Inc.*, 678 F.3d 1362, 1367 (Fed. Cir. 2012); *AK Steel*, 344 F.3d at 1343-45; *Alza Corp.*, 603 F.3d at 937, 939-41) In Amneal's view, the fact that the patentee specifically recited once-daily and SR formulations in the claims means that those formulations were not unforeseeable improvements or merely "tangential" to the claimed invention but, rather, were fundamental to what was claimed. (*See* D.I. 264 at 16)

Galderma responds that Amneal misunderstands the fundamental nature of the claimed invention, which, in Galderma's view, is not a particular formulation of doxycycline, but rather the novel insight that a low dose of doxycycline is effective in treating the papules and pustules of rosacea while avoiding unwanted side effects. (*See* D.I. 244 at 33) Galderma emphasizes that many of the asserted claims of the Ashley patents are not limited to once-daily or SR

formulations,[12] proving that the claims are not limited to any particular method of practicing the claimed invention. (*See* D.I. 244 at 23-24) Accordingly, Galderma argues that the Ashley patents need only describe one mode of practicing the claimed invention. (*See* D.I. 244 at 24-27) (citing, among others, *Invitrogen Corp. v. Clontech Labs.*, 429 F.3d 1052, 1070-71 (Fed. Cir. 2005); *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1335 (Fed. Cir. 2003); *Del. Display Group LLC v. VIZIO, Inc.*, 2017 WL 784988, at *5 (D. Del. Mar. 1, 2017); *Advanced Fiber Techs. (AFT) Tr. v. J&L Fiber Servs., Inc.*, 2015 WL 1472015, at *17-18 (N.D.N.Y. Mar. 31, 2015)) Galderma argues that they do so by citing to Periostat®, a 20 mg twice-daily dose of doxycycline, as an "especially preferred embodiment" of the Ashley patents. (*E.g.*, PTX-008 at 5:59-63)

On this issue, the Court agrees with Amneal. While Galderma is correct that the Ashley patents are generally directed to low doses of doxycycline for the treatment of acne rosacea, the patentee also specifically claimed SR and once-daily formulations – a fact that differentiates this case from those on which Galderma relies. For example, in *Invitrogen*, 429 F.3d at 1070, the asserted claims "describe[d] genetically engineered [reverse transcription] ***without regard for the method used*** to mutate the genes" (emphasis added). Because the claims were unrestricted as to the method of mutation, the Court held that the patent need only enable one mode of achieving the claimed mutation. *See id.* at 1070-71 (stating defendant's arguments "might have force had [plaintiff] limited its claims to [a particular method of mutation]"). Here, however, the Ashley

[12]Claims 14 and 23 of the Ashley '572 patent; claim 3, 15, and 16 of the Ashley '506 patent; claims 13 and 14 of the Ashley '946 patent; and claim 30 of the Ashley '267 patent recite oral administration of a 40 mg doxycycline daily dosage without restricting administration to a particular frequency or mode. (PTX-002 at 33:10-12, 34:17-20; PTX-008 at 32:6-8, 32:46-55; PTX-010 at 32:51-63; PTX-001 at 34:45-48)

patents specifically claim methods of administration by once-daily and SR dosages. (*See, e.g.*, PTX-001 at 9:5-7, 9:21-23) Thus, unlike in *Invitrogen*, the enablement requirement is not met by enabling one mode of making and using the claimed invention.[13] Having claimed multiple, particular methods of administration, the patentee was required to enable them. Accordingly, the full scope of the Ashley patents includes "once a day" and "sustained release" doxycycline formulations, and, thus, the Ashley patents must enable those particular formulations.

2. The Ashley patents enable SR and once-daily formulations

Regardless, the Ashley patents do enable "once a day" and "sustained release" formulations.

Amneal contends that every *Wands* factor suggests that the specification would not have allowed a POSA to practice SR or once-daily formulations of doxycycline without undue experimentation. Amneal's expert, Dr. Elder, testified that there were no once a day or SR 40 mg formulations of doxycycline in the prior art, doxycycline's absorption window was unknown as of 2000-2001, the specification provided no additional guidance beyond the prior art, drug absorption is unpredictable, and significant trial and error would have been required to achieve once a day formulations, as evidenced by Faulding's failure to formulate a once a day doxycycline product. (*See* Elder Tr. at 345-47)

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[13]The other cases Galderma cites are unhelpful for similar reasons. *See, e.g.*, *Amgen*, 314 F.3d at 1335 ("***[W]here the method is immaterial*** to the claim, the enablement inquiry simply does not require the specification to describe technological developments concerning the method by which a patented composition is made that may arise after the patent application is filed." (emphasis added; internal quotation marks omitted)); *Advanced Fiber Techs.*, 2015 WL 1472015 at *17-18 (distinguishing between argument that patents failed to enable "certain disclosed alternative modes," where patent need only disclose one mode of practicing claimed invention, from those where "scope of the claims . . . is at issue," and disclosing one mode is insufficient).

Amneal also places particular emphasis on Dr. Rudnic's testimony in the Chang IPRs. During the Chang IPRs, Dr. Rudnic opined that the Ashley specification "does not disclose or teach ***any*** actual formulation that at once-daily dosage will give steady state blood levels" within the required therapeutic window; a "skilled artisan would have to engage in excessive trial-and-error experimentation . . . to determine, which, if any, of the numerous hypothetical formulations within the broad scope of the Ashley references might actually work" to achieve "a once-daily doxycycline formulation that . . . would effectively treat inflammatory conditions like rosacea while remaining below blood levels linked to antibacterial side effects;" and the Ashley specification, in combination with the Ashley '854 application, articulated no more than "a mere ***wish*** for a low-dose once-daily doxycycline formulation, without any guidance on how to obtain one." (DTX-241 ¶¶ 94, 128)

Galderma counters by pointing to Amneal's admissions in its portion of the proposed final pretrial order filed in *Amneal I*, which unequivocally state that the Ashley patents were enabled and described. As to once-daily formulations, Dr. Rudnic testified that the Ashley specification's description of target blood levels, as well as the availability of the Periostat® Label and Approval Package – which disclosed "substantial" single dose and steady state pharmacokinetic data for 20 mg twice-daily doxycycline – would provide a POSA with very useful information for formulating a once-daily dosage. (*See* Rudnic Tr. at 772-74) Indeed, Dr. Rudnic testified that once a POSA had that information, additional pharmacokinetic testing to formulate a once-daily formulation "would be routine." (Rudnic Tr. at 774) Galderma also points to two Whelton papers, which described where the absorption of doxycycline occurs, as providing a POSA with valuable information for formulating a once-daily dosage. (*See* Rudnic

Tr. at 780-81)

As to SR formulations, Galderma contends that the information in the Ashley '854 application, which is incorporated by reference in the Ashley patents, would have provided a POSA with sufficient information about gastroretentive dosages to enable SR formulations. (*See* Rudnic Tr. at 782-84) Galderma also argues that gastroretentive formulations were well-known in the art as of 2000-2001. (*See* Rudnic Tr. at 785-86) Galderma also takes issue with Amneal's use of Dr. Rudnic's IPR testimony, contending that Dr. Rudnic was focused only on whether the specific 30 mg IR/10 mg DR once-daily composition claimed in Chang was obvious. (*See* D.I. 244 at 32)

The Court sides with Galderma. The Ashley patents cite Periostat®, a 20 mg twice daily dosage of doxycycline, as an "especially preferred embodiment" of the claimed invention. (*E.g.*, PTX-008 at 5:59-63) Periostat® was commercially available at the time the Ashley patents were filed, so a POSA would have had access to the Periostat® Label and Approval Package. (*See* PTX-008 at 5:59-63) The Court agrees with Galderma that these materials would have given a POSA substantial information about the pharmacokinetic properties of Periostat®, including its Cmax, Tmax, and half-life, in various modes of administration. (*See* PTX-519 at Amneal-Doxy2016-00023434; PTX-518 at Amneal-Doxy2016-00290255, -281, -320, -334-348; Rudnic Tr. at 773) Additionally, Example 38 would have provided a POSA with valuable clinical and efficacy data for a twice-daily 20 mg dosage. (*See* Rudnic Tr. at 795) This information would have provided a POSA attempting to formulate a once-daily formulation with a good starting point.

In addition, a POSA would have had the information disclosed in the Ashley '854

application. The Ashley patents incorporate by reference the Ashley '854 application, which provides information about administering tetracycline compounds by sustained release. (*See e.g.*, PTX-008 at 9:11-19; Rudnic Tr. at 782) Specifically, the Ashley '854 application identifies as a "preferred embodiment" a controlled release composition that becomes entrapped in the upper portion of the gastrointestinal tract (i.e., a gastroretentive formula). (DTX-206 at 16:9-14) The '854 application goes on to explain that "[s]uch compositions are typically manufactured by utilizing controlled-release agents of a larger particle size, as is known in the art." (DTX-206 at 16:11-14) Galderma proved at trial that, as of 2000-2001, there were 19 patents covering gastroretentive technologies that would have been available to a POSA attempting to formulate an SR formulation, including patents or patent applications that specifically mention the use of doxycycline in gastroretentive formulations. (*See* Rudnic Tr. at 784-87, 790-92; PTX-125; PTX-126; PTX-197; PTX-198; PTX-199; PTX-200; PTX-201; PTX-202; PTX-203; PTX-204; PTX-205; PTX-206; PTX-207; PTX-208; PTX-209; PTX-210; PTX-211; PTX-212; PTX-215) Moreover, Galderma demonstrated that, while the exact absorption window of doxycycline was unknown as of 2000-2001, a POSA would have known that absorption of doxycycline occurs primarily in the upper GI tract, and not in the colon or lower portion of the GI. (*See* Rudnic Tr. at 780-81; PTX-284) This knowledge would have allowed a POSA to practice the claimed invention, including once-daily and SR formulations, without undue experimentation.

Dr. Rudnic's IPR testimony, while undoubtedly helpful to Amneal's case, does not carry Amneal's heavy burden, particularly in light of the information Galderma proved would have been available to a POSA in the 2000-2001 time frame. In assessing whether there is clear and convincing evidence of invalidity, the Court must also take account of Amneal's own prior

statements in *Amneal I*, to the effect that each of the allowed claims of the Ashley patents is enabled and disclosed once-daily and sustained release compositions of 40 mg doxycycline. (*E.g.*, PTX-129 ¶ 102 ("Each of the allowed claims of the [Ashley] '572 patent is supported by an enabling disclosure in the [Ashley] '572 patent specification."); *id.* ¶ 180 ("The [Ashley] '572 patent . . . disclose[s] administering doxycycline once-a-day to achieve steady state serum concentrations between 0.1 μg/ml to 0.8 μg/ml, more preferably between 0.4 and 0.7 μg/ml.")) While these pretrial statements are not binding "admissions" in the sense that Amneal is foreclosed from contesting the issue, they nonetheless must be factored into the Court's evaluation of how a POSA would view the Ashley patents, and here they help persuade the Court that the Ashley patent claims have not been proven invalid.

Accordingly, the Court concludes that Amneal has not met its burden to prove lack of enablement by clear and convincing evidence.

B. Written Description

Amneal also asserts that the Ashley patents are invalid for lack of written description. "[W]ritten description and enablement often rise and fall together." *Ariad*, 598 F.3d at 1352. Such is the case here.

As discussed above, Mr. Ashley recognized enough about the particulars of his invention to include in the patents Example 38, which reports clinical and efficacy data for a 20 mg twice-daily (40 mg daily) dosage of doxycycline; a citation to Periostat® as an especially preferred embodiment of the claimed invention; and the '854 patent application, which was incorporated by reference into the asserted Ashley patents and provides additional information about gastroretentive formulations. (*See* Rudnic Tr. at 769-70, 782-83) This is sufficient to

demonstrate Mr. Ashley was in possession of the claimed invention.

The fact that Mr. Ashley, who was not a formulator, would not himself have known how to make the claimed invention is inapposite. *See Newman v. Quigg*, 877 F.2d 1575, 1581-82 (Fed. Cir. 1989) (rejecting notion that it is "a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works"); *see also Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014) (citing same).

Accordingly, Amneal has failed to prove by clear and convincing evidence that a POSA would not have understood Mr. Ashley to be in possession of the claimed invention.

C. Dr. Feldman's and His Patient's Use of Periostat® Did Not Anticipate the Ashley Patents

Amneal asserts that Dr. Feldman's and his patient's use of Periostat® anticipated claim 30 of the '267 Ashley patent, claim 15 of the '506 Ashley patent, and claim 13 of the '946 Ashley patent. For such a use to anticipate, it "must be a public use with all of the claim limitations." *Clock Spring, L.P. v. Wrapmaster, Inc.*, 560 F.3d 1317, 1325 (Fed. Cir. 2009). Neither Dr. Feldman's nor his patient's use satisfies this requirement.

In *Mylan*, the Court concluded that Dr. Feldman's use of Periostat® – both personally, as prescribed by his periodontist, and in treating his patient with rosacea – did not anticipate any of the claims of the asserted Ashley I patents because (1) Periostat®, like Oracea®, was not a commercial embodiment of the Ashley patents; (2) Dr. Feldman's testimony about his personal use of Periostat® was uncorroborated; and (3) the treatment of his patient was not public. *See Mylan*, 809 F. Supp. 2d at 322-24.

Amneal candidly acknowledges that it did not present any new or additional evidence in

support of its anticipation contentions beyond what was before the Court in *Mylan*, and there has been no relevant intervening change in the law since the Court's decision in *Mylan*. (*See* Tr. at 952) Thus, as Amneal concedes, the Court would have to reverse course to find the relevant claims invalid as anticipated. Amneal has not proven that the Court should do so, regardless of whether Periostat® is an embodiment of the Ashley patents.

Dr. Feldman's testimony remains uncorroborated and insufficient to prove invalidity. *See TypeRight Keyboard Corp. v. Microsoft Corp.*, 374 F.3d 1151, 1159-60 (Fed. Cir. 2004) ("Corroboration is required of any witness whose testimony alone is asserted to invalidate a patent.") (internal quotation marks and citations omitted); *see also Finnigan Corp. v. Int'l Trade Comm'n*, 180 F.3d 1354, 1370 (Fed. Cir. 1999) (explaining corroboration requirement). Amneal did not offer any additional evidence at trial to corroborate Dr. Feldman's personal use of Periostat®. Consequently, Dr. Feldman's account of his use of Periostat® is insufficient to invalidate the relevant claims of the Ashley patents.

Additionally, Amneal has not proven Dr. Feldman's patient's treatment was public. Amneal asks the Court to revisit its previous conclusion that the use was not public, contending that Dr. Feldman was under no obligation to keep the treatment of his patient secret. (*See* Tr. at 951-52) However, Dr. Feldman was obligated to keep his patient's name and treatment confidential. (*See* Feldman Tr. at 394-95 (discussing patients' "right for privacy of anything regarding their medical information"), 431-32 (acknowledging legal duties regarding patient confidentiality)) Moreover, there is no evidence that Dr. Feldman's patient ever filled the prescription, took the prescription, or experienced any improvement in her rosacea. (*See* Feldman Tr. at 422-23) Nor is there evidence that Dr. Feldman used this experience as a basis to

publish, patent, or attempt to commercialize a treatment for rosacea. (*See* Feldman Tr. at 425-28) Thus, the Court finds Dr. Feldman's use was not public.

Accordingly, the Court concludes that Amneal has failed to present clear and convincing evidence that claim 30 of the '267 Ashley patent, claim 15 of the '506 Ashley patent, and claim 13 of the '946 Ashley patent are anticipated by Dr. Feldman's or his patient's use of Periostat®.

D. Dr. Feldman's and His Patient's Use of Periostat® Did Not Make the Claimed Invention Obvious

Amneal asserts that, in the event the claims are found to be enabled, Dr. Feldman's use of Periostat® invalidates the remaining claims of the Ashley patents as obvious. (*See* Elder Tr. at 347-48) (offering obviousness opinion in alternative) In *Mylan*, the Court rejected the argument that Dr. Feldman's use, in combination with three prior art references, rendered the Ashley I patents obvious, having found Periostat® not to be an embodiment of the Ashley I patents. *See Mylan*, 809 F. Supp. 2d at 324. Amneal has failed to persuade the Court to change its conclusion.

The Court is not persuaded that a POSA would have been motivated to practice the claimed invention based on either Dr. Feldman's or his patient's use of Periostat®. To the contrary, Galderma demonstrated that the conventional wisdom in 2000-2001 was that "large doses" of antibiotics were needed to treat acne and rosacea. (*See* Webster Tr. at 48; Feldman Tr. at 420 (acknowledging that use of doxycycline "was not a typical treatment [for rosacea] as of 2000")) Amneal did not explain how a POSA would have learned of Dr. Feldman's or his patient's use, or that a POSA would have had any reasonable expectation of success in using 40 mg doxycycline daily (or in an SR formulation) to treat the papules and pustules of rosacea. (*See*

Feldman Tr. at 407 (stating he only expected patient's rosacea to improve because of his personal experience with Periostat®), 427-28 (stating he had never disclosed, made public, attempted to sell, attempted to patent, or written about use of Periostat®), 431-33 (discussing confidentiality obligations and limitations on access to patients' records, which were kept in locked storage locker), 436-37 (stating he did not discuss either use with anyone prior to litigation))

Thus, Amneal has not met its burden of proving by clear and convincing evidence that claims 3, 4, 5, and 16 of the Ashley '506 patent; claims 14, 15, and 16 of the Ashley '946 patent; and all of the asserted claims of the Ashley '572 patent are obvious in light of Dr. Feldman's or his patient's prior use of Periostat®.[14]

E. The Ashley I Asserted Claims Are Not Indefinite

Finally, Amneal argues that the asserted claims of the Ashley I patents are invalid as indefinite because of the sub-antibacterial amount limitations. According to Amneal, a POSA would not be reasonably certain about the minimum amount of inhibition allowed by the claims' requirement that doxycycline be administered in an amount that "from a clinical point of view, does not inhibit a significant amount of microorganisms, e.g., bacteria even though a few of the more sensitive bacterial cells may be inhibited." (PTX-378 at 0008) Galderma counters that a POSA would understand that "a few" in the Court's construction allows for inhibition that is not "significant." The Court agrees with Galderma.

The Ashley patents provide sufficient guidance to allow a POSA to understand the boundaries of the sub-antibacterial term. While Amneal contends that "a few" is not "readily

[14]In light of the Court's findings based on Amneal's evidence, it is unnecessary to analyze Galderma's evidence of secondary considerations of non-obviousness.

quantifiable," Amneal's expert, Dr. Kreiswirth, testified that a POSA would understand "that 'a few' resides somewhere between" zero and significant inhibition. (Kreiswirth Tr. at 567) These boundaries were ones Dr. Kreiswirth "fe[lt] comfortable" testifying that the Ashley patents establish. (Kreiswirth Tr. at 567) Dr. Zhanel offered consistent testimony, stating that at least "statistically significant" reductions in bacteria fall outside the scope of the claims. (*See* Zhanel Tr. at 739-40) While not an exact figure, the Court concludes that this understanding, in combination with the Ashley '572 patent's recitation of 40 mg doxycycline daily as an "especially preferred embodiment" of the claimed invention, shows that the Ashley I patents provide a POSA with reasonable certainty about the scope of the claimed invention. (*See* PTX-002 at 6:9-11, 19-23) Thus, Amneal has not proven by clear and convincing evidence that the asserted claims of the Ashley I patents are indefinite.

CONCLUSION

Galderma has proven by a preponderance of the evidence that Amneal infringes claim 1 of the Chang '740 patent; claims 1 and 3 of the Chang '405 patent; claims 1 and 2 of the Chang '364 patent; claims 3, 4, 5, 15, and 16 of the Ashley '506 patent; and claims 13, 14, 15, and 16 of the Ashley '946 patent. Galderma has not proven Amneal infringes claim 1 of the Chang '532 patent; claim 30 of the Ashley '267 patent; or claims 14, 15, 23, 24, and 26 of the Ashley '572 patent.

Amneal has failed to prove by clear and convincing evidence that (1) any of the asserted claims of the Ashley patents are invalid for lack of enablement; (2) any of the asserted claims of the Ashley patents are invalid for lack of written description; (3) claim 30 of the Ashley '267 patent; claim 15 of the Ashley '506 patent; or claim 13 of the Ashley '946 patent are invalid as

anticipated; (4) claims 3, 4, 5, and 16 of the Ashley ’506 patent; claims 14, 15, and 16 of the Ashley ’946 patent; or any of the asserted claims of the Ashley ’572 patent are obvious; or that (5) the asserted claims of the Ashley I patents are indefinite.

An appropriate Order follows.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GALDERMA LABORATORIES, L.P.; NESTLÉ SKIN HEALTH S.A.; and TCD ROYALTY SUB, LLC,	:	
Plaintiffs,	:	
v.	:	C.A. No. 16-207-LPS
AMNEAL PHARMACEUTICALS, LLC and AMNEAL PHARMACEUTICALS CO. (I) PVT. LTD.,	:	
Defendants.	:	

ORDER

At Wilmington this **27th** day of **August, 2018**:

For the reasons set forth in the Opinion issued this date,

IT IS HEREBY ORDERED that:

1. Galderma has proven Amneal's ANDA product infringes claim 1 of the Chang '740 patent, claims 1 and 3 of the Chang '405 patent, and claims 1 and 2 of the Chang '364 patent.

2. Galderma has not proven Amneal's ANDA product infringes claim 1 of the Chang '532 patent.

3. Galderma has not proven Amneal's ANDA product infringes claim 30 of the Ashley '267 patent or claims 14, 15, 23, 24, and 26 of the Ashley '572 patent.

4. Galderma has proven Amneal's ANDA product infringes claims 3, 4, 5, 15, and 16 of the Ashley '506 patent and claims 13, 14, 15, and 16 of the Ashley '946 patent.

5. Amneal has failed to prove claim 30 of the Ashley '267 patent; claims 14, 15, 23,

24, and 26 of the Ashley '572 patent; claims 3, 4, 5, 15, and 16 of the Ashley '506 patent; and claims 13, 14, 15, and 16 of the Ashley '946 patent are invalid for lack of enablement, lack of written description, or obviousness.

6. Amneal has failed to prove claim 30 of the Ashley '267 patent, claim 15 of the Ashley '506 patent, and claim 13 of the Ashley '946 patent are invalid as anticipated.

7. Amneal has failed to prove claim 30 of the Ashley '267 patent and claims 14, 15, 23, 24, and 26 of the Ashley '572 patent are invalid for indefiniteness.

8. The parties shall meet and confer and submit, no later than **August 31, 2018**, a proposed order consistent with the Opinion, to enter final judgment (a) **FOR** Plaintiffs and **AGAINST** Defendants with respect to the asserted claims of the Chang '740, '405, and '364 patents and Ashley II patents, and (b) **FOR** Defendants and **AGAINST** Plaintiffs with respect to the asserted claims of the Chang '532 and Ashley I patents. By the same date, the parties shall submit a joint status report, providing their position(s) as to whether any further proceedings are required.

9. As the Opinion has been issued under seal, the parties shall meet and confer and shall, no later than **August 29, 2018**, submit a proposed redacted version. Thereafter, the Court will issue a publicly-available version.

HONORABLE LEONARD P. STARK
UNITED STATES DISTRICT COURT