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. SUN PHARMACEUTICAL INDUSTRIES LIMITED and SUN PHARMACEUTICAL INDUSTRIES, INC., Defendants.	C.A. No. 16-1003-LPS

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UNSEALED ON
OCTOBER 4, 2019

MEMORANDUM OPINION

September 30, 2019
Wilmington, Delaware

STARK, U.S District Judge:

Galderma Laboratories, L.P., Nestlé Skin Health S.A., and TCD Royalty Sub, LLC (together, "Galderma" or "Plaintiffs") sued Sun Pharmaceutical Industries Limited and Sun Pharmaceutical Industries, Inc. (together, "Sun" or "Defendants") under the Hatch-Waxman Act, 35 U.S.C. § 271(e). (*See* D.I. 1) Sun seeks to bring to market a new drug ("Sun's NDA Product" or "Sun NDA Product") which is bioequivalent to Galderma's Oracea Capsules ("Oracea"), a once-daily 40 milligram ("mg") administration of doxycycline for the treatment of the papules and pustules of acne rosacea. (D.I. 1 ¶ 17) Galderma alleges that Sun's NDA Product infringes U.S. Patent Nos. 8,206,740 ("Chang '740 patent"), 8,394,405 ("Chang '405 patent"), 8,470,364 ("Chang '364 patent"), and 7,749,532 ("Chang '532 patent") (collectively, the "Chang patents").[1] (*See* D.I. 1) The Chang patents are generally directed to low-dose doxycycline formulations with immediate-release and delayed-release portions, which are used for the treatment of the papules and pustules of acne rosacea.

In December 2018, the Court held a three-day bench trial. (*See* D.I. 208-10 ("Tr.")) Thereafter, the parties submitted proposed findings of fact (D.I. 204, 206) and post-trial briefing (D.I. 205, 207, 211, 212). In August 2019, the Court ordered supplemental claim construction briefing. (*See* D.I. 222; *see also* D.I. 226, 227, 228, 229)

[1] Galderma also alleged infringement of U.S. Patent Nos. 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) Before trial, Galderma dropped assertion of the Ashley '267 and '572 patents (D.I. 202), and Sun stipulated to infringement and validity of the Ashley '506 and '946 patents (subject to certain conditions) (D.I. 203). Hence, the only issues for trial (and this Opinion) pertain to infringement and validity of the Chang patents.

Pursuant to Federal Rule of Civil Procedure 52(a), and having considered the entire record in this case and the applicable law, the Court concludes that: (1) Sun's NDA Product infringes the asserted claims of the Chang patents; and (2) the asserted claims of the Chang patents are not invalid for obviousness.

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

FINDINGS OF FACT

I. Introduction

1. This is a patent infringement action arising out of Defendant Sun Pharmaceutical Industries Limited's ("Sun") submission of New Drug Application ("NDA") No. 209259 to the U.S. Food and Drug Administration ("FDA") under § 505(b)(2) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(b)(2), seeking FDA approval of doxycycline hyclate tablets, 40 mg. (D.I. 1)

2. Plaintiff Galderma Laboratories, L.P. ("Galderma") holds NDA No. 50-805 on Oracea capsules, which was approved by the FDA on May 26, 2006. (D.I. 1 at ¶ 17; D.I. 195 Ex. 1 at ¶ 58) Galderma purchased rights to the Oracea product and other assets from CollaGenex Pharmaceuticals, Inc. in 2008. (Grabowski Tr. at 481)[2]

3. At trial, Galderma asserted infringement of claim 1 of the '740 patent, claims 1 and 3 of the '405 patent, and claims 1 and 2 of the '364 patent. (D.I. 202) Each of the asserted claims of these Chang patents covers a once-daily oral composition containing 30 mg or about 30 mg of immediate release ("IR") doxycycline and 10 mg or about 10 mg of delayed release

[2] Citations to the trial transcript (which can be found at D.I. 208, 209, 210) are in the form of ("[Witness last name] Tr. at [page]").

("DR") doxycycline, resulting in a steady state doxycycline blood level of a minimum of 0.1 μg/ml and a maximum of 1.0 μg/ml. Some claims are directed to the amounts of doxycycline in the form of ratios, such as 75% IR:25% DR.

4. Sun contends that it does not infringe any of the asserted claims of the Chang patents because (i) the Sun NDA product does not contain the claimed amounts of IR formulation or portion of doxycycline; (ii) the Sun NDA product does not contain any DR formulation or portion of doxycycline; and (iii) Plaintiffs have presented no evidence that the administration of Sun's NDA Product results in the claimed steady-state blood levels.

5. Sun further contends that the asserted claims of the Chang patents would have been obvious over the Ashley Applications (Published International Patent Application WO02/080932 ("the '932 publication") and U.S. Provisional Application No. 60/281,854 ("the Ashley '854 application")) (together, the "Ashley Applications") in light of the available pharmacokinetic information concerning Periostat® ("the Periostat Package").

II. Patents-in-Suit

6. The Chang patents all claim priority back to Provisional Application No. 60/460,963, filed on April 7, 2003. Thus, the priority date for the Chang patents is April 7, 2003. (PTX-4.1; Statement of Uncontested Facts (D.I. 195 Ex. 1) ("SUF") at ¶¶ 32, 36, 47; Chambliss Tr. at 306)

7. Galderma asserts claim 1 of the Chang '740 patent against Sun. Claim 1 of the '740 patent recites:

> 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/ml 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.

8. Galderma asserts claims 1 and 3 of the Chang '405 patent. Claim 1 of the '405 patent recites:

> An oral pharmaceutical composition comprising about 40 mg of total doxycycline, which at a once-daily dosage will give steady state blood levels of doxycycline of a minimum of 0.1 μg/ml and a maximum of 1.0 μg/ml, 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.

9. Claim 3 of the '405 patent recites "[t]he composition of claim 1, wherein the ratio of IR to DR is 75:25."

10. Galderma asserts claims 1 and 2 of the Chang '364 patent. Claim 1 of the '364 patent recites:

> 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.

11. Claim 2 of the '364 patent recites:

> 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/ml and a maximum of 1.0 μg/ml, the composition consisting of (i) an immediate release formulation (IR) comprising about 30 mg doxycycline; as [sic] a delayed release formulation (DR) comprising about 10 mg doxycycline; and optionally, (iii) one or more pharmaceutically acceptable excipients.

III. Witnesses

A. Galderma's Experts

12. Dr. Edward Rudnic is the Chief Executive Officer of DisperSol Technologies, a biopharmaceutical company in Georgetown, Texas. (Rudnic Tr. at 102) Dr. Rudnic was offered and recognized as an expert in the invention, design, development, testing, manufacturing, and commercialization of drug products, including pharmaceutical formulations. (Rudnic Tr. 106)

13. Dr. Henry Grabowski is the Director of the Duke University program in Pharmaceuticals and Health Economics. (Grabowski Tr. at 473) Dr. Grabowski was offered and recognized as an expert in economics in the pharmaceutical field, including in determining commercial success and nexus to patents. (Grabowski Tr. at 474)

B. Sun's Experts

14. Dr. Walter Galloway Chambliss is a Professor in Pharmaceutics and Drug Delivery, a Research Professor in the Research Institute of Pharmaceutical Sciences, and Interim Associate Vice Chancellor for Research at the University of Mississippi. (Chambliss Tr. at 267) Dr. Chambliss was offered and recognized as an expert in the field of pharmaceutical sciences and pharmaceutical formulations, including the development of pharmaceutical formulations with varying release mechanisms. (Chambliss Tr. at 271-72)

15. Mr. Ivan Hofmann is a vice president and managing director at Gleason IP, an economics, finance, and accounting firm, where he is the head of the intellectual property practice. (Hofmann Tr. at 498) Mr. Hofmann was offered and recognized as an expert in pharmaceutical economics. (Hofmann Tr. at 501)

C. Fact Witnesses

16. Dr. Richard Rong-Kun Chang is one of the named inventors of the Chang patents. (Chang Tr. at 394-95; *see also* PTX-4; PTX-5; PTX-7)

17. Dr. Chang was formerly employed at Shire Laboratories ("Shire") and at Supernus Pharmaceuticals, Inc. ("Supernus"), and was involved in the development of an oral doxycycline product. (Chang Tr. at 400)

18. Mr. Arash Raoufinia is one of the named inventors of the Chang patents. (Raoufinia Tr. at 408; *see also* PTX-4; PTX-5; PTX-7) Mr. Raoufinia worked at Shire as a scientist between March 2002 and January 2004. (Raoufinia Tr. at 408)

19. Dr. Romi Singh is the Vice President of Formulation Development in the Formulation Development Group at Sun. (Singh Tr. at 193-94) Dr. Singh previously led the Formulation Development Group for differentiated and complex oral products and was involved in the formulation development of Sun's NDA product. (Singh Tr. at 194-96)

20. Dr. Rajeev Mathur is the Vice President and Head R&D Regulatory Affairs Gurgaon for Sun Pharmaceuticals. (Mathur Tr. at 230) Dr. Mathur works with Sun's global regulatory markets, and has knowledge of Sun's regulatory submissions. (Mathur Tr. at 231)

21. Dr. Bharati Nadkarni is a Vice President at Sun Pharmaceuticals. (Nadkarni Tr. at 244)

IV. Person of Ordinary Skill in the Art

22. A person of ordinary skill in the art ("POSA") in the field of the Chang patents as of the priority date had education and experience in drug delivery and formulation. In this field, education and experience levels may vary among persons of ordinary skill, with some persons holding a Bachelor's degree with many years of experience and others holding higher degrees,

but having less work experience. (Rudnic Tr. at 109) Through education or 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. (*Id.*)

V. Oracea Capsules

23. Oracea capsules are an oral pharmaceutical composition indicated for once-daily use for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients. (Webster Tr. at 69; *see also* PTX-309.6)

24. The Oracea capsules composition is 40 mg hard gelatin capsule shells filled with two types of doxycycline beads, 30 mg immediate release beads and 10 mg delayed release beads. (Webster Tr. at 69, 153-54; Rudnic Tr. at 153-54; *see also* PTX-344.5)

25. Oracea capsules are administered in an amount that is effective to treat the papules and pustules of rosacea. (Webster Tr. at 70-72; *see also* PTX-242.3)

26. The patents-in-suit are listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") for Oracea capsules. (SUF ¶ 57)

27. Study COL-101-SSPK-106 (the "Pivotal PK Study") is a clinical pharmacokinetic study of Oracea capsules and is the source of the steady-state pharmacokinetic data for Oracea capsules reported in the Oracea label. (PTX-309.6-7; PTX-344.5; Rudnic Tr. at 143-45)

28. The Pivotal PK Study reports that 30 of 31 subjects who were administered Oracea capsules had plasma concentrations of a minimum of 0.1 μg/ml and a maximum of 1.0 μg/ml at steady-state (Day 7). (PTX-309.6-7; PTX-327.1, 6-8; PTX-343.12; *see also* Rudnic Tr. at 141, 143-45) One subject (Subject No. 14) maintained plasma concentrations at steady-state

of a minimum of 0.1 μg/ml but briefly exceeded a plasma concentration of 1.0 μg/ml (with a measured concentration of 1.08 μg/ml). (PTX-343.12)

VI. Sun's NDA Product

29. Sun Ltd. submitted NDA No. 209259 to the FDA pursuant to § 505(b)(2) of the Federal Food, Drug and Cosmetic Act, seeking approval of Sun's NDA Product: a once-daily 40 mg doxycycline hyclate tablet. In order to demonstrate that Sun's NDA Product is safe and effective, Sun included in its application data showing that Sun's NDA Product is bioequivalent to Galderma's Oracea capsules. (PTX-327.5; *see also* Rudnic Tr. at 127-28; Nadkarni Tr. at 245; Mathur Tr. at 231-32; Singh Tr. at 197; Chambliss Tr. at 364-65) The FDA has tentatively approved Sun's NDA Product. (PTX-343.1)

30. Sun's NDA Product is a once-daily doxycycline tablet product, with an active ingredient equivalent to that of Oracea capsules, as well as the same strength, route of administration, and indication for use as Oracea capsules. (PTX-343.11-12; Rudnic Tr. at 116; Chambliss Tr. at 351-52; Nadkarni Tr. at 244-45; Singh Tr. at 197)

31. The active ingredient in Sun's NDA Product is doxycycline hyclate. (*See, e.g.*, PTX-343.11; Singh Tr. at 204) The total amount of doxycycline in each tablet of Sun's NDA Product is 40 mg. (*See, e.g.*, PTX-343.12; Rudnic Tr. at 116; Chambliss Tr. at 352; Singh Tr. at 197)

32. The Sun NDA Product is a bilayer tablet consisting of two distinct layers, each of which contains doxycycline. (DTX-574.50-51, 126-27; Rudnic Tr. at 117, 168; Chambliss Tr. at 273-74)

33. The Sun NDA describes these two layers as an immediate release ("IR") layer and a modified release ("MR") layer. (DTX-574.50-51, 126-27; Rudnic Tr. at 117; Chambliss Tr. at 273-74)

34. The IR and MR layers of the Sun NDA Product are manufactured separately, using different ingredients and different processes. (DTX-574.126-27; Chambliss Tr. at 286-87)

35. Sun's NDA Product contains pharmaceutically acceptable excipients, including at least the following: microcrystalline cellulose (Avicel PH 102); crospovidone (Type A) (Polyplasdone XL); povidone (i.e., polyvinylpyrrolidone) (Kollidon 30); colloidal silicon dioxide (Aerosil 200); iron oxide sicovit yellow; magnesium stearate (vegetable grade); microcrystalline cellulose (Avicel PH 200); hypromellose (Methocel K 4M Premium CR); hypromellose (Methocel K 100 Premium LV CR); opadry 03F570012 beige; and purified water. (PTX-328. 2-3; *see also* Singh Tr. at 205-06; Rudnic Tr. at 151, 153; Chambliss Tr. at 277, 285-86)

A. The IR Layer

36. The IR layer of the Sun NDA Product contains 26.4 mg of doxycycline. (DTX-574.50; Rudnic Tr. at 117-18, 168-69; Chambliss Tr. at 276-77)

37. The IR layer of the Sun NDA Product is formulated with 1.75 % w/w of povidone and 3.0 % w/w of crospovidone, which corresponds to 3.5% w/w and 6% w/w of the IR layer. (DTX-574.50; Rudnic Tr. at 170-72, 184-87) Crospovidone is a superdisintegrant, which causes the IR layer of the Sun NDA Product to disintegrate within 60 seconds upon administration. (Rudnic Tr. at 132, 170, 183-87; PTX-330.85-87)

38. The IR layer of the Sun NDA Product releases all 26.4 mg of its doxycycline immediately upon administration without any enhanced, delayed, or extended effect. (Rudnic Tr. at 132; Chambliss Tr. at 276-78)

B. The MR Layer

39. The MR layer of the Sun NDA Product contains 13.6 mg of doxycycline. (DTX-574.50-51; Rudnic Tr. at 117-18, 132-33, 168-69; Chambliss Tr. at 273-74, 285-86)

40. The MR layer of the Sun NDA Product contains hypromellose ("HPMC") in two different viscosity grades: Methocel K4M and Methocel K100LV. (DTX-574.50-51; Rudnic Tr. at 132-33; Chambliss Tr. at 285-86) The doxycycline and HPMC are mixed together in a single step in the process of manufacturing the MR layer Product and then blended. (DTX-574.127; Chambliss Tr. at 286-87)

41. Methocel K100LV is a low viscosity grade of hypromellose. (DTX-574.73-74; Rudnic Tr. 132-33; Chambliss Tr. at 290-91) In contrast, Methocel K4M is a medium viscosity grade of hypromellose. (DTX-574.73-74; Chambliss Tr. 290-91, 294-99; Rudnic Tr. 132-33 (testifying that Methocel K4M is "higher viscosity polymer" than Methocel K100 LV))

42. Both the Methocel K4M and Methocel K100 LV polymers, as used in the MR layer in the Sun NDA Product, control the release of doxycycline in the MR layer. (DTX-574.73-74; Rudnic Tr. at 172-73 ("Q: . . . So the third line down, there's an excipient listed as hypromellose USP, methocel K4M? A: Yes. Q: That's defined as a release controlling excipient; is that correct? A: That's what they call it. . . . Q: In the next line down, there's hypromellose, USP methocel K100; is that correct? A: Correct. Q: That's also defined as a release controlling excipient; is that correct? A: That's what they call it."); Chambliss Tr. at 287-92)

43. The MR layer releases doxycycline continuously – with no plateau or stoppage of release – starting immediately after administration and continuing until the MR layer is completely dissolved. (Chambliss Tr. at 292-94, 355-57; DTX-279.17)

44. Sun's "MR Layer" was designed so that it would release some doxycycline (approximately 3.6 mg) in the first 30 minutes after administration, and release the remaining doxycycline (approximately 10 mg) later than 30 minutes after administration. (*See, e.g.*, PTX-329.10-11; PTX-330.4, -65, -78, -82; PTX-331.1-3; Singh Tr. at 205-06, 211-12, 214-16, 218-19, 221-23; Rudnic Tr. at 119-27, 131, 133; Chambliss Tr. at 355-37, 362-64, 376)

45. The mechanism that delays the release of about 10 mg doxycycline in Sun's NDA Product is: (1) the deliberate use of two hypromellose polymers that, once hydrated and set up into a gel, serve as an intervention that entangles the drug and slows the penetration of water into the "MR Layer" of Sun's NDA Product, precluding the release of approximately 10 mg until at least 30 minutes after oral administration; and (2) the location of the approximately 10 mg doxycycline on the interior part of Sun's "MR Layer," which has a plane hidden from the gastric fluid at the interface of the bilayer tablet. (*See* Rudnic Tr. at 136-37)

46. By using a combination of low molecular weight (Methocel K 100 Premium LV) and higher molecular weight (Methocel K 4M Premium CR) hypromellose polymers, Sun's NDA Product allows for a burst of approximately 3.6 mg doxycycline from the surface of the "MR Layer" in the first 30 minutes after administration, before both polymers have gelled; and then, when both polymers have gelled, they "entangle" the remaining portion of approximately 10 mg doxycycline and prevent it from releasing until a time at least 30 minutes after oral administration. (*See, e.g.*, PTX-330.78; Singh Tr. at 206, 220-23; Rudnic Tr. at 132-34, 136-37, 150, 157-58; Chambliss Tr. at 346-47, 353-56, 359-60)

C. Pharmacokinetic Data

47. In a single-dose clinical pharmacokinetic study reported in Sun's NDA, Sun's NDA Product was shown to be bioequivalent to Oracea Capsules under fasting conditions.

(PTX-327.5; PTX-343.12; *see also* Rudnic Tr. at 127-28; Nadkarni Tr. at 245; Mathur Tr. at 231; Singh Tr. at 197; Chambliss Tr. at 364-65) The relevant pharmacokinetic parameters under fasting conditions are reproduced below:

Parameter	**Reference Product (Oracea)**	**Sun's NDA Product**
T_{max} (h)	2.7071	2.2946
C_{max} (ng/mL)	391.1515	397.5441
AUC_{0-t} (ng*hr/mL)	6899.0348	6522.4895
$AUC_{0-\infty}$ (ng*hr/mL)	7146.2988	6880.4922
Half-life (h)	16.9167	16.6048

(PTX-327.5-6) Sun noted that "[t]he 90% confidence intervals for the ratios of [Sun's NDA Product and Oracea] (least-squares means) for doxycycline derived from the analysis of log transformed pharmacokinetic parameters C_{max} (87.62% - 107.89%), AUC_{0-t} (86.14% - 100.13%) and $AUC_{0-\infty}$ (89.20% - 100.60%), were well within the 80-125% bioequivalence acceptance criteria." (*Id.*) Sun also noted that "[t]he ratios of [Sun's NDA Product and Oracea] (least-squares means) for doxycycline derived from the analysis of log transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 97.23%, 92.87% and 94.73%, respectively." (*Id.*)

48. Sun has represented that all of the information contained in its NDA is true and correct. (Singh Tr. at 206-07; Mathur Tr. at 230, 233-34, 236; Nadkarni Tr. at 249; *see also* Chambliss Tr. at 347, 362)

49. The FDA's tentative approval of the Sun NDA Product and Sun's label is based in part on the FDA's acceptance of Sun's single-dose pharmacokinetic study showing bioequivalence of Sun's NDA Product to Oracea capsules. (PTX-343.1-2; *see also* Chambliss Tr. at 364-67; Rudnic Tr. at 142-43)

50. In order to obtain FDA approval, Sun relied on information regarding the clinical safety and efficacy of Oracea capsules from the Oracea label, including safety and efficacy data

from the 16-week Phase III clinical studies for Oracea capsules in treating papules and pustules of rosacea, and information regarding the "long-term" results of clinical microbiology studies of up to 18 months. (*See* PTX-343.14; PTX-344.5; *see also* Rudnic Tr. at 142-43; Chambliss Tr. at 366-67)

51. The therapeutically relevant blood levels for both Sun's NDA Product and Oracea capsules are the steady-state blood levels, and bioequivalence based on a single-dose study was sufficient for the FDA to tentatively approve Sun's NDA Product as safe and effective for long-term use. (*See, e.g.*, PTX-343; Chambliss Tr. at 366-68; Rudnic Tr. at 142; *see also* PTX-376.11)

52. As reflected in FDA policy, single-dose bioequivalence studies are generally more sensitive and discriminating than multiple-dose studies, and therefore are typically the best evidence to show that two products will be bioequivalent at steady-state. (Rudnic Tr. at 142-43; PTX-376.11, 18-19)

VII. Facts Relating to Infringement of the Chang Patents

53. The specifications of the Chang patents set forth the following definition for the claim term "immediate release formulation": "a dosage form that is intended to release substantially all of the active ingredient on administration with no enhanced, delayed or extended release effect." (Chang '740 patent, 4:5-8) The parties agree that this is the appropriate construction for IR formulation (*see* D.I. 205 at 8; D.I. 207 at 4; *see also* Rudnic Tr. at 110-12; Chambliss Tr. at 276) The Court adopts this construction of "immediate release formulation."

54. The Court construed the claim term "delayed release" to mean "release of drug at a time other than immediately following oral administration." (D.I. 78 at 5-7; *see also* Rudnic Tr. at 113; Chambliss Tr. at 282-83)

55. Nothing in the Court's construction of "delayed release" limits the way in which that delay is created. *Galderma Labs., L.P. v. Amneal Pharm., LLC*, 337 F. Supp. 3d 371, 406 (D. Del. 2018) ("*Amneal*," "*Amneal* Trial Opinion," or "*Amneal* Tr. Op."); Rudnic Trial Tr. at 156; Chambliss Trial Tr. at 368-69)

56. The Court's construction of "delayed release" does not require that to be a DR portion there needs to be substantially no release of drug at any time in the stomach or in an acidic environment – and only requires that there be release at a time other than immediately following oral administration. (*Amneal* Tr. Op. at 50-51, 56-58; *see also* Rudnic Tr. at 156; Chambliss Tr. at 368-69)

57. Nothing in the Court's construction of "delayed release" requires that there be no release or substantially no release of drug for a period of time (such as the plateau in release exhibited in the dissolution data for Oracea Capsules in acidic medium). (*Amneal* Trial Op. at 58-59; Rudnic Tr. at 156; Chambliss Tr. at 368-69)

58. The Court's construction of "delayed release" does not exclude portions that also provide a "sustained release," so long as the release is at a time other than immediately following oral administration. (*See, e.g.*, *Amneal* Op. at 57-58; *see also* Raoufinia Tr. at 413)

59. The claim terms "formulation" and "portion" are used interchangeably across the asserted claims of the Chang patents (*compare* Chang '740 patent, cl. 1 *with* Chang '405 patent, cl. 1), and both sides' experts used these terms interchangeably (*see generally* Rudnic Tr. at 102-63; Chambliss Tr. at 266-344).

60. The Court construed the claim term "about" as applied to the claimed amounts "about 30 mg" and "about 10 mg" of doxycycline to mean "within the pharmaceutically

acceptable limits found in the United States Pharmacopeia (USP-NF-21), 2003 Annual Edition." (D.I. 78 at 9-10; *see also* Chambliss Tr. at 278)

61. The General Notices and Requirements section of the USP provide "the basic guidelines for the interpretation and application of the standards, tests, assays, and other specifications of the [USP]" when no specific language is given to the contrary in the remainder of the USP. (DTX-237.8; Chambliss Tr. at 279) That same section of the USP defines "about" as a "quantity within 10% of the specified weight or volume." (DTX-237.12; *see also* Chambliss Tr. at 279)

62. A POSA would rely on the definition of "about" in the General Notices section of the USP to interpret the claim terms "about 30 mg" and "about 10 mg" as used in the asserted claims of the Chang patents. (Chambliss Tr. at 278-79)

63. A POSA would understand that "about 30 mg" of doxycycline represents at most a range of 27 to 33 mg of doxycycline. (Chambliss Tr. at 280)

64. Dr. Rudnic testified that Sun chose a bilayer tablet to "hide a good portion" of the MR layer from hydrating until a time other than immediately following oral administration. (Rudnic Tr. at 137) A part of the MR layer begins to disintegrate in less than 60 seconds (PTX-330.85, Rudnic Tr. at 186-87), while the remaining about 10 mg of the doxycycline in Sun's MR layer does not dissolve until sometime well after oral administration.

VIII. Facts Relating to Obviousness

65. At trial, Sun contended that the asserted claims of the Chang patents were invalid as obvious in view of two prior art references: (1) the Ashley Applications, and (2) the Periostat Package. (Tr. at 265-66; Chambliss Tr. at 380-82; Rudnic Tr. at 425-26)

66. None of the prior art cited by Sun, alone or in combination, discloses, teaches or suggests the claimed compositions of the asserted claims of the Chang patents. (Rudnic Tr. at 426, 454-55; Chambliss Tr. at 382-83)

67. For example, none of the alleged prior art cited by Sun, alone or in combination, discloses, teaches, or suggests a 40 mg once-daily doxycycline composition consisting of an IR portion and a DR portion, or a composition consisting of IR and DR portions in a ratio of 30 mg IR and 10 mg DR. (Rudnic Tr. at 426; Chambliss Tr. 382)

68. In addition, none of the alleged prior art cited by Sun, alone or in combination, discloses, teaches, or suggests a 40 mg once-daily doxycycline composition consisting of an IR portion and a DR portion wherein the IR/DR ratio is between 70% IR 30% DR and 80% IR 20% DR. (Rudnic Tr. at 427-28, 430-31, 437-38; Chambliss Tr. at 322-23, 382-83)

69. The goal of the Chang patents was to provide a once-daily doxycycline composition that would yield steady-state blood levels sufficient to treat inflammatory conditions such as rosacea, while at the same time maintaining steady-state blood levels well below the threshold of 1.0 μg/mL associated with the undesirable, antibacterial side effects of higher doses of doxycycline. (*See, e.g.*, PTX-4 at 2:28-42, 2:64-67; Rudnic Tr. at 425)

70. None of the alleged prior art cited by Sun, alone or in combination, would have motivated a POSA in 2002 or 2003 to make the claimed 30 mg IR, 10 mg DR doxycycline compositions of the asserted claims of the Chang patents, or would have given a POSA a reasonable expectation that such compositions would have succeeded in meeting the formulation goal addressed by the claimed invention of the Chang patents. (Rudnic Tr. at 426, 454-55)

71. Sun's primary prior art references, the Ashley Applications, are not materially different from the Ashley prior art this Court considered – and rejected – in *Mylan* as a basis for

the alleged obviousness of the Chang patents. *See Research Found. of State Univ. of New York v. Mylan Pharm. Inc.*, 809 F. Supp. 2d 296, 314-15, 332 (D. Del. 2011), *aff'd in relevant part*, 531 F. App'x 1008 (Fed. Cir. 2013) ("*Mylan* Trial Opinion" or "*Mylan* Tr. Op."); Chambliss Tr. at 389-92; Rudnic Tr. at 428-29, 435-36)

A. The Ashley Applications

72. Doxycycline was first discovered in the 1960s and has long been commercially available. (Chambliss Tr. 307-08)

73. Doxycycline was regularly prepared as a salt, such as doxycycline hydrochloride or "hyclate," and was known to be soluble in water. (Chambliss Tr. 308)

74. Sun contends that the asserted claims of the Chang patents would have been obvious over Published International Patent Application WO02/080932 ("the Ashley '932 application") and U.S. Provisional Application No. 60/281,854 ("the Ashley '854 application") (together, "the Ashley Applications"), in light of available pharmacokinetic information concerning Periostat Package."

75. Neither the Ashley '932 application, nor the Ashley '854 application (which is incorporated by reference into the Ashley '932 application) discloses, teaches, or suggests the 40 mg IR/DR doxycycline compositions of the asserted claims of the Chang patents. (Rudnic Tr. at 427-28, 430-31; Chambliss Tr. at 382-84; *see also Mylan* Tr. Op. at 332)

76. The Ashley '932 application did not disclose, teach, or suggest any 40 mg once-daily doxycycline composition consisting of an IR portion and a DR portion, or any IR/DR doxycycline ratios. (Rudnic Tr. at 426-31, 435-36; Chambliss Tr. at 382-84; *Mylan* Tr. Op. at 314 (¶¶ 261, 264), 332)

77. The Ashley '932 application did not disclose, teach, or suggest any composition that contains a 30 mg IR portion or a 10 mg DR portion. (Rudnic Tr. at 426-29, 435-36; Chambliss Tr. at 382-84; *Mylan* Tr. Op. at 314, 332)

78. Dr. Chambliss admitted that the Ashley Applications are the closest prior art to the asserted claims of the Chang patents. (Chambliss Tr. at 383)

79. Dr. Chambliss admitted that the Ashley Applications are the only documents that he cited describing a 40 mg once-daily doxycycline dosage form that is controlled release (i.e., modified release, sustained release, delayed release, etc.). (Chambliss Tr. at 383)

80. The Ashley '932 application generally discusses administering a tetracycline compound by "sustained release" – which the Ashley '932 publication defines as "a method of drug delivery to achieve a certain level of the drug over a particular period of time." (Ashley '932 application (DTX-271) at 15; Rudnic Tr. at 429-30)

81. The Ashley '932 application states that "[f]urther description of methods of delivering tetracycline compounds by sustained release" can be found in the Ashley '854 application. (DTX-271 at 15; Rudnic Tr. at 430; Chambliss Tr. at 314-16)

82. The Ashley '854 application does not disclose, teach, or suggest any 40 mg once-daily doxycycline composition consisting of an IR portion and a DR portion, or any IR/DR doxycycline ratios. (Rudnic Tr. at 427, 430-31, 435-36; Chambliss Tr. at 382-84; *see also Mylan* Tr. Op. at 314)

83. The Ashley '854 application does not disclose, teach, or suggest any composition that contains a 30 mg IR portion or a 10 mg DR portion. (Rudnic Tr. at 427, 430-31, 435-36; Chambliss Tr. at 382-84; *see also Mylan* Tr. Op. at 314)

84. In contrast to the IR/DR compositions claimed in the Chang patents, the Ashley '854 application is directed to tetracycline compositions that release the drug "at a substantially constant rate" over a long, extended period of time, e.g., 6-24 hours, or preferably 12-24 hours. (*See, e.g.*, DTX-230 at 5-7, 13-15; Rudnic Tr. at 430-31)

85. By consistently referring to compositions with a "substantially constant rate of release," the Ashley '854 application instructed a POSA to use compositions predominated by a slow, sustained release component that releases at a substantially constant rate over the course of, e.g., 6-24 hours – and would have discouraged the use of compositions consisting of only IR and DR portions, as claimed in the Chang patents. (*See, e.g.*, Rudnic Tr. at 430-31, 457)

86. The Ashley '854 application describes a preferred embodiment as follows:

> In a preferred embodiment, the controlled-release composition is ***entrapped*** in the upper portion of the gastrointestinal tract, for example, the stomach or duodenum. Such compositions are typically manufactured by utilizing controlled-release agents of a ***larger particle size***, as is known in the art. It is preferred that at least 50%, more preferably greater than 80% of the tetracycline in the composition be released in the upper GI tract.

(DTX-230 at 16:9-14) (emphasis added)

87. A POSA reading this portion of the Ashley '854 application would have understood that it describes gastroretentive compositions that are entrapped in the stomach (due to, e.g., the use of agents that swell the composition to a large size), and release the drug at a "substantially constant rate." (Rudnic Tr. at 431; Chambliss Tr. at 385-86)

88. As of 2002-2003, a POSA would have known of gastroretentive formulation technology that could entrap a dosage form in the stomach for a prolonged time by swelling to a certain size, preventing the dosage form from exiting the pylorus (the valve that joins the stomach and the upper part of the small intestine), and allowing for drug to slowly release in the

stomach for an extended period and be available at a site of absorption further down in the GI tract, e.g., in the duodenum. (Rudnic Tr. at 431-32)

89. In addition to the Ashley Applications, the literature as of 2002-2003 discussed several gastroretentive technologies for use with doxycycline. (PTX-203 at 6:31-34, 8:41-44, 19:10-13, 17-27; PTX-204 at 9:1-20, 58-60; PTX-211 at 8:8-16, 42:6-14, 19; Rudnic Tr. at 432-33)

90. A POSA reading the Ashley Applications would not have been motivated to make compositions consisting of only an IR portion and a DR portion as claimed in the Chang patents, but rather would have looked to compositions providing a "substantially constant rate" of release, such as the preferred gastroretentive formulation approach identified by the Ashley Applications. (Rudnic Tr. at 423-24, 429-31, 435-36)

B. The Periostat® Package

91. Based on the disclosures of Periostat® ("Periostat") as a preferred embodiment of the Ashley Applications, a POSA would have been motivated to review whatever formulation and clinical data was publicly available about that product, and would have pursued and reviewed the formulation and clinical data disclosed in the Periostat Drug Approval Package ("Periostat Package"). (Chambliss Tr. at 321; Rudnic Tr. at 463, 471 (testifying that Periostat Package was information POSAs "would have gotten to and they would have looked at it for sure"))

92. It is undisputed that the Periostat Package contains substantial single dose and steady-state clinical pharmacokinetic data regarding not only the twice-daily dosage of 20 mg doxycycline found in commercial Periostat, but also once-daily 40 mg dosages. (DTX-186; Chambliss Tr. at 321-23; Rudnic Tr. at 463)

93. In particular, the Periostat Package contains a study entitled "A Bioavailability and Dose Proportionality Study of Three Dosing Levels of Doxycycline Capsules in Normal Healthy Male," which had the objective of determining whether the C_{max} values for twice-daily 20 mg, once-daily 40 mg, and twice-daily 50 mg dosages of doxycycline exceeded a threshold level of 1.0 μg/ml. (DTX-186.187; Chambliss Tr. 322-23) C_{max} is the maximum or peak blood level that a patient will achieve when taking a drug product. (Chambliss Tr. 322)

94. The above-referenced study disclosed the following mean C_{max} values generated by the administration of each of the dosage regimens:

Dosage Regimen	**Mean C_{max} Values**
20 mg twice daily	0.772 μg/ml ± 0.380
40 mg once daily	0.834 μg/ml ± 0.284
50 mg twice daily	"Well above 1.0 μg/ml"

(DTX-186.189; Chambliss Tr. 325)

95. The Periostat Package also provides individual data for the above dosage regimens, disclosing the number of subjects out of 13 evaluable subjects who exceeded the recommended 1.0 μg/ml threshold:

Dosage Regimen	**Individual C_{max} Data**
20 mg twice daily	3/13 exceeded 1.0 μg/ml
40 mg once daily	3/13 exceeded 1.0 μg/ml
50 mg twice daily	12/13 exceeded 1.0 μg/ml

(DTX-186.189; Chambliss Tr. 325)

96. A POSA would have understood from these disclosures that while a 40 mg once-daily dose regimen of doxycycline could provide mean C_{max} values below the recommended threshold of 1.0 μg/ml, some individuals taking such a regimen would exceed that recommended threshold. (Chambliss Tr. 325-26)

97. However, nothing in the Periostat Package, alone or in combination with the Ashley Applications, discloses, teaches, or suggests the 40 mg IR/DR doxycycline compositions of the asserted claims of the Chang patents. (Rudnic Tr. at 437-38; Chambliss Tr. at 322-23, 382-83)

98. The Periostat Package contains only pharmacokinetic data for IR compositions of doxycycline. (Rudnic Tr. at 437-38; Chambliss Tr. at 322-23)

99. Nothing in the Periostat Package or the Ashley Applications provides pharmacokinetic data for DR or IR/DR compositions of doxycycline. (Rudnic Tr. at 437-38; Chambliss Tr. at 322-23)

100. Nothing in the Periostat Package discloses, teaches, or suggests once-daily doxycycline compositions with controlled release (e.g., delayed or extended release). (Rudnic Tr. at 437-38; Chambliss Tr. at 322-23, 388)

101. Nothing in the Periostat Package discloses, teaches, or suggests a 40 mg once-daily doxycycline composition having a combination of an IR portion and a DR portion, or any IR/DR doxycycline ratios. (Rudnic Tr. at 437-38; Chambliss Tr. at 322-23, 388)

102. Nothing in the Periostat Package discloses, teaches, or suggests a 40 mg once-daily doxycycline composition with a 30 mg IR portion and a 10 mg DR portion. (Rudnic Tr. at 437-38; Chambliss Tr. at 322-23, 388)

103. The pharmacokinetic data for IR doxycycline compositions in the Periostat Package, alone or in combination with the Ashley Applications, would not have motivated a POSA to use an IR/DR doxycycline composition to meet the formulation goal addressed by the Chang patents. (Rudnic Tr. at 436-38; *see also* Chambliss Tr. at 322-23)

104. The pharmacokinetic data for IR doxycycline compositions in the Periostat Package, alone or in combination with the Ashley Applications, would not have given a POSA a reasonable expectation that an IR/DR doxycycline composition would have worked for the formulation goal addressed by the Chang patents. (Rudnic Tr. at 437-38, 445)

105. In view of the information available to a POSA as of 2002-2003, a POSA would not have reasonably expected an IR/DR doxycycline composition to be suitable for the formulation goal addressed by the claimed inventions of the Chang patents, and would have been concerned that such an IR/DR composition would fail. (Rudnic Tr. at 445)

106. As of 2002-2003, it was known that doxycycline, when administered in an IR form, was rapidly and almost completely absorbed in the duodenum, a section of the small intestine that is immediately after the stomach and the pylorus. (Rudnic Tr. at 438-39; *see also* PTX-283.2-4)

107. The data available as of 2002-2003 regarding the absorption of IR doxycycline would not have indicated to a POSA anything about how well doxycycline might be absorbed from DR doxycycline compositions that may release further down in the GI tract. (Rudnic Tr. at 439)

108. Nothing in the Periostat Package or other literature available to a POSA as of 2002-2003 indicated that doxycycline was well-absorbed throughout the entire GI tract. (Rudnic Tr. at 439-41)

109. A POSA as of 2002-2003 would have expected that doxycycline, like other oral antibiotics, had reduced absorption as it travels further down the GI tract, and would have suspected that doxycycline could possibly have a narrow "absorption window," limiting its absorption beyond the duodenum. (Rudnic Tr. at 438-41; *see also* PTX-213.8)

110. Taken together, the available information as of 2002-2003 on absorption of doxycycline would have informed a POSA that, while doxycycline is very rapidly and well absorbed from the duodenum, there is a strong possibility that absorption will not be as efficient throughout the remainder of the GI tract. (Rudnic Tr. at 438-45; PTX-213.8; PTX-283.4)

111. In 2002, CollaGenex commissioned a study to characterize the absorption characteristics of doxycycline. (Rudnic Tr. at 443-45; *see also* PTX-315.1, 6; PTX-319.2-87)

112. The unpublished data from the 2002 CollaGenex study, as well as internal testing conducted by Shire Labs on behalf of CollaGenex, demonstrated that doxycycline has a narrow absorption window that is limited principally to the duodenum. (Rudnic Tr. at 443-45; *see also* PTX-315.16; PTX-319.2-87)

113. The data generated by the 2002 CollaGenex study were not publicly available in the 2002-2003 timeframe. (Rudnic Tr. at 443-45)

114. For reasons including beliefs about an absorption window, in 2002 and 2003 a POSA would not have reasonably expected an IR/DR doxycycline composition to work for the goal addressed by the Chang patents, because a POSA would have been concerned that DR doxycycline compositions could not be reliably targeted to release in the duodenum. (Rudnic Tr. at 445)

115. A POSA as of 2002-2003 would have been discouraged from using an IR/DR doxycycline composition to address the formulation goal of the Chang patents, and would have instead looked to formulation approaches such as the gastroretentive technology described in the Ashley Applications. (Rudnic Tr. at 445)

116. As of the 2002-2003 timeframe, the available computer software for modeling pharmacokinetic data would not have motivated a POSA to make the 40 mg IR/DR doxycycline

compositions of the asserted claims of the Chang patents, and would not have given a POSA a reasonable expectation of success in doing so. (Rudnic Tr. at 452-55)

117. The pharmacokinetic modeling software available as of 2002-2003 could not have been used to model the performance of IR/DR compositions of doxycycline without first inputting information that was not available to a POSA as of 2002-2003 – including the extent of absorption of doxycycline at points past the duodenum. (Rudnic Tr. at 452-53; *see also* Rudnic Tr. at 438-45)

118. A POSA as of 2002-2003 would not have been able to generate a computer model for the pharmacokinetic performance of DR or IR/DR doxycycline compositions solely using the information in the Periostat Package, which only described pharmacokinetic data for IR compositions of doxycycline. (Rudnic Tr. at 437-38, 452-54; Chambliss Tr. at 322-23, 380-81)

119. The Chang inventors, in order to develop a computer-based pharmacokinetic model of IR/DR compositions in the course of developing their invention, had to first (1) manufacture prototype IR and DR compositions, then (2) test the compositions in a human clinical pharmacokinetic study, and then (3) develop a model based on the results of that human clinical study, in combination with other non-public data available to Shire. (Rudnic Tr. at 452-53; *see also* Rudnic Tr. at 438-45; Raoufinia Tr. at 408-10; DTX-615.2)

120. For the Chang inventors, the computer-based pharmacokinetic modeling work leading to the development of the claimed invention took place only after they had conceived of pursuing an IR/DR formulation approach, and had expended significant resources and effort toward that formulation approach by manufacturing test compositions and then clinically testing them in human subjects. (Rudnic Tr. at 452-53; *see also* Rudnic Tr. at 438-45; Raoufinia Tr. at 408-10, 415-17; *Mylan* Tr. Op. at 333 ("But the fact remains that skill was involved in picking

the precise formulation to achieve CollaGenex's parameters, and the precise formulation ultimately settled upon was novel."))

C. Other Prior Art

121. Additional documents cited by Sun in connection with obviousness – including documents regarding "Doryx®" and U.S. Patent No. 4,250,166 (DTX-261) ("the '166 patent") – do not alter the conclusion that the Chang patents would not have been obvious. (Tr. at 56, 265; Rudnic Tr. at 446, 448-52; Chambliss Tr. at 380, 383)

122. Doryx® ("Doryx") did not disclose, teach, or suggest any IR/DR doxycycline compositions or any IR/DR doxycycline ratios. (Rudnic Tr. at 448-49; Chambliss Tr. at 388)

123. Nothing known to a POSA as of 2002-2003 concerning the commercial product Doryx would have motivated a POSA to use a 40 mg IR/DR doxycycline composition to meet the formulation goal addressed by the Chang patents, or would have given a POSA a reasonable expectation that a 40 mg IR/DR doxycycline composition would have worked for that purpose. (Rudnic Tr. at 448-49; Chambliss Tr. at 388)

124. The exact composition of Doryx was unknown to a POSA as of 2002-2003. (Rudnic Tr. at 447-48)

125. A POSA as of 2002-2003 would have had insufficient information regarding the composition and performance of Doryx to determine whether Doryx was a DR doxycycline composition. (Rudnic Tr. at 447-48)

126. Doryx does not disclose, teach, or suggest any doxycycline composition providing steady-state blood levels of a minimum of 0.1 μg/ml and a maximum of 1.0 μg/ml. (Rudnic Tr. at 448-49)

127. Doryx was an antibiotic product given in high doses to treat infections, and was not designed to remain under a ceiling concentration. (Rudnic Tr. at 447-48)

128. Doryx was indicated for use at high antibiotic doses, e.g., 200 mg on the initial dose, followed by 100 mg per day. (Rudnic Tr. at 447-48)

129. Doryx was indicated for twice-daily administration, not once-daily administration. (Rudnic Tr. at 447-48)

130. The Maekawa '166 patent did not disclose, teach, or suggest any doxycycline compositions directed to meeting the formulation goals addressed by the Chang patents or even any oral compositions of doxycycline. (Rudnic Tr. at 450-52)

131. The Maekawa '166 patent did not teach compositions intended to remain below a ceiling concentration associated with antibiotic effect, and instead was aimed at obtaining high, antibiotic concentrations of cephalexin. (Rudnic Tr. at 452; *see also* DTX-261 at 3:9-15, 3:30-45, 10:17-21, 10:51-59)

132. Cephalexin is a concentration-dependent antibiotic: the higher the plasma concentration of cephalexin, the more effective it is in treating infections. (Rudnic Tr. at 452)

133. The cephalexin compositions disclosed in the Maekawa '166 patent are to be administered twice-daily, not once-daily. (Rudnic Tr. at 452; *see also* DTX-261)

134. The computer-based pharmacokinetic modeling depicted in the Maekawa '166 patent was not based on actual data for DR compositions of cephalexin – and the resulting computer-generated curves for hypothetical IR/DR ratios of cephalexin are possibly erroneous and impossible to achieve in humans. (Rudnic Tr. at 450-51; DTX-261 at Figs. 3, 5-6, 8-9, 4:48-6:17, 7:5-9:35)

IX. Related Litigation And Pertinent Decisions

135. The Chang patents were litigated in this Court in an earlier case, *Galderma Labs., L.P. v. Amneal Pharm., LLC*, which culminated in a February 2018 trial and the issuance of the *Amneal* Trial Opinion on August 27, 2018.

136. On May 9, 2017, the Court issued a claim construction opinion in *Amneal*. *See Amneal*, 2017 WL 1882499 ("*Amneal* Construction Opinion" or "*Amneal* CC Op.").

137. In the *Amneal* Construction Opinion, the Court construed "delayed release" as "release of a drug at a time other than immediately following oral administration." (*Amneal* CC Op. at *5)

138. In the *Amneal* Construction Opinion, the Court construed "portion" and "formulation" has having their "[p]lain and ordinary meaning." (*Amneal* CC Op. at *5-6)

139. In the *Amneal* Trial Opinion, the Court that its "construction of 'delayed release' is agnostic as to how the delay is accomplished." (*Amneal* Trial Op. at 406-07)

140. Amneal litigated a petition for *inter partes* review ("*Amneal* IPR") directed at invalidating the Chang patents.

141. On December 9, 2017, the Patent Trial and Appeal Board ("PTAB") issued a Final Written Decision ("FWD"), upholding the validity of the challenged claims of the Chang '740 patent. (*See* PTX-364) ("*Amneal* IPR FWD")

142. In the instant case, the Court issued a claim construction opinion and order on November 21, 2017. (D.I. 78,79) ("*Sun* Construction Opinion" or "*Sun* CC Op.")

143. In the *Sun* Construction Opinion, the Court rejected Sun's proposed construction of "delayed release," which was "release of a drug at a time other than immediately following oral administration, excluding formats that result in release of drug starting promptly after oral

administration." Instead, the Court adopted Galderma's proposed construction of "delayed release," which is: "release of a drug at a time other than immediately following oral administration."

144. The Court's construction of "delayed release" does not require that to be a DR portion there needs to be substantially no release of drug at any time in the stomach or in an acidic environment – and only requires that there be release at a time other than immediately following oral administration. (*Amneal* Tr. Op. at 50-51, 56-58; *Amneal* CC Op. at 9-10; *Sun* CC Op. at 5-7; *Amneal* IPR FWD at 8-9; Rudnic Tr. at 156; Chambliss Tr. at 368-69)

145. Nothing in the Court's construction of "delayed release" requires that there be no release or substantially no release of drug for a period of time (such as the plateau in release exhibited in the dissolution data for Oracea Capsules in acidic medium). (*Amneal* Op. at 58-59; Rudnic Tr. at 156; Chambliss Tr. at 368-69)

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 n.9.

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 set forth in a claim must be 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 those 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).

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." *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. Int'l Trade Comm'n*, 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 & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990).

III. Obviousness

A patent may not issue "if the differences between the claimed invention and the prior art 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. of Kan. City*, 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 Hydrochloride Extended-Release Capsule Patent Litig.*, 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 in a determination that an invention would have been obvious, 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, 1357-58 (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).

DISCUSSION

I. Galderma Has Proven Infringement of the Chang Patents

Galderma asserts that Sun's NDA 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, both literally and under the doctrine of equivalents. (D.I. 204 ¶ 21) Sun argues that Galderma has failed to meet its burden on infringement in three ways (any one of which would, if Sun is correct, be fatal to Galderma's infringement case). In Sun's view, Galderma has failed to prove that Sun's NDA Product: (1) has "an immediate release (IR) portion" comprising 30 mg (or about 30 mg) of doxycycline (D.I. 207 at 2-10); (2) has "a delayed release (DR) portion" comprising 10 mg (or about 10 mg) of doxycycline (*id.* at 11-16); and (3) provides "steady state blood levels" of doxycycline between 0.1 μg/mL and 1.0 μg/mL (*id.* at 17-18). As explained below, the Court finds that Galderma has met its burden to prove infringement.

A. The Parties' Contentions Regarding "IR Portion" and "DR Portion" Reveal A Material Claim Construction Dispute

The asserted claims all require the claimed composition to include an "immediate release portion" or "immediate release formulation"[3] comprising either 30 mg or about 30 mg of doxycycline. The asserted claims all also require the claimed composition to include a "delayed release portion" or "delayed release formulation" comprising either 10 mg or about 10 mg of doxycycline.[4]

The parties agreed at trial that ***"immediate release" ("IR")***, as defined in the Chang patents, 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." ('405 patent, 4:14-17; D.I. 205 at 8-9; D.I. 207 at 4) Prior to trial, in its claim construction order, the Court construed ***"delayed release" ("DR")*** to mean "release of a drug at a time other than immediately following oral administration." (D.I. 79 at 3) The case was tried without any specific construction of ***"portion"*** as the parties agreed throughout trial (and even for some time after trial) that the term would be given its "plain and ordinary meaning." (*See Sun* CC Op. at 6)

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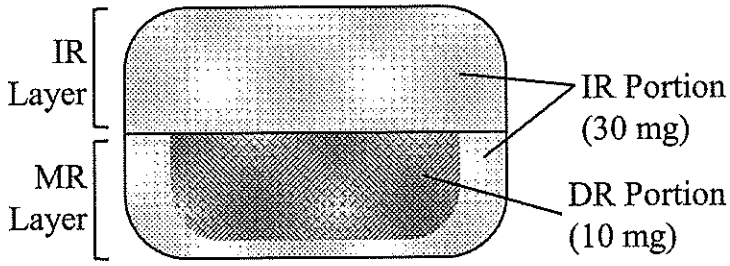
[3] The parties, like the Chang patents, use the terms "portion" and "formulation" interchangeably. *Compare* Chang '740 patent, cl. 1 *with* Chang '405 patent, cl. 1; *see also generally* Rudnic Tr. at 102-63; Chambliss Tr. at 266-344. In the post-trial briefing, including the supplemental claim construction briefing ordered by the Court, the parties continue to adhere to the agreed-upon view that "portion" and "formulation" carry the same meaning. (*See, e.g.*, D.I. 226 at 4 n.2 (Galderma), D.I. 227 at 2) Therefore, the Court's discussion (and construction) of "the portion terms" applies equally to the asserted "formulation" terms.

[4] The Court follows the parties' practice and considers all asserted claims together, first for purposes of infringement and then for validity. Except where otherwise noted, neither party appears to argue that there are differences among the asserted claims that are material to the outcome of the infringement or invalidity analysis.

Galderma contends that the ***"immediate release portion"*** limitations are met by the combination of: (1) the Sun NDA Product's IR layer; and (2) the part of the Sun NDA Product's MR layer that dissolves in the first 30 minutes after administration. (D.I. 205 at 8-14) Under Galderma's theory, the Sun NDA Product's IR portion, therefore, has about 30 mg of doxycycline, consisting of: (1) the entire 26.4 mg of doxycycline in the IR layer, and (2) the about 3.6 mg of doxycycline that is released from the MR layer in the first 30 minutes after administration. (*Id.*) Similarly, on Galderma's view, the ***"delayed release"*** portion of Sun's NDA Product is the remaining 10 mg of doxycycline – all from the MR layer – which is released following the first 30 minutes after administration. (*Id.*)

Galderma's infringement theory can be depicted as follows:

GALDERMA'S INFRINGEMENT THEORY

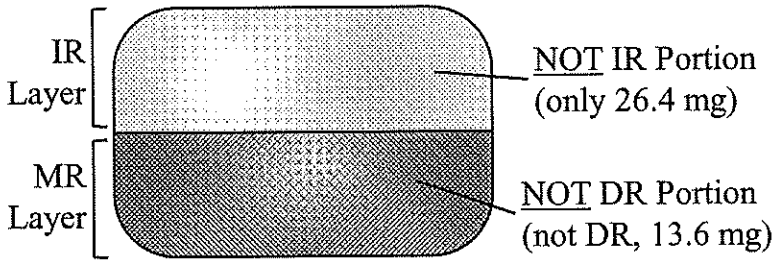


Sun counters that its NDA Product's ***"immediate release portion"*** includes ***only*** the 26.4 mg of doxycycline in the IR layer. (D.I. 207 at 3) Thus, because the IR ***layer*** has less than the about 30 mg of doxycycline claimed by the Chang patents, Sun's view is that its NDA Product does not meet the IR ***portion*** limitations. (*Id.*) Sun contends that its NDA Product also does not meet the ***"delayed release portion"*** limitations, for two reasons: (1) the MR layer is not "delayed release" because it releases doxycycline starting immediately after administration and the amount of doxycycline released "continuously increases over time, with no plateau or stoppage

of release" (*id.* at 11); and (2) even if the MR layer were a "delayed release portion," the MR layer has 13.6 mg of doxycycline, which is greater than the about 10 mg of doxycycline required by the claims. (*Id.* at 13-16)

Sun's non-infringement theory is depicted below:

SUN'S NON-INFRINGEMENT THEORY



After careful review, the Court has concluded that the parties' dispute over whether the IR portion and DR portion limitations are met by Sun's NDA Product turns on the meaning of "portion." If "portion" is a functional term – such that the "IR portion" limitation is satisfied if a formulation dissolves in a manner in which 30 mg (or about 30 mg) of doxycycline is released immediately after oral administration, regardless of where in the product that doxycycline comes from – then the Sun NDA Product infringes. If, alternatively, "portion" is a structural term – such that each part of an accused product must be analyzed for its structure and then characterized as either an IR or DR structure (or some other sort of structure, such as sustained release ("SR")) – then the Sun NDA Product does not infringe.

B. How We Got To This Point

Having determined that there is a material claim construction dispute, the Court must determine what to do about it. There is not necessarily a straightforward answer. While the Court generally has an obligation, before entering judgment, to resolve the parties' material

claim construction disputes, *see O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1361 (Fed. Cir. 2008), there may also come a point where it is simply too late for a party to ask for a new construction, *see, e.g.*, *Lighting Ballast Control LLC v. Philips Elecs. N. Am. Corp.*, 790 F.3d 1329, 1341 (Fed. Cir. 2015) ("[Party] waived its right to seek a new claim construction because [Party] did not seek that construction until after trial."); *Edwards Lifesciences AG v. CoreValve, Inc.*, 2011 WL 446203, at *3-4 (D. Del. Feb. 7, 2011) (rejecting post-trial attempt at claim construction, raised without pre-trial notice in motions for judgment as a matter of law following jury trial, as untimely). In this case, where ***the claim construction dispute did not become apparent until the Court reviewed the parties' post-trial briefs, and the parties had never asked the Court to construe the disputed claim term***, the Court must try to understand how we got here, as a step toward deciding what to do about it.

As Sun explains: "At no point did the parties raise the construction of either term [i.e., portion or formulation] as an issue for resolution, instead relying upon the Court's construction of both terms as having their 'plain and ordinary meaning' from Plaintiffs' prior litigation concerning the same patents." (D.I. 227 at 1) The prior litigation Sun is referring to here is *Amneal*, which was tried in this Court in February 2018 and resolved by the *Amneal* Trial Opinion in August 2018. In *Amneal*, the Court had construed portion as having its "plain and ordinary" meaning. *See Amneal* CC Op., 2017 WL 1882499, at *5-*6.

Because the Court had issued the *Amneal* Construction Opinion in May 2017, Galderma and Sun knew throughout almost the entire course of the instant case that the Court had held (at least for purposes of the *Amneal* case, and presumptively for all cases involving the Chang patents) that "portion" had its "plain and ordinary meaning." It was perhaps for this reason that the parties did not identify "portion" as a term requiring construction when they filed their Joint

Claim Construction Chart on July 5, 2017. (D.I. 54) Hence, "portion" was not addressed in the parties' claim construction briefs filed in August and September of 2017. (*See* D.I. 61, 62, 64, 65)

During the claim construction process, the parties did brief, and argue at the October 2, 2017 claim construction hearing, whether "delayed release" should be construed to "exclude[] formats that result in the release of drug starting promptly after oral administration." Sun proposed that this exclusion be included as part of the construction of "delayed release" based on Sun's contention that, during the *Amneal* IPR, Galderma had disclaimed from the scope of "delayed release" any formulation in which the purported "delayed release" component began to release some drug promptly upon administration. (*See, e.g.*, D.I. 75 at 12-19)

The Court issued its claim construction opinion and order in this case on November 21, 2017. (*See Sun* CC Op.) In its opinion, the Court rejected Sun's disclaimer argument, writing about the "delayed release" term: "[A]t no point did the patent owner clearly and unambiguously disclaim all [delayed release] embodiments that release drug at a time other than immediately after oral administration solely because they also release some amount of drug 'starting promptly after oral administration." (*Id.* at 6-7) Thus, the Court construed "delayed release" as "release of a drug at a time other than immediately following administration." (*Id.* at 5)

Having failed to persuade the Court to read a disclaimer into the DR terms, Sun did not file a motion for reconsideration or at any point formally request that the Court modify its construction of any DR term, including "DR portion." There was no indication in the parties' proposed pretrial order that Sun was seeking any modification of the Court's claim constructions (*see* D.I. 195, 196), nor was there any such indication at the pretrial conference (*see* D.I. 200), or at any point during trial ***until after the close of evidence.***

It was only during closing argument, which the Court heard on the last day of trial, that it began to appear as if Sun was, in fact, seeking additional claim construction. During her argument, Sun's counsel stated, for example:

> Your Court's claim construction states that, "delayed release is release of a drug at any time other than immediately following oral administration."
>
> So our reading of delayed release [is that it] means that if there is immediate release following oral administration, then that is not delayed release. That is something else.

(D.I. 210 at 585) In effect – although not expressly stated as such, and as was not recognized by the Court at the time – Sun was essentially asking the Court to modify its construction of "DR" to include the exclusion language Sun had unsuccessfully asked the Court to read into the construction as a disclaimer as part of the claim construction process (i.e., "exclude[] formats that result in the release of drug starting promptly after oral administration").

Part of Galderma's response in its rebuttal closing argument was to point out how late Sun's claim construction argument was arising:

> Portion was a term that was tendered to the Court for construction in the *Amneal* case, and *Amneal* asked that it be construed in such a way that it would require unitary portions for each of the immediate release and delayed release functions, and the Court declined to do so in the *Amneal* claim construction opinion and gave portion its plain and ordinary meaning. Certainly, Sun was aware of that. It never asked this Court to construe the claim throughout the course of this entire proceeding.

(D.I. 210 at 606)

In her rebuttal closing, counsel for Sun began by stating the following:

> Your Honor, there was some discussion about the "portion[/]formulation" construction. That should be given a plain and ordinary reading given that there is no construction of it. And I think Rudnic's testimony and the Skelly references is helpful on that point.

(D.I. 210 at 613) Hence, when the Court left the bench at the conclusion of trial and closing argument, it seemed that Sun was ***not*** asking the Court to construe "portion" but, instead, to apply its "plain and ordinary meaning."

Subsequently, throughout the originally-ordered post-trial briefing, the parties continued to apply the "plain and ordinary meaning" of the "portion" terms, without asking the Court to construe "portion" – yet it then became clear that the parties did not actually agree on the "plain and ordinary meaning." Instead, each side contended that what it believed to be the "plain and ordinary meaning" supported its side and only its side. (*See, e.g.*, D.I. 205 at 16-19 (Galderma noting Court had rejected narrowed construction of "portion"/"formulation" in *Amneal* "and instead ruled that these claim elements are not so limited, and have their plain and ordinary meaning," as Sun had long been aware); D.I. 211 at 5 (Sun faulting Galderma for "ignor[ing] these claim terms [including "portion" and "formulation"] and their ordinary meaning," adding that "a POSA would understand that the claim terms 'formulation' and 'portion' to mean 'a listing of the ingredients and composition of the dosage form and its method of manufacture'"))

Therefore, on August 29, 2019, the Court issued an order, advising the parties: "It appears that it may be necessary in order to resolve the infringement dispute to construe the word 'portion' as used in the claim terms 'immediate release portion' and 'delayed release portion.'" (D.I. 222 at 1) The Court provided the parties with what it ***inferred*** to be their proposed constructions, because "the parties ha[d] not expressly briefed their dispute as a claim construction dispute." (*Id.*)[5] The Court added that what it understood to be the parties'

[5] The Court set out its understanding of the parties' claim construction positions in the following table it included in its order:

constructions appeared "to be incompatible and to compel different outcomes on infringement in the present case." (*Id.* at 2) Accordingly, the Court ordered and received two supplemental briefs from each side. (*See* D.I. 226-29)

C. Sun Is Seeking A New Construction – But Its Request Is Too Late

One or both of the parties should have clearly identified the dispute regarding "portion" either during the claim construction process or in connection with preparation of the pretrial order, or during trial or – at the very latest – during the original round of post-trial briefs. That this did not occur is unfortunate for all involved. While both sides (and the Court) share some responsibility for the predicament in which the Court found itself – only learning after reviewing the post-trial briefs that a dispositive, material claim construction dispute had not been

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	Galderma	**Sun**
"portion"	a functional limitation	a structural limitation
"immediate release portion"	***any part*** of the claimed composition that ***actually dissolves*** immediately upon administration, without enhanced, delayed, or extended release effect	a ***physically discrete part*** of the claimed composition that ***entirely dissolves*** immediately upon administration
"delayed release portion"	***any part*** of the claimed composition that ***does not actually*** begin to dissolve until a time other than immediately following administration, where such delay in release is intended	a ***physically discrete part*** of the claimed composition that ***does not dissolve at all*** until a time other than immediately following administration

(D.I. 222 at 1-2) As will be seen below, the parties' actual preferred constructions are slightly different from what the Court had understood prior to receiving the most recent briefing.

sufficiently identified, nor briefed, by the parties – in the Court's view it is Sun that bears principal responsibility.

Sun knew (or at minimum should have known) from the Court's constructions in this case (rejecting Sun's proposed disclaimer in the DR term) and in the *Amneal* case (rejecting Amneal's proposed structural narrowing of the DR term), as well as the Court's statements in the *Amneal* post-trial opinion (e.g., that the claims are "agnostic" as to how any delay in release in a DR portion occurs), that the Court did not understand the "DR portion" as being narrow or as being restricted to specific types of structures.[6] Therefore, it was Sun – and throughout this case, it is now clear, has always been Sun – that has desired for the Court to ***modify*** its understanding of what constitutes a DR portion (as well as an IR portion). It is Sun that cannot prevail on infringement if the Court applies what it understands to be the "plain and ordinary meaning" of the portion terms (as would be understood by a POSA reviewing the Chang patents). Therefore, it was incumbent on Sun somehow to have asked the Court to alter its understanding of the scope of the asserted claims by construing the portion terms.[7]

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[6] As the Court noted in its claim construction opinion in this case:

> The Court previously construed the delayed release terms according to their plain and ordinary meaning as "release of a drug at a time other than immediately following oral administration." *See Amneal II*, 2017 WL 1882499, at *5. The PTAB provided the same construction in its Final Written Decisions in the *Amneal* IPRs.

(*Sun* CC Op. at 6)

[7] When Sun argued for a disclaimer during the initial round of claim construction in this case, it was, by definition, seeking a construction that "narrows the ordinary meaning" of the "portion" terms. *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1324 (Fed. Cir. 2003). When, thereafter, and throughout trial and the initial post-trial briefing, Sun argued for the "plain and

Sun has now done so, but it is far too late.[8] Its request that the Court construe the portion terms came only in response to the Court's August 29, 2019 order; in fact, the request was first made in Sun's September 9, 2019 brief. (*See* D.I. 227) By then, the parties and the Court had invested enormous resources into trying (and trying to decide) this case based on a "plain and ordinary" meaning "construction" of the portion terms. Under these circumstances, at this late post-trial moment, it would not be appropriate for the Court, nonetheless, to change the construction and narrow it in the manner requested by Sun. *See, e.g.*, *Lighting Ballast Control*, 790 F.3d at 1341; *Edwards*, 2011 WL 446203, at *3-4; *see also Broadcom Corp. v. Qualcomm Inc.*, 543 F.3d 683, 694 (Fed. Cir. 2008) (affirming district court holding that party "waived any claimed error by virtue of its failure to offer a proposed construction at or prior to trial"); *Conoco, Inc. v. Energy & Envtl. Int'l, L.C.*, 460 F.3d 1349, 1359 (Fed. Cir. 2006) ("[L]itigants waive their right to present new claim construction disputes if they are raised for the first time

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ordinary meaning," it seemed to be accepting (at least given the Court's earlier claim construction ruling) that the "portion" terms had a broader meaning than Sun now asserts.

[8] Sun's contention that Galderma is responsible for the delay in the parties' realization that they had a dispute as to the proper construction of the "portion" terms (D.I. 227 at 1-2) is unpersuasive. Sun's argument rests on the premise that Galderma's position that "the term 'portion' as used in the claims of the Chang patents sets forth a ***functional*** rather than a structural or compositional limitation" (*id.* at 1) only became clear in Galderma's post-trial briefs. This is incorrect. Galderma's position has not changed; its interpretation of the "portion" terms has remained constant not only throughout this case, but also throughout all of the prior litigation involving the Chang patents (including the *Amneal* case and the *Amneal* IPR). Even assuming (without deciding) that Sun, too, has been consistent (*see, e.g.*, D.I. 228 at 1) (Sun arguing that "[t]hroughout this litigation" it "has treated the 'IR portion' and 'DR portion' limitations structurally"), it is Sun whose case depends on the Court changing its understanding of the asserted claims' scope, so it is Sun that bears the loss of not having timely asked for the relief it needed.

after trial."); *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1360 (Fed. Cir. 2004) (stating that by failure to raise claim construction dispute, party "implicitly conceded that the meanings of the terms in [the asserted claim] are clear and not in need of construction"); *see also generally Nuvo Pharm. (Ireland) Designated Activity Co. v. Dr. Reddy's Labs., Inc.*, 923 F.3d 1368, 1378 (Fed. Cir. 2019) (noting, in context of Hatch-Waxman appeal: "litigants waive their right to present new claim construction disputes if they are raised for the first time after trial") (internal quotation marks omitted).

For reasons further explained below, without adoption of its belatedly-proposed construction, Sun cannot prevail on the infringement disputes. Therefore, the Court's decision that Sun has waived its opportunity to seek the narrow construction it has belatedly proposed is essentially dispositive on the issues of whether the Sun NDA Product meets the IR portion and DR portion limitations.

Nevertheless, in the interests of completeness, and recognizing all the work that has been done (by the parties and the Court) in this case, the Court will, in the alternative, address the claim construction dispute (which it resolves in favor of Galderma), and apply this construction to the evidence presented at trial.

D. The Court Adopts Galderma's Proposed Constructions of "Portion," "IR Portion," and "DR Portion"

The constructions proposed by the parties in their supplemental post-trial briefing, as well as the Court's adopted constructions, are set out in the table below:

Term	Galderma Construction	Sun Construction	Court's Construction
"portion"	A functional limitation	A structurally discrete part of a composition	A functional limitation
"immediate release (IR) portion"	Any part of the claimed composition that releases drug immediately upon administration, with no enhanced, delayed or extended release effect	A structurally discrete part of the claimed composition that is intended to release drug immediately upon administration with no enhanced, delayed or extended release effect	Any part of the claimed composition that releases drug immediately upon administration, with no enhanced, delayed or extended release effect
"delayed release (DR) portion"	Any part of the claimed composition that delays release of drug until a time other than immediately following oral administration, e.g., through coating, uncoated matrix, or other impediment to delay release	A structurally discrete part of the claimed composition that does not allow any release of drug until a time other than immediately following administration	Any part of the claimed composition that delays release of drug until a time other than immediately following oral administration, e.g., through coating, uncoated matrix, or other impediment to delay release

The Court adopts and incorporates herein by reference the Legal Standards governing claim construction as set out in the claim construction opinion it issued earlier in this case. (*See Sun* CC Op. at 2-5)

In the Court's view, although the parties' disputes relate to three separate terms – portion, IR portion, and DR portion – all three are highly interrelated and must be resolved in the same manner (i.e., all for Galderma or all for Sun). Further, the Court understands there to be three key differences between the parties' proposed constructions: (i) is "portion" construed in a narrower, structural fashion (as proposed by Sun) or a broader, functional fashion (as proposed by Galderma); (ii) must a "portion" be structurally discrete from all other parts of the composition (as Sun proposes and Galderma opposes); and (iii) can a structurally discrete part of

a formulation include a "DR portion" even if some subset of the structurally discrete part releases drug at a time immediately following administration (to which Galderma answers yes and Sun answers no)? Although a close call, the Court is persuaded, after reviewing the intrinsic and extrinsic evidence, that Galderma's positions on all three disputes are more supported. Therefore, the Court will adopt Galderma's proposed constructions.

1. The Claims

The language of the asserted claims does little to help the Court resolve the claim construction dispute.

As Galderma points out (*see* D.I. 205 at 18 n.6), some of the unasserted claims expressly include structural limitations. "For example, claim 1 of the unasserted Chang '532 patent includes the specific structural limitation that 'the DR portion is in the form of pellets coated with at least one enteric polymer.'" (*Id.*) The absence of an explicit structural requirement in the asserted claims suggests that the inventors intended "portion" by itself not to impose a structural requirement. Essentially, Galderma is relying on the doctrine of claim differentiation. *See generally Clearstream Wastewater Sys., Inc. v. Hydro-Action, Inc.*, 206 F.3d 1440, 1446 (Fed. Cir. 2000). While the Court finds that this doctrine provides some limited support for Galderma's proposed construction – and, as importantly, the claim language itself provides ***no support*** for Sun's proposal – the Court does not place great weight on this conclusion. *See generally Atlas IP, LLC v. Medtronic, Inc.*, 809 F.3d 599, 607 (Fed. Cir. 2015) (explaining that because "patentees often use different language to capture the same invention," doctrine of claim differentiation is discounted "where it is invoked based on independent claims rather than the relation of an independent and dependent claim").

2. The Specification

The specification, too, does not provide strong support for either side's proposed construction. As with the claim language itself, however, the Court finds some limited support for Galderma's broader, functional view of "portion" and no support for Sun's narrower, structural view.

The term "portion" is used four times in the specification's detailed description section – as shown below – and none of those uses indicates that the term is being used in a restrictive or narrowing manner:

> Combination IR/DR Dosage Forms . . . .
>
> The first immediate release dose of the composition can be in the form of powder, granule, beadlet, or tablet; the second delayed-release ***portion*** can be coated granular, coated beadlet, coated tablet, or uncoated matrix tablet. The ratio between the immediate-release ***portion***, or component, and the delayed-release ***portion***, or component, can be used to adjust the in vitro drug release profile and in vivo blood concentration profile. . . .
>
> Several dosage form variations can be used to achieve a product with these attributes. . . . [F]or example, a delayed-release tablet can be used as a core and the immediate-release ***portion*** can be compressed as an outer layer using a press coater or overcoated using a drug layering technique . . . .

('405 patent, 5:32-59) (emphasis added)

Nothing in this usage of "portion" indicates that the patent is using the term to refer to a physically or structurally discrete part of the composition. The Court discerns nothing in the specification that would support reading out of the claim scope an embodiment in which the "IR portion," for example, is found in more than one part of the composition. *See generally Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1372 (Fed. Cir. 2014) (noting impact of "words

or expressions of manifest exclusion or restriction" – which are absent from specifications of Chang patents).

3. The Prosecution History, Especially the *Amneal* IPR

The prosecution history, and particularly Galderma's statements during the *Amneal* IPR distinguishing the Sheth prior art reference (identified further below), supports Sun's proposed construction.[9] *See generally Spectrum Int'l, Inc. v. Sterilite Corp.*, 164 F.3d 1372, 1378 (Fed. Cir. 1998) (noting that public has "right to rely" on "explicit arguments made during prosecution to overcome prior art").

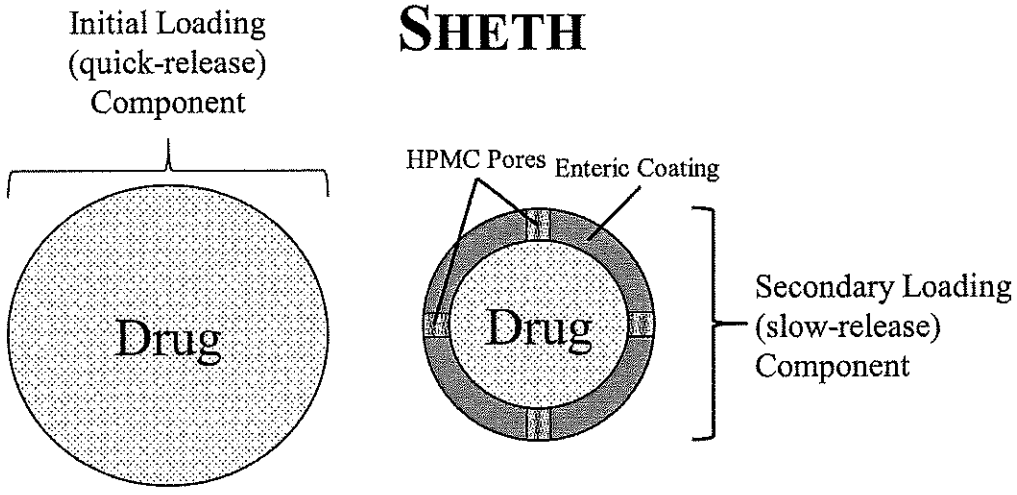
Amneal's IPR challenged the Chang '740 patent as obvious in view of U.S. Provisional Application No. 60/281,854 ("Ashley '854") and U.S. Patent No. 5,348,748 ("Sheth"). (*See* DTX-273.1) Amneal argued that the Ashley '854 patent discloses every limitation of the Chang '740 patent claims except the specifically claimed 30 to 10 ratio of "immediate release" drug to "delayed release" drug. (*Id.* at 11) Amneal argued that Sheth teaches the 30:10 ratio of IR to DR. (*Id.*)

Sheth discloses a once-daily formulation of minocycline (which, like doxycycline, is in the tetracycline class of compounds). (Sheth, 1:10-37) Sheth's formulation includes (1) an "initial loading component" of quick-release pellets; and (2) a "secondary loading component" ("SLC") of slow-release pellets. (*Id.*) Sheth's quick-release pellets are immediate release: they

[9] As already noted, during the claim construction process the Court was not persuaded by Sun's contention that Galderma's statements during the IPR constituted a "clear and unmistakable disavowal" of claim scope. Nevertheless, the Court agrees with Sun that the same prosecution history remains relevant to the claim construction dispute. *See generally Iridescent Networks, Inc. v. AT&T Mobility, LLC*, 933 F.3d. 1345, 1353 (Fed. Cir. 2019) ("[W]here there is no clear ordinary and customary meaning of a coined term of degree, we may look to the prosecution history for guidance without having to first find a clear and unmistakable disavowal.").

completely dissolve quickly after administration. (*Id.* at 2:63-3:5, 6:64-7:7) The slow-release pellets in Sheth consist of the drug coated with both a pH-sensitive enteric coating (which does not break down in the stomach but does in the small intestine) and a pH-insensitive polymer like HPMC (which breaks down in the stomach). (*Id.* at 4:67-5:10) Thus, when the slow-release pellets enter the stomach, the enteric coating forms pores that allow for a slow but consistent release of the drug. (*Id.*) Later, when the slow-release pellets enter the small intestine, the pH rises and the enteric coating entirely breaks down. (*Id.*) This causes a total release of the drug. (*Id.*) Sheth discloses a 30:10 ratio of drug in the initial loading (quick release) component to that in the secondary loading (slow release) component. (*Id.* at 6:10-13, 6:15-20, 18:24-26)

A diagram of the Sheth formulation is provided below:



During the IPR, Galderma,[10] relying on expert testimony by Dr. Rudnic (the same Dr. Rudnic who testified for Galderma at trial), argued that Sheth fails to disclose Chang's IR/DR

[10] The owner of the Chang '740 patent at the time of the IPR was Supernus Pharmaceuticals, Inc. ("Supernus"). Galderma, as Supernus' successor-in-interest, is bound by Supernus' statements in connection with the Amneal IPR. For readability, the Court will refer to representations made

ratio because the secondary loading component of Sheth was not "delayed release," as that term is used in the Chang patent claims. (DTX-273.12) In particular, Galderma argued that Sheth's SLC is not a "delayed release" portion because the SLC begins releasing drug immediately after administration. (*Id.*) In its Final Written Decision, the Patent Trial and Appeal Board ("Board") agreed, construing "delayed release" as follows:

> [T]he [Chang] '740 patent does not provide an express definition of "delayed release." We turn, therefore, to other evidence of how the term is understood and used by persons of ordinary skill in the art. We find, upon consideration of this evidence, that ***the term "delayed release" is used, more-or-less uniformly, to refer to formats that allow for release of a drug only after some delay following oral administration***. . . . For these reasons, we determine that the broadest reasonable construction of "delayed release," consistent with the '740 patent, is "release of a drug at a time other than immediately following oral administration."

(DTX-273.8) (emphasis added)

Applying this construction, the Board concluded that Sheth fails to teach a "delayed release" portion, explaining:

> Sheth's secondary loading portion is not a "delayed release" portion. A "delayed release" format, when that term is used to mean "release of a drug at a time other than immediately following oral administration," ***specifically excludes formats that result in release of drug starting immediately after oral administration***. . . . . Amneal has not explained how there is any appreciable delay in onset of drug release from the secondary loading portion once water in the patient's saliva or gastric fluid has begun to solubilize the pH-insensitive polymer in that coating.

(DTX-273.13-14) (emphasis added)

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by Supernus (and any other predecessor-in-interest to the patents-in-suit) as being made by Galderma.

In sum, Galderma argued – and the Board agreed – that Sheth did not teach a "delayed release" portion because Sheth's SLC started releasing some drug immediately after administration.

For purposes of determining the proper construction of the "portion" terms to apply in the instant litigation, the IPR provides some limited – but not dispositive, and, ultimately, not sufficiently persuasive – support for Sun's proposed construction. While Galderma's statements – and the Board's conclusions – indicate that a part of a drug composition that starts releasing drug immediately after administration is ***not*** a delayed release portion, this does ***not*** mean that Galderma (or the Board) was saying, as a general proposition, that a "portion" must be a structurally discrete part of a composition. Nor did Galderma (or the Board) state that, as a general matter, a structurally discrete part of a composition that begins releasing any bit of itself immediately after administration ***cannot***, per se, include (as a subset) a "delayed release portion" – no matter what else that structurally discrete part consists of. That broader question was not before the Board during the *Amneal* IPR.

The Court is not persuaded by Sun's interpretation of Galderma's statements. Galderma did not limit "delayed release portion" solely to "a structurally discrete part of the claimed composition that does not allow any release of drug until a time other than immediately following administration." *See generally Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1366 (Fed. Cir. 2012). In contrast to Sun's broad reading of Galderma's statements, the *Amneal* IPR proceedings supply a much narrower distinction of Sheth.

As Galderma correctly states, Sheth and Sun's NDA Product "differ in fundamental ways." (D.I. 205 at 19; *see also* D.I. 212 at 14) These differences would be understood by a POSA and would, in the Court's view, lead a POSA to understand what Galderma was saying

about "DR portion" and what it was not. Hence, the Court agrees with the following argument from Galderma:

> . . . Sun errs by conflating *Sheth*'s pore-forming grade of HPMC (*i.e.*, designed to rapidly dissolve and leave behind holes) with the very different "release-controlling" grades of HPMC in Sun's NDA Product (*i.e.*, designed to stay in place and swell, gel, and entangle drug). . . . Further, the evidence showed that *Sheth* and Sun used "HPMC" for entirely opposite purposes – with the *Sheth* pore-forming polymer allowing for release beginning immediately with no intervention; and with Sun's NDA Product in contrast forming a gel layer (after an initial burst) that entangles and prevents release of about 10 mg doxycycline until a time other than immediately following oral administration.

(D.I. 212 at 14)[11]

Galderma's distinction from Sheth can reasonably be read to focus on Sheth's use of HPMC in a manner such that the SLC releases drug beginning immediately and continuing at an ***accelerating rate***. The Sun NDA Product MR layer, by contrast, uses HPMC quite differently: to ***slow the rate*** of drug release after the initial "burst." Because this reading of Galderma's distinction from Sheth does not require Sun's structural construction of "portion," it would be improper for the Court to limit the claims in the manner Sun suggests. *See generally Massachusetts Inst. of Tech. v. Shire Pharm., Inc.*, 839 F.3d 1111, 1119 (Fed. Cir. 2016) ("Where the alleged disavowal is ambiguous, or even amenable to multiple reasonable interpretations, we have declined to find prosecution disclaimer.") (internal quotation marks omitted).

[11] Sun does not contend that its NDA Product is an embodiment of Sheth. To the contrary, Sun has obtained patents on its NDA Product formulation. *See* U.S. Patent Nos. 9,132,092, 9,463,196, and 9,561,242, 9,566,287. (Mathur Tr. at 238-42)

The Court does not agree with Sun that, in the IPR, "[t]o distinguish Sheth, a structural approach was used to evaluate ***all*** of the drug in Sheth's secondary loading portion." (D.I. 228 at 5) This is based on a misreading of the IPR record, and particularly on just two sentences in Dr. Rudnic's lengthy IPR declaration. Sun directs the Court's attention to two sentences in Dr. Rudnic's IPR declaration, in which he stated:

> [A] skilled artisan would understand that a "DR portion" as claimed in the Chang '740 patent is a portion of a formulation that confers delayed release (i.e., preventing release until a later time) to ***all*** of the drug contained in that portion. Accordingly, in the understanding of a person of ordinary skill, a formulation portion that, like the secondary loading portion in Sheth, begins slow, sustained release of some drug promptly after administration, and effectively delays release of only ***some*** of the drug therein, cannot not be a "DR portion."

(*See* D.I. 229 at 2; D.I. 229 Ex. 5 at 104-05) Nothing in that declaration – or anything else to which Sun has directed the Court in the *Amneal* IPR record – discusses whether "portion" should be construed structurally or functionally.

Were one to view Galderma's statements during the IPR in the manner proposed by Sun, that would seem to require one to conclude that the following embodiment does not meet the "portion" limitations of the asserted claims: (i) a 25 mg IR layer combined with a (ii) structurally discrete "MR layer" which itself consists of 5 mg IR on top of a coating having the intent and result of delaying all release of 10 mg DR buried under that coating, where the 10 mg DR did not begin to release until two hours after administration.[12] The Court does not find a persuasive basis in the record to conclude that a POSA would read the *Amneal* IPR to exclude such a trivial

[12] In fact, Sun's position seems to be that if any even minimal part of an "MR" layer releases immediately after oral administration, then the entirety of that layer cannot be considered to be or to have any "DR portion," regardless of how the rest of that "MR" layer dissolves. The Court does not find such a position to persuasive based on the record here.

modification to the preferred embodiment of the formulation from the claims. *See Smith & Nephew, Inc. v. Ethicon, Inc.*, 276 F.3d 1304, 1309-10 (Fed. Cir. 2001) ("A claim interpretation that would exclude the reasonable practice of the method taught in the patent is rarely the correct interpretation.") (internal quotation marks omitted); *see also generally Dayco Prod., Inc. v. Total Containment, Inc.*, 258 F.3d 1317, 1323 (Fed. Cir. 2001) ("If an argument offered in support of a particular claim construction is so convoluted and artificial that it would not be apparent to a skilled artisan reading the patent and the prosecution history, the argument is simply unhelpful . . . .").

In sum, while the Court acknowledges that the prosecution history supports Sun's proposed construction, the Court is not persuaded that a POSA would, in the end, read that prosecution history to mean that a "portion" must be structurally discrete, or that a "DR portion" cannot allow "any release" of drug until a time other than immediately following administration.

4. Extrinsic Evidence

Plaintiff's expert, Dr. Rudnic, testified credibly that the "plain meaning" of "portion" to a POSA, in the context of the Chang patents, allows for an IR or DR "portion" to be found in multiple, structurally distinct parts of a composition. (*See* Rudnic Trial Tr. at 191-92)

The American Heritage College Dictionary, at 1086 (4th ed. 2002), defines "portion" as a "section or quantity within a larger thing . . . a part of a whole." (D.I. 226 Ex. A) Similarly, Webster's dictionary defines "portion" as "an often limited part of a whole." *Portion*, MERRIAM-WEBSTER, https://www.merriam-webster.com/dictionary/portion (last visited Sept. 30, 2019). These definitions provide support for Galderma's proposed constructions and none for Sun's, as they do not suggest that "portion," in general usage, is narrowly limited to structurally discrete parts.

Sun also points to a Skelly 1994 publication, which defines "formulation" as "a listing of the ingredients and composition of the dosage form and its method of manufacture." (D.I. 207 at 4) (citing J.P. Skelly et al., *Workshop II Report: Scaleup of Oral Extended Release Dosage Forms*, 48 J. PHARMACEUTICAL SCI. & TECH. 95-101 (1994) (PTX-287.0007) ("Skelly")) Skelly defines "formulation" as "a listing of the ingredients and composition of the dosage form and its method of manufacture." (PTX-287.0007) Sun argues from this extrinsic evidence that Skelly provides the proper construction of "portion" and "formulation" in the asserted claims of the Chang patents. Putting aside the lack of a persuasive reason to treat Skelly's definition as controlling, the Court agrees with Galderma that this definition in Skelly "says nothing about structure." (D.I. 226 at 7) Skelly's construction (which, notably, is ***not*** the construction Sun is proposing, at this point, that the Court adopt) does not support Sun's narrow proposed constructions.

The extrinsic evidence supports Galderma, and not Sun.

5. Other Constructions

As noted, the Chang patents have been litigated previously. The Court's earlier constructions – and other statements this Court has made about the breadth of the claims of the Chang patents – strongly support Galderma's proposed constructions of the "portion" terms.

In *Galderma Labs., L.P. v. Amneal Pharm. LLC*, 2017 WL 1882499, at *5-6 (D. Del. May 9, 2017), the Court construed "portion" and "formulation" (in the context of the same Chang patents as those that are at issue here, as well as several other patents) as having their "plain and ordinary meaning." Importantly, the Court rejected Amneal's proposal that the Court construe these terms as being "a single type of unit in a multiple unit dosage form that is [delayed] [immediate] release." The Court found that Amneal's proposed construction

improperly narrowed the scope of the claims and rejected Amneal's argument for finding a prosecution history disclaimer (based on Galderma's distinction of different, non-Sheth, prior art). *See id.*

Then, in the *Amneal* Trial Opinion, the Court considered statements Dr. Rudnic made about Sheth in the *Amneal* IPR, and concluded that prosecution history estoppel did not apply because "Amneal has failed to show a clear disavowal of claim scope." 337 F. Supp. 3d 371, 403-04 (D. Del. 2018).

The Court's claim construction opinion in the instant case also supports Galderma's current position. There, as already noted, the Court rejected Sun's proposed construction of "delayed release," which would have been: "release of a drug at a time other than immediately following oral administration, ***excluding formats that result in release of drug starting promptly after oral administration.***" *Galderma Laboratories, L.P. v. Sun Pharmaceutical Industries Limited*, 2017 WL 5592278, at *3-4 (D. Del. Nov. 21, 2017) (emphasis added). The "negative limitation" Sun proposed that the Court should read into the claims was based on the same statements Galderma made about Sheth during the Amneal IPR. In rejecting Sun's disclaimer argument, the Court stated:

> While the patent owner consistently distinguished Sheth '748 based on the timing of release, and the overall release profile of Sheth '748 is not a delayed release format – and, therefore, is not within the claim scope – at no point did the patent owner clearly and unambiguously disclaim all embodiments that release drug at a time other than immediately after oral administration solely because they also release some amount of drug "starting promptly after oral administration."

Id. at *4 (internal citation omitted). The same reasoning that supported the Court's finding of no prosecution history disclaimer persuades the Court that Galderma's IPR statements do not (given

the entirety of the intrinsic and extrinsic evidence) support construing "portion" as a narrow, structural limitation.

The Court has also considered two additional claim construction decisions not involving the Chang patents, which Sun contends support its proposed constructions. The Court disagrees.

In *Reckitt Benckiser Inc. v. Watson Labs., Inc.*, 430 F. App'x 871, 874 (Fed. Cir. 2011) ("*Watson*"), and *Reckitt Benckiser LLC v. Aurobindo Pharma Ltd.*, 239 F. Supp. 3d 822, 827-28 (D. Del. 2017) ("*Aurobindo*"), the patents claimed a drug formulation with two separately claimed "portions." There, as here, the plaintiff alleged that a single, homogenous, polymer matrix formulation contained both claimed "portions" because the allegedly infringing formulation was functionally (i.e., looking at dissolution data) identical to the patentee's product, which had a discrete IR portion and a discrete portion that released drug over time. *See Watson*, 439 F. App'x at 876-78; *Aurobindo*, 239 F. Supp. 3d at 828-30. The *Watson* and *Aurobindo* Courts construed the term "portion" to mean "a discrete part of the product," reasoning that a single homogenous formulation could not include two distinct "portions" even if the dissolution profile of that formulation is identical to a two-portion product. *See Watson*, 439 F. App'x at 876-78 (rejecting infringement theory that because accused single-formulation product's dissolution profile matched that of patentee's product, which had two discrete portions, accused product contained both claimed "portions"); *Aurobindo*, 239 F. Supp. 3d at 828-30 (same).

Contrary to Sun's contentions here (*see* D.I. 207 at 6-7; Trial Tr. at 575-77), the constructions of "portion" in *Watson* and *Aurobindo* were premised on the specifications and prosecution histories of the patents-in-suit there, which are entirely different than the intrinsic evidence of the patents-in-suit here. *See Watson*, 439 F. App'x at 876-78; *Aurobindo*, 239 F. Supp. 3d at 828-30. Thus, while *Watson* and *Aurobindo* adopted structural constructions of

"portion," such a construction is not warranted here, where the patents and prosecution history are quite different. *See generally Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1584 (Fed. Cir. 1996) (noting that use of prior art to construe claims is improper where intrinsic evidence is clear).

Collectively, these other constructions – both those directly involving the Chang patents, and those involving other patents – support the Court's decision to adopt Galderma's constructions of the portion terms and to reject Sun's narrower constructions.

6. Conclusion Regarding Proper Construction of "Portion" Terms

The Court will adopt Galderma's proposed construction of the "portion" terms, which are consistent with the Court's understanding of what a POSA would believe to be the "plain and ordinary meaning" of these terms. That is, the Court believes the plain and ordinary meaning to a POSA of the "portion" terms, as used in the context of the Chang patents, would be broad and functional, not narrow and structural.

No one argues that the patentee was its own lexicographer or has asked the Court to reconsider its conclusion during claim construction that Galderma's statements during the *Amneal* IPR do not constitute a disclaimer.[13] Neither the claim language nor the specification provides much support to Galderma, although the doctrine of claim differentiation supports Galderma's functional view and nothing in the specification is inconsistent with Galderma's construction. While the prosecution history, and especially Galderma's statements distinguishing Sheth, supports Sun's proposals, Galderma's statements do not persuade the Court

[13] Sun's untimely request is that the Court ***construe*** the "portion" terms, ***not*** that it change its holding as to whether the prosecution history reveals a clear and unmistakable disclaimer.

that a POSA would read the "portion" terms as narrowly as Sun proposes. The extrinsic evidence provides additional support for Galderma's construction. More importantly, so, too, do the Court's prior claim construction orders and other conclusions in cases in which the Chang patents have been previously litigated.

Hence, Galderma has persuaded the Court that a POSA would understand the "portion" terms to have a broad, functional meaning, rather than a narrow, structural meaning.[14] Accordingly, the Court will adopt Galderma's proposed constructions.

B. Sun's NDA Product Has an IR Portion

As already explained above, Galderma's proof that Sun's NDA Product meets the IR portion limitation essentially follows from the Court's adoption of Galderma's claim construction position.[15] It is undisputed that Sun's Product contains 26.4 mg of immediate release doxycycline, that is 26.4 mg of doxycycline that is released immediately upon oral administration. Under the Court's construction of "IR portion," which is "***any part*** of the claimed composition that releases drug immediately upon administration, with no enhanced, delayed or extended release effect" (emphasis added), Sun's NDA Product contains an additional 3.6 mg of doxycycline that is part of the "IR portion" because it, too, releases immediately upon administration with no enhanced, delayed or extended release effect – notwithstanding that this

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[14] The Court agrees with Galderma that the core requirement of Sun's proposed constructions, the requirement that a "portion" be "'structurally discrete,'" is "***nowhere*** in the intrinsic evidence – not in the claims, the specification, the prosecution history, or the IPR record that Sun now cites." (D.I. 229 at 2)

[15] To be clear, the Court finds that Sun's NDA Product meets the IR and DR portion limitations, and infringes, literally and under the doctrine of equivalents, under an unspecified "plain and ordinary meaning" of "portion," and also under Galderma's proposed construction of "portion" – the latter being what the Court has been persuaded is the "plain and ordinary meaning" to a POSA in the context of the Chang patents.

additional 3.6 mg is physically contained within the Sun NDA Product's MR layer, and not within that product's IR layer.

In addition to the Sun claim construction arguments the Court has already rejected, Sun levels other criticisms against Galderma's contention that it has proven that Sun's NDA Product meets the IR portion limitation. The Court has considered each of Sun's points and addresses the more important of them below.

Sun contends that the 30-minute framework for assessing immediate release is arbitrary and not part of the claims. (*See, e.g.*, D.I. 207 at 5; Trial Tr. at 581-82) However, as Galderma points out, Sun's formulator, Dr. Singh, testified that 75% release within 30 minutes is what Sun considered to be IR; it is what Sun targeted in its design and what it achieved with its NDA Product. (*See* D.I. 205 at 11-12; *see also* Singh Trial Tr. at 218) The Court is persuaded that a POSA's understanding of "release immediately after oral administration" would include release of about 75% of active ingredient within 30 minutes of oral administration. The 30-minute framework is not, then, arbitrary. In any event, nothing about Sun's argument about the pertinence of the 30-minute framework undermines the Court's finding that Sun's NDA Product meets the IR portion limitation.

Sun argues that Galderma's infringement analysis places improper weight on Sun's "intent" in how it designed its NDA Product. It is generally true that intent plays no role in assessing direct patent infringement. *See Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 761 n.2 (2011) ("[A] direct infringer's knowledge or intent is irrelevant."). Here, however, the parties agreed at trial to a construction (which the Court has now adopted) of "immediate release" that expressly takes into account an accused infringer's intent. IR is construed (as the parties ***agreed*** and further agree is based on a definition in the Chang patents) to mean "a dosage

form that is ***intended*** to release substantially all of the active ingredient ***on administration***, with ***no enhanced, delayed, or extended release effect.***" (Chang '405 patent, 4:14-17 (emphasis added); PTX-375.0036 (defining "immediate release" in relevant part as "with no intention of delaying or prolonging the dissolution;" Rudnic Tr. at 110-11; Chambliss Tr. at 276) In this case, then, intent is a pertinent consideration.

Properly taking Sun's intent into account supports, and does not undermine, the Court's finding that the Sun NDA Product literally infringes the Chang patents. As Galderma proved, Sun "***intentionally*** designed" its NDA Product to provide the "biphasic" release profile recited by the claims. (D.I. 205 at 9; *see also, e.g.*, *id.* (citing Sun NDA Product's dissolution data showing that "Sun met its goal of mimicking" claimed release profile); *id.* at 10-13 (citing testimony by Dr. Singh as confirming that Sun "consistently targeted" release of 30 mg immediately and 10 mg after that and that Sun "specially selected" and "specifically calibrated" excipients to achieve "initial burst" of precisely 3.6 mg from MR layer)) The evidence shows that Sun attempted to – and succeeded in – designing a product that matches Oracea's release profile of 30 mg doxycycline within 30 minutes, and 10 mg after that. Further, by demonstrating bioequivalence to Oracea, Galderma's reference listed drug, Sun was permitted by the FDA to use Oracea's clinical trial data to avoid having to conduct its own costly and time-consuming clinical trials.[16]

[16] While "bioequivalence is not the test for infringement," *Reckitt Benckiser LLC v. Aurobindo Pharma Ltd.*, 239 F. Supp. 3d 822, 833 (D. Del. 2017), and a bioequivalent drug may not necessarily infringe patent claims covering the patented drug, bioequivalence may nonetheless be relevant to the infringement inquiry, *see Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1289 (Fed. Cir. 2010) (relying on bioequivalence data as circumstantial evidence of infringement). Sun's NDA was filed under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. (*See* D.I. 195 Ex. 1, SUF ¶ 59) New Drug Applications under Section 505(b)(2)

Accordingly, the Court finds that Galderma has proven by a preponderance of the evidence that Sun's NDA Product meets the IR portion limitations of the asserted claims of the Chang patents.

C. Sun's NDA Product Has a DR Portion

As with the IR portion, Galderma's proof that Sun's NDA Product meets the Chang patents' DR portion limitations follows largely from the Court's adoption of a functional construction of the DR portion term.

As Sun's Dr. Chambliss explained, the MR layer of Sun's NDA Product contains two grades of HPMC "so combined, you are getting the release profile [of doxycycline] that you are looking for." (Chambliss Tr. at 290-91) He added that the HPMC is "intentionally added to extend [the] release" and "slow it down," "so you are slowing down the diffusion of [Sun's] drug." (Chambliss Tr. at 288-89, 297) Moreover, the Sun NDA Product's dissolution data establishes that it releases approximately 10 mg of doxycycline later than 30 minutes after administration. (PTX-331.1-3) The evidence is essentially undisputed that the amount of drug that is released from the Sun NDA Product's MR layer "at a time other than immediately following oral administration" is 10 mg of doxycycline or about 10 mg of doxycycline. (*See* Findings of Fact, *supra* ("FF"), ¶ 44) In the Court's view, this means that the MR layer releases

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may rely on safety and effectiveness data from previously-approved drugs by "establish[ing] a bridge (e.g., by using comparative bioavailability data) between the proposed drug product and each listed drug)." Determining Whether to Submit an ANDA or a 505(b)(2) Application, Guidance for Industry, U.S. Food and Drug Administration (May 9, 2019), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applications-covered-section-505b2.

drug at a time other than immediately after oral administration, meeting the construction of DR portion.

The Court agrees with Galderma's general characterization of the Sun NDA Product MR layer: "By Sun's design, these two [HPMC] polymers swell and gel at different rates – with the low molecular weight polymer swelling at a faster rate, but forming a weak and ineffective gel that permits the immediate release of about 3.6 mg doxycycline; and the high molecular weight polymer taking longer to swell and gel, but eventually forming a complete gel that effectively cuts off the immediate release burst by 'entangling' the remaining portion of about 10 mg doxycycline." (D.I. 205 at 5) This characterization is supported by the record, including the testimony of Sun's own expert, Dr. Chambliss, that "there is an initial release of doxycycline from the MR layer, as the doxycycline at the surface of the matrix is dissolved before the gel barrier forms, and then there is a continuous, slow release of doxycycline over the period of several hours." (Chambliss Trial Tr. at 356-57)

In response to Galderma's infringement evidence, Sun raises numerous challenges, most of which have already been discussed and rejected (mostly in the context of resolving the claim construction disputes). Additional points made by Sun will be addressed now.

Sun insists that the dissolution profile of Sun's NDA Product is not identical to that of Galderma's Oracea embodiment. Oracea has an "initial burst" of about 30 mg of doxycycline release (in the first 30 minutes after oral administration), and then essentially no additional release of doxycycline occurs until around two hours after oral administration. (Chang '405 patent, Fig. 2) Oracea, hence, has a stoppage in all release of doxycycline which is not present in Sun's NDA Product. Instead, according to Sun, its NDA Product's MR layer begins releasing

essentially concurrently with its IR layer and never stops releasing. (*See generally* D.I. 211 at 11-13)

The Court agrees with Sun that the release profile of Sun's NDA Product shows no stoppage, gap, or plateau. (*See, e.g.*, DTX-279.17 (Methocel manufacturer's data sheet displaying its dissolution profile, showing initial quick release followed by lengthy slow release, all with no stop of release); *see also* PTX-331.1-3 (Sun's NDA Product dissolution profile, showing increasing release of doxycycline when measured at 15 minutes, 30 minutes, and 1, 2, 4, and 6 hours, with no stop in release)) Galderma's efforts to persuade the Court that Sun's NDA Product does have such a stoppage are unavailing. (*See, e.g.*, D.I. 205 at 16-17) Galderma's characterization of the release profile of the Sun NDA Product's MR layer largely relies on statements made by Sun in development documents and by Dr. Romi Singh, Sun's lead formulator. (*See* D.I. 205 at 11, 20) (quoting Dr. Singh characterizing Sun's NDA Product as having a "biphasic" release profile in "two pulses," where "some release . . . happens immediately, ***and then*** some release happens over a period of time") (emphasis added) These statements, however, do not mean what Galderma insists they mean: that there is some stop or pause in the release of doxycycline contained in the Sun NDA Product's MR layer. The dissolution profile evidence – which the Court has found to be important to Galderma's successful showing of infringement – entirely and persuasively rebuts Galderma's contention that there is any stoppage of release of doxycycline at any point following oral administration of Sun's NDA Product.

Although Sun is correct on this factual point, Sun is wrong about the implications of this finding for the ultimate infringement decision. Indeed, because the Court's construction of delayed release does not require a stoppage in release of doxycycline, the lack of such a pause in

the release profile of Sun's NDA Product is not fatal to Galderma's infringement case. In fact, in the *Amneal* Trial Opinion, 337 F. Supp. 3d at 407, the Court specifically stated: "[N]othing in the Court's construction [of 'delayed release'] 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).". The Court further explained:

> ***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) . . . 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."
>
> [T]he Court's construction of 'delayed release' is agnostic as to how the delay is accomplished.

Id. at 406-07 (emphasis added).

Sun also argues that it cannot be found to have a DR portion, given the reasons Galderma relied on during the Amneal IPR to persuade the PTAB that Sheth lacks a DR portion. To overcome the Sheth reference during the IPR, Galderma repeatedly argued that Sheth did not teach a "delayed release portion." (*See, e.g.*, IPR2013-00368 Paper 40, Patent Owner Resp. at 9) ("[T]he teaching throughout Sheth that the secondary loading portion has a ***'slow release'*** profile [] ***distinguishes it from the 'DR portion'*** recited in the Chang '740 patent claims.") (emphasis added)

The Court agrees with Sun to this extent: if application of the Court's claim construction and the arguments Galderma makes in support of infringement here would lead to the conclusion that Sheth's secondary loading component ***is*** a delayed release portion, that would tend to

undermine (if not entirely defeat) Galderma's infringement case. But the Court parts company with Sun because it does not agree that application of its claim constructions and Galderma's reasoning logically leads to a conclusion that Sheth contains a DR portion. Instead, the Court agrees with Galderma that Sheth's SLC does ***not*** have ***any part*** that delays release of drug until a time other than immediately following oral administration. Instead, the SLC ***does*** begin to release immediately upon oral administration and never stops.

By contrast, Sun's MR layer contains about 3.6 mg of doxycycline that actually dissolves immediately upon oral administration, without enhanced, delayed, or extended release effect. combined with about 10 mg of doxycycline that (intentionally) does not actually release until a time other than immediately following administration. That this about 3.6 mg and the about 10 mg are manufactured and compressed into a single layer does not, for all the reasons stated, mean that the about 3.6 mg and the about 10 mg would not be viewed by a POSA as performing the functions they are actually performing in Sun's formulation. *See generally Union Paper-Bag Mach. Co. v. Murphy*, 97 U.S. 120, 125 (1877) ("[I]n determining the question of infringement, the court [is] not to judge about similarities or differences by the names of things, but [is] to look at the machines or their several devices or elements in the light of what they do, or what office or function they perform, and how they perform it . . . .")

Crucially, applying the Court's "portion" constructions to the formulation of Sheth results in a conclusion that Sheth does not have a delayed release portion – which is consistent with the Board's conclusion. Under the Court's understanding of the functional nature of the "portion" limitations, a DR portion is "[a]ny part of the claimed composition that delays release of drug until a time other than immediately following oral administration, e.g., through coating, uncoated matrix, or other impediment to delay release." Sheth has no such part. Sheth's secondary

loading component begins to release immediately following oral administration; its release is ***not*** delayed "until a time other than immediately following oral administration." As Galderma puts it: "Under Plaintiffs' proposal, the 'secondary loading' composition described in U.S. Patent No. 5,348,748 ('*Sheth*') is not a 'delayed release (DR) portion,' because it begins release immediately after administration and continues to release at an accelerating rate, with no intervention to delay release." (D.I. 226 at 2)

It is true that, by design, the overall rate of release of Sheth's SLC is slower than it would be had Sheth not designed other ingredients (e.g., the pore-forming enteric coating) into it. Still, however, Sheth's secondary loading component is materially different than Sun's MR layer, which by design releases about 3.6 mg of active ingredient immediately after administration and then intentionally slows release of (only) the remaining 10 mg of active ingredient. Consequently, while the release rate of Sheth's SLC starts out above zero and accelerates over time, the release rate of Sun's MR layer starts out above zero, then decreases, and only later increases. In the Court's view, then, a POSA would understand the MR layer to be functioning first as an IR portion and then functioning as a DR portion. Sheth's secondary loading component never functions as a DR portion.

In sum, the Court finds that Galderma has proven by a preponderance of evidence that Sun's NDA Product satisfies the delayed release portion limitation.

D. Sun's NDA Product Also Satisfies the Portion Limitations Under the Doctrine of Equivalents

Galderma argues that Sun's NDA Product also meets the "immediate release portion" and "delayed release portion" limitations under the doctrine of equivalents ("DOE").[17] Galderma puts forth equivalence theories under both the "insubstantial differences" test and the "function-way-result" test. The Court again agrees with Galderma.

The Sun NDA Product is insubstantially different from a composition with an IR portion consisting of 30 mg of doxycycline "because the undisputed evidence shows that Sun's NDA Product was intentionally designed to immediately release a portion of about 30 mg doxycycline within the first 30 minutes, from a combination of Sun's 26.4 mg doxycycline 'IR Layer' and an initial burst of 3.6 milligrams of doxycycline from Sun's 'MR Layer.'" (D.I. 205 at 20) The Sun NDA Product is insubstantially different from a composition with a DR portion consisting of 10 mg of doxycycline "because a portion of about 10 mg doxycycline on the interior of Sun's 'MR Layer' is not released until a time other than immediately following oral administration, due to the intervention of the gel barrier that cuts off immediate release and 'entangles' the remaining doxycycline." (*Id.* at 21)

The Court further agrees with Galderma that "[t]he portion of about 30 mg doxycycline that is immediately released from Sun's NDA Product . . . performs substantially the same function (immediate release of about 30 mg doxycycline), in substantially the same way (releasing about 30 mg immediately after oral administration from a combination of Sun's 'IR

[17] Galderma does not separately contend that the steady-state limitations are met under the DOE, only literally. (D.I. 205 at 22-23) As will be explained below, the Court is persuaded by Galderma that the steady-state limitations are met literally.

Layer' and the initial burst from Sun's 'MR Layer'), to achieve substantially the same result (bioequivalence to 30 mg IR, 10 mg DR Oracea® Capsules) as an IR portion of about 30 mg doxycycline." (D.I. 205 at 20-21) With respect to the DR portion limitations, "[t]he portion of about 10 mg doxycycline that is not released from Sun's 'MR Layer' until a later time . . . performs the substantially the same function (delaying release of about 10 mg until a time other than immediately following oral administration), in substantially the same way (precluding release of the interior 10 mg of Sun's 'MR Layer' until a later time due to the intervention of a gel barrier), to achieve substantially the same result (bioequivalence to 30 mg IR, 10 mg DR Oracea® Capsules) as the claim elements covering an DR portion of about 10 mg doxycycline." (*Id.* at 21) The evidence supporting these statements is set out throughout this Opinion.

The Sun NDA Product fulfills these functions and achieves these results in substantially the same way as the asserted claims.

For the reasons already given above in relation to claim construction and direct infringement, the Court concludes that Galderma's DOE theory of infringement is also not inconsistent with the statements Galderma made to distinguish Sheth during the Amneal IPR. Galderma distinguished Sheth on the basis that Sheth did not disclose a "delayed release portion" because no part of the Sheth formulation was designed not to begin release until sometime after immediately following oral administration. By contrast, the Sun NDA Product contains 10 mg of doxycycline – within the MR layer – that is designed not to begin release until some time other than immediately following oral administration. Recognizing the facts that these 10 mg perform substantially the same result, fulfilling substantially the same function, and in substantially the same way as the 10 mg DR portion of the claimed compositions is not precluded by anything that Galderma said or did during the IPR.

Accordingly, the Court finds that Galderma has proven the portion limitations are met under the doctrine of equivalents.

E. Sun's NDA Product Meets the Steady State Plasma Concentration Limitations

The asserted claims all require the claimed oral pharmaceutical composition to provide "steady state blood levels of doxycycline of a minimum of 0.1 μg/ml and a maximum of 1.0 μg/ml." (*E.g.*, '740 patent, cl. 1) The Court agrees with Galderma that at least the following evidence proves, by a preponderance of the evidence, that Sun's NDA Product meets the "steady state blood levels" limitations: (1) a pharmacokinetic study for Oracea, the Pivotal PK Study, which showed that 30 out of 31 subjects taking Oracea had steady-state blood levels between 0.1 μg/ml and 1.0 μg/ml when taken once daily during the dosage period (FF ¶ 28); and (2) a pharmacokinetic study in which a single dose of Sun's NDA Product was shown to be bioequivalent to a single dose of Oracea under fasting conditions (FF ¶ 47). (*See* D.I. 205 at 22)

Sun does not dispute that its NDA Product is bioequivalent to Oracea, or that Oracea causes the steady state blood levels of doxycycline specified by the claims. Sun nevertheless contends that this evidence is insufficient to carry Galderma's burden as the party claiming infringement. (D.I. 207 at 17-18) The Court disagrees. Since Oracea's steady state blood levels are within the limits specified by the claims, and Sun proved to the FDA's satisfaction that its NDA Product is bioequivalent to Oracea, it follows that the Sun NDA Product's blood levels are also within the limits specified by the claims.

As Galderma points out (D.I. 205 at 23), it would make little sense for the FDA to allow Sun's NDA Product to use Oracea's safety and effectiveness data if there was any doubt as to whether the Sun NDA Product's steady state blood levels of doxycycline (i.e., the very property

that gives Sun's NDA Product its clinical effectiveness) matched those of Oracea. Sun's conduct supports this conclusion; if Sun believed that its NDA Product had significantly different steady state blood levels than Oracea, it would have notified the FDA. (Chambliss Tr. at 365) (Dr. Chambliss acknowledging that it would "probably" be "a matter of concern" for FDA if Sun's steady state blood levels were not within range of 0.1 μg/mL to 1.0 μg/mL)

Sun points out that, under FDA standards, bioequivalence can be met so long as blood levels are within 80 to 125% of the bioavailability of the reference-listed drug. (*See* D.I. 207 at 17-18) Thus, Sun argues, its NDA Product could be bioequivalent to Oracea yet have blood levels outside the 0.1 μg/mL to 1.0 μg/mL range claimed by the Chang patents. (*Id.*; *see also id.* at 18 n.10 (citing Pivotal PK Study, and noting that 125% of blood levels measured certain subjects would be greater than 1.0 μg/mL)) However, the Pivotal PK Study shows that the vast majority of subjects' blood levels were always between 0.125 μg/mL to 0.8 μg/mL. (FF ¶¶ 27-28) Therefore, even if Sun's NDA Product were just barely bioequivalent (i.e., either 80% or 125% as bioavailable as Oracea), Sun's NDA Product would nevertheless provide blood levels inside the claimed 0.1 μg/mL to 1.0 μg/mL range for the vast majority of patients.[18] Moreover,

[18] Some patients at times reported steady-state blood levels greater than 0.8 μg/mL or less than 0.125 μg/mL. (FF ¶¶ 27-28) If these patients were to take Sun's NDA Product, and Sun's NDA Product were just barely bioequivalent (i.e., 80% or 125% as bioavailable as Oracea, respectively), then some of those patients' blood levels might fall outside the claimed 0.1 μg/mL to 1.0 μg/mL range. Even if true, however, this would be of little significance to the Court's infringement analysis. As explained in the *Mylan* Trial Opinion, which also involved Chang patents, "even if only 1 of 31 subjects in the pivotal pK study had [blood levels within the claimed range], this is a sufficient basis from which to find infringement." *Research Found. of State Univ. of N.Y. v. Mylan Pharm. Inc.*, 809 F. Supp. 2d 296, 330-31 (D. Del. 2011), *aff'd in relevant part, vacated in part, remanded*, 531 F. App'x 1008 (Fed. Cir. 2013). On essentially the same evidence as Galderma marshals here, the Court found the steady state limitations to be satisfied in *Mylan*. *See* 809 F. Supp. 2d at 330-31.

Sun's single-dose experiments show that its NDA Product's bioavailability parameters are significantly inside the 80-125% range allowed by the FDA's bioequivalence test. (FF ¶ 47) (Sun: "The ratios of [Sun's NDA Product] and [Oracea] (least-squares means) for doxycycline derived from the analysis of log transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 97.23%, 92.87% and 94.73%, respectively.") As such, the Sun NDA Product's steady-state blood levels are likely to be substantially closer to those measured for Oracea than would be expected from a product that was just barely bioequivalent.

Therefore, the Court finds it is more likely than not that Sun's NDA Product meets the "steady state blood levels" limitations. *See SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1123 (Fed. Cir. 1985) (stating that patentee bears burden of proving infringement by "preponderance of the evidence"); *LaLonde v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1338 (Fed. Cir. 2014) (stating that burden under "preponderance" standard is met when trier of fact "believe[s] that the existence of a fact is more probable than its nonexistence" and does not require proof "to a level of scientific certainty").

For all of the foregoing reasons, the Court finds that Galderma has proven, by a preponderance of the evidence, that Sun's NDA Product infringes the asserted claims of the Chang patents, both literally and under the doctrine of equivalents.

II. Sun Has Failed to Prove that the Chang Patents Are Invalid As Obvious

Sun seeks to invalidate the Chang patents as obvious in view of the Ashley Applications (the Ashley '932 publication, which incorporates by reference the Ashley '854 application) and the Periostat Package. (D.I. 207 at 18-28) Sun has failed to prove obviousness by clear and convincing evidence.

A. Prior Art

Tetracyclines, including doxycycline, have long been used as antibiotics. (Chang '405 patent, 1:30-32; Chambliss Tr. at 308-09) The Ashley '932 publication, which is entitled "Methods of Treating Acne," explains that tetracyclines have also been known in the art to be effective in treating acne. (Ashley '932 publication, at 4) At the time the Ashley '932 publication was filed, this effect was thought to result from tetracyclines' antibiotic properties. (*Id.*) However, the use of antibiotic-strength tetracycline to treat acne can lead to undesirable side effects, such as a reduction in healthy gut flora, and the production of antibiotic-resistant organisms. (Chang '405 patent, 2:15-21) Ashley improved on the prior art by disclosing that acne can be effectively treated with a ***sub-antibiotic*** dose of tetracycline, thereby avoiding these side effects. (Ashley '932 publication, at 5) Specifically, Ashley noted that steady-state doxycycline blood levels should be kept below 1.0 μg/mL to avoid antibiotic effects. (*Id.* at 11; Ashley '854 application, at 5) To achieve these blood levels, Ashley discloses "a preferred embodiment" in which doxycycline is administered in a daily amount from about 30 to about 60 mg, and "an especially preferred embodiment" in which doxycycline hyclate is administered at a 20 mg dose twice daily. (Ashley '932 publication, at 9) This especially preferred embodiment is practiced by Periostat, a drug for the treatment of periodontal disease. (*Id.*) Alternatively, tetracycline may be administered by sustained release using the formulations disclosed in the Ashley '854 application, which the '932 publication incorporates by reference. (*Id.* at 15-16)

The Ashley '854 application, entitled "Controlled Delivery of Tetracycline and Tetracycline Derivatives," is not directed specifically to the treatment of acne, but more generally to tetracycline drug formulations that keep steady-state blood levels at an effective but sub-antibiotic range (i.e., between 0.1 μg/mL and 1.0 μg/mL). (Ashley '854 application, at 5)

Ashley achieves these blood levels through a formulation that includes a tetracycline compound "and at least one controlled-release agent." (*Id.* at 5) A controlled release agent can be "an instantaneous-release agent, a sustained-release agent, a delayed-release agent, and combinations thereof." (*Id.*) Ashley explains that the use of a controlled release agent means that the formulation need only be taken once or twice per day, as opposed to many times per day, while still maintaining blood levels at an effective but sub-antibiotic range. (*Id.* at 6)

The Periostat Package includes formulation and clinical pharmacokinetic data for the twice-daily 20 mg doxycycline formulation used in commercial Periostat and for the once-daily 40 mg doxycycline formulation disclosed in the Ashley Applications. (FF ¶ 92) This pharmacokinetic data shows that a once-daily 40 mg IR formulation of doxycycline produced blood levels in the target range of between 0.1 μg/mL and 1.0 μg/mL for test subjects on average, but, notably, levels greater than 1.0 μg/mL for 3 of 13 subjects. (FF ¶ 95)

Importantly, none of the prior art references on which Sun's obviousness case is based discloses anything other than IR formulations.

B. Sun's Attempted Prima Facie Case

Sun acknowledges that its prior art references do not disclose a 30:10 IR/DR ratio. Instead, Sun's contention is that this ratio would have been obvious to a POSA with the Ashley Applications and the Periostat Package in hand. (D.I. 207 at 21-25) Sun argues that a POSA would be motivated by the Periostat Package pharmacokinetic data to modify the 40 mg once-daily doxycycline formulation disclosed in the Ashley Applications and instead use a combination of IR drug and DR drug, and after such a realization "it would have been a matter of routine optimization" for a POSA to arrive at a range of effective IR/DR ratios. (*Id.*)

Sun has failed to persuade the Court of the correctness of these contentions by the required clear and convincing evidence. *See Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012).

The Court does not find that a POSA would have been motivated by the Periostat Package's pharmacokinetic data to use an IR/DR composition. The Periostat Package pharmacokinetic data indicates that a once-daily 40 mg IR formulation of doxycycline produced blood levels in the target range of between 0.1 μg/mL and 1.0 μg/mL for most test subjects, but measured levels greater than 1.0 μg/mL for some subjects. (FF ¶ 95) Sun's Dr. Chambliss opined that a POSA would want to ensure that substantially no subjects exceed doxycycline's 1.0 μg/mL antibiotic blood level threshold, and so would "lengthen and flatten" a 40 mg IR formulation's blood level curves by delaying the release of "at least some" of the doxycycline. (D.I. 207 at 22-23; Chambliss Tr. at 326) Dr. Chambliss added that, to a POSA, the "most straightforward way" to achieve this delay would be to use some combination of IR drug and DR drug. (*See* Chambliss Tr. at 326-27)

However, in the Court's view, the Ashley Applications' teaching that the drug is to be released at a ***substantially constant rate*** would have discouraged a POSA from using an IR/DR formulation. (*See* Ashley '854 application, at 8) ("The composition of the invention . . . provid[es] a dose of tetracycline . . . at a substantially constant rate over a longer period of time.") Moreover, the Ashley '932 publication cites the Ashley '854 application specifically for its teaching of "***sustained release***" (SR) compounds (Ashley '932 application, at 15) (emphasis added), which the Ashley '854 application distinguishes from both IR and DR formulations (*see* Ashley '854 application, at 10-11) (separately defining "instantaneous release agent," "delayed release agent," and "sustained release agent"). Taken together, these teachings suggest that a

POSA reading the Ashley Applications would have been motivated to use an SR formulation instead of an IR/DR combination. *See generally Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999) ("A reference may be said to teach away when a person of ordinary skill, upon reading the reference, . . . would be led in a direction divergent from the path that was taken by the applicant . . . .").

Sun's characterization of IR/DR compositions as a "preferred way[]" to achieve a substantially constant rate of release lacks merit. (*See* D.I. 207 at 25-26) Although the Ashley '854 application contemplates that IR/DR compositions ***could*** be used, that does not mean that ***all*** IR/DR compositions meet Ashley's teaching of a substantially constant rate of release. To take an extreme example, a composition with 99.99% IR and 0.01% DR would be an IR/DR composition, but would clearly not release drug at a substantially constant rate. Sun, as the patent challenger, has the ultimate burden of demonstrating that the Ashley Applications would have motivated a POSA to formulate the Chang patents' specific IR/DR combination – for example, by showing that the Chang patents' 30:10 IR/DR ratio results in doxycycline being released for at least 60% of the release period (i.e., that the Chang patents' formulation provides for substantially constant release). (*See* Ashley '854 application, at 13) (defining "substantially constant rate," in relevant part, as "maintaining a release rate of the active ingredient, i.e., tetracycline, within a desired range over at least about 60% of the designated time period for release") Sun has failed to do so.

Nor has Sun proven by clear and convincing evidence that a POSA would have used the Periostat Package's pharmacokinetic data and computer simulations to arrive at a ***30:10*** IR/DR ratio. For this contention, Sun relies on the testimony of Dr. Chambliss (*see, e.g.*, Chambliss Tr. at 326-30), but the Court is not persuaded. Dr. Chambliss cites U.S. Patent No. 4,250,166, which

was issued decades before the Chang patents were filed, as describing how pharmacokinetic data for an IR formulation (like the pharmacokinetic data in the Periostat Package) could be used to simulate blood levels for a combined IR/DR formulation. (*Id.* at 329-30) The Court, however, credits the testimony of Galderma's Dr. Rudnic, who opined that a POSA would not have been able to use the Periostat Package pharmacokinetic data for this purpose because that data relates only to ***immediate*** release, and not ***delayed*** release drug. (FF ¶ 98) He explained that IR and DR formulations are absorbed at different locations in the digestive tract, which may vary the effectiveness with which drug is absorbed. (FF ¶ 109; *see also* Rudnic Tr. at 440 (Dr. Rudnic testifying that "in 2002 and 2003, a POSA would have some information about the absorption [of doxycycline] in the GI tract, but not the whole story")) The Court finds that a POSA would not have had a reasonable expectation of success in using the Periostat Package pharmacokinetic data to accurately determine an effective IR/DR ratio.[19] *See Endo Pharm. Inc. v. Actavis LLC*, 922 F.3d 1365, 1373 (Fed. Cir. 2019) (noting that, for prior art to render invention obvious, POSA must have "reasonable expectation of success" in combining prior art teachings to arrive at invention).

The Court's conclusions are supported by the history of Oracea's development. The Chang patent inventors did develop a computer model for a doxycycline IR/DR composition, but only after conducting a study that specifically tested IR/DR compositions. (FF ¶ 120)

Accordingly, the Court will enter judgment of no invalidity.

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[19] The Court's conclusion of no obviousness in *Mylan*, 809 F. Supp. 2d at 330-31, also supports the Court's similar conclusion here. In the *Mylan* Trial Opinion, the Court rejected a claim of obviousness based on the Ashley '932 application and other prior art. There, as here, no prior art references, alone or in combination, taught the 30:10 IR/DR ratio disclosed in the Chang patents.

C. Objective Indicia of Obviousness

Because Sun has failed to make out a prima facie case of obviousness, the Court need not address Galderma's evidence of secondary considerations of non-obviousness. *See Alza Corp. v. Mylan Labs., Inc.*, 391 F.3d 1365, 1373 n.9 (Fed. Cir. 2004).

CONCLUSION

Galderma has proven by a preponderance of the evidence that Sun's NDA Product will infringe the asserted claims of the Chang patents, both literally and under the doctrine of equivalents. Sun has not proven by clear and convincing evidence that the asserted claims of the Chang patents are invalid due to obviousness. 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. SUN PHARMACEUTICAL INDUSTRIES LIMITED and SUN PHARMACEUTICAL INDUSTRIES, INC., Defendants.	C.A. No. 16-1003-LPS

ORDER

At Wilmington this **30th** day of **September, 2019**:

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

IT IS HEREBY ORDERED that:

1. Plaintiffs have proven that Sun's NDA 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. Defendants have not proven that claim 1 of the Chang '740 patent, claims 1 or 3 of the Chang '405 patent, or claims 1 or 2 of the Chang '364 patent are invalid for obviousness.

3. The parties shall meet and confer and submit, no later than **October 7, 2019**, a proposed order consistent with the Opinion, to enter final judgment **FOR** Plaintiff and **AGAINST** Defendants with respect to the asserted claims of the Chang '740, '405, and '364 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.

4. Because today's opinion was issued under seal, the parties shall meet and confer and, no later than **October 3**, submit a proposed redacted version of it, as well as argument supporting why (if at all) any portion of the Court's Opinion meets the applicable standard for redaction. Thereafter, the Court will issue a public version of its Opinion.

HONORABLE LEONARD P. STARK
UNITED STATES DISTRICT JUDGE