IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVEN PHARMACEUTICALS, INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	C.A. No. 18-699-LPS
	:	**REDACTED PUBLIC**
AMNEAL PHARMACEUTICALS LLC,	:	**VERSION**
	:	
Defendant.	:	

John G. Day and Andrew C. Mayo, ASHBY & GEDDES, Wilmington, DE

Liane M. Peterson, FOLEY & LARDNER, LLP, Washington, D.C.

R. Jan Pirozzolo-Mellowes, FOLEY & LARDNER, LLP, Milwaukee, WI

Ryan A. Schmid, FOLEY & LARDNER, LLP, Miami, FL

Attorneys for Plaintiff/Counterclaim Defendant Noven Pharmaceuticals, Inc.

Anne Shea Gaza and Samantha G. Wilson, YOUNG CONAWAY STARGATT & TAYLOR, LLP, Wilmington, DE

Steven Maddox, Jeremy Edwards, Anthony Son, Matthew Ruedy, Kaveh Saba, MADDOX EDWARDS, PLLC, Washington, D.C.

Attorneys for Defendant/Counterclaim Plaintiff Amneal Pharmaceuticals LLC

OPINION

September 2, 2020
Wilmington, Delaware

STARK, U.S District Judge:

On May 8, 2018, Plaintiff Noven Pharmaceuticals, Inc. ("Noven" or "Plaintiff") sued Defendant Amneal Pharmaceuticals LLC ("Amneal" or "Defendant") for infringement of U.S. Patent Nos. 9,833,419 ("the '419 patent"); 9,730,900 ("the '900 patent"); and 9,724,310 ("the '310 patent") (collectively, "the Patents-in-Suit" or the "Asserted Patents"). (*See* D.I. 1; *see also* D.I. 182 (Joint Statement of Uncontested Facts) ("UF")) Amneal seeks to market a new drug bioequivalent to Noven's Minivelle® product. (UF ¶ 8) Amneal contends that its drug product does not infringe the claims of the asserted patents and, further, that those claims are invalid.[1] (D.I. 7)

In November 2019 and January 2020, the Court held a six-day bench trial on the parties' claims and defenses. (*See* D.I. 200-06) ("Tr.") The parties submitted post-trial briefing (D.I. 191, 192, 195, 197, 207, 208, 215, 216) and proposed findings of fact (D.I. 193, 194, 196, 198).

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) Amneal's product literally infringes the '419 patent; (2) Amneal's product does not infringe the '900 patent under the doctrine of equivalents ("DOE"); (3) Amneal's product does not infringe the '310 patent under the DOE; (4) the asserted patents are invalid for lack of enablement and written

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[1] On June 1, 2018, Amneal filed a third-party complaint against Hisamitsu Pharmaceutical Co, Inc., seeking a declaratory judgment of non-infringement of United States Patent No. 6,841,716. (D.I. 11) On July 9, 2018, the Court resolved the third-party complaint by entering a Consent Decree and Final Judgment Pursuant to Fed. R. Civ. P. 54(b). (D.I. 28)

Amneal's Answer and Counterclaims originally contained a counterclaim for a declaratory judgment of non-infringement of U.S. Patent No. U.S. 8,231,906 ("the '906 patent"). (D.I. 7 at 32) The '906 patent has been the subject of prior litigation in this Court. *See Noven Pharmaceuticals, Inc. v. Actavis Laboratories UT, Inc.*, C.A. No. 15-249-LPS ("the '906 Litigation"). Noven and Amneal have stipulated to an order dismissing Amneal's counterclaim based on the '906 patent, which the Court so ordered on January 28, 2019. (D.I. 97)

description under 35 U.S.C. § 112; and (5) the asserted patents are not invalid due to the on-sale bar of 35 U.S.C. § 102(b).

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

FINDINGS OF FACT

This section contains the Court's findings of fact ("FF") on disputes raised by the parties during trial, as well as the facts stipulated to by the parties. Additional findings of fact are also provided in connection with the Court's legal discussion later in this Opinion.

I. Introduction

1. This patent infringement action arises out of Amneal's submission of Abbreviated New Drug Application ("ANDA") No. 211396 to the U.S. Food and Drug Administration ("FDA") pursuant to 21 U.S.C. § 355(j), seeking FDA approval of generic versions of Noven's Minivelle® product in 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day dosage strengths ("Amneal's ANDA Product" or "ANDA Product") before the expiration of the Patents-in-Suit. (UF ¶ 8)

2. Noven asserts that Amneal's ANDA Product infringes claims 1-9, 11, and 15 of the '419 patent; claims 1-11, 15-16, and 18-19 of the '900 patent; and claims 1-11 and 15 of the '310 patent (the "Asserted Claims").

3. Pursuant to Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(b)(1), and corresponding FDA regulations, Noven has listed the '419, '900, and '310 patents in the FDA's "Orange Book" as covering the Minivelle® system and methods for using it. The Patents-in-Suit

are directed to transdermal drug delivery systems ("TDDSs") for estradiol and methods of manufacturing and using them. (UF ¶¶ 3-6; JTX-1; JTX-2; JTX-3; Guy Tr. 18-22[2])

4. Minivelle® is an FDA-approved transdermal product for delivery of the hormone estradiol, indicated for the treatment of moderate to severe vasomotor symptoms due to menopause. (UF ¶ 4) The active ingredient in Minivelle® is estradiol. (*Id.* ¶ 6)

II. Noven's Vivelle®, Vivelle-Dot®, and Minivelle®

5. Before the inventions of the Patents-in-Suit, Noven's Vivelle® and Vivelle-Dot® "patch"-type products were among the transdermal dosage forms of estradiol that were already approved for sale in the United States and elsewhere. (Guy Tr. 53-56; PTX-11; PTX-69)

6. Vivelle® is an estradiol patch that delivers 0.1 mg/day estradiol from a 29 cm^2 patch. (Guy Tr. 54)

7. Noven sought to improve upon Vivelle® and proceeded to develop Vivelle-Dot®, which is an estradiol patch that delivers 0.1 mg/day estradiol from a 10 cm^2 patch – that is, a patch that is only about one-third the size of the corresponding Vivelle® patch. (Guy Tr. 54-55; PTX-11)

8. After the development of Vivelle-Dot®, Noven developed Minivelle®, an even smaller estradiol patch, which delivers 0.1 mg/day estradiol from a 6.6 cm^2 patch. (Guy Tr. 55-56; PTX-65.6; PTX-82.18)

9. The weight per unit area of the adhesive polymer matrix is referred to as the "coat weight." (Guy Tr. 53-54; PTX-73; DTX-157 at 12105) Noven discovered that, unexpectedly, increasing the coat weight of the adhesive polymer matrix layer (which includes the estradiol)

[2] References to the trial transcript are in the form: "([Witness last name] Tr. [transcript page number(s)])."

increased the estradiol flux (delivery rate) and allowed a smaller TDDS to deliver the same daily dose of estradiol. (Dash Tr. 40; Guy Tr. 55-56; PTX-69; JTX-1 at 3:58-4:2; JTX-4.121-126; JTX-5.341-347)

III. Patents-In-Suit

10. The '419, '900, and '310 patents all claim a priority date of July 10, 2008 – a priority claim that Amneal does not contest for purposes of this litigation. (UF ¶ 14) Noven is the legal owner of all right, title, and interest in the asserted patents. (UF ¶ 15)

11. The claims of the Patents-in-Suit are generally directed to TDDSs or "patches" for the delivery of estradiol, including methods of administering estradiol to a patient using the claimed TDDSs, and methods for making them. (Guy Tr. 18-22; JTX-1; JTX-2; JTX-3)

12. All of the Asserted Patents arise from the same original patent application or continuations thereof and, thus, share a common specification. They share a title as well, "Transdermal Estrogen Device and Delivery," and all list Juan Mantelle as the sole inventor. (UF ¶¶ 18, 22, 25)

A. U.S. Patent No. 9,833,419

13. The '419 patent issued on December 5, 2017, from U.S. Application No. 14/870,574, which was filed on September 30, 2015, as a continuation of U.S. Application No. 14/738,255. (UF ¶ 24) The '574 application was a continuation of the '985 application, which issued as the '310 patent. (*Id.*)

14. The '419 patent has 15 claims, including independent claim 1. (UF ¶ 26)

B. U.S. Patent No. 9,730,900

15. The '900 patent issued on August 15, 2017 from U.S. Application No. 13/553,972 (the "'972 application"), which was filed on July 20, 2012 as a continuation of U.S. Application No. 12/216,811, which issued as the '906 patent. (UF ¶¶ 16-17)

16. The '900 patent has 23 claims, including independent claims 1 and 16. (UF ¶ 19)

C. U.S. Patent No. 9,724,310

17. The '310 patent issued on August 8, 2017 from U.S. Application No. 14/024,985, (the "'985 application"), which was filed on September 12, 2013, as a continuation of the '972 application, which issued as the '900 patent. (UF ¶¶ 20-21)

18. The '310 patent has 15 claims, including independent claim 1. (UF ¶ 23)

IV. Amneal's ANDA Product

19. Amneal submitted its ANDA in order to seek approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of generic versions of Minivelle® in 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day dosage strengths before the expiration of the Patents-in-Suit. (UF ¶ 8)

20. Amneal's ANDA Product received tentative FDA approval on February 8, 2019. (Gupta deposition transcript April 25, 2019 ("Gupta") at 21-22;[3] PTX-68)

21. On April 26, 2019, Amneal submitted an unsolicited amendment of its ANDA to the FDA, proposing to lower the upper limits of its in-process manufacturing guidelines for the coat weight of the adhesive polymer matrix of its ANDA Product. (Dash Tr. 48-49, 61; Dr. Jay Audett May 31, 2019 deposition transcript ("Audett II") at 16-31; DTX-85.2; DTX-159) The FDA has not acted on the unsolicited amendment. (Audett II 19; PTX-85)

V. Witnesses

A. Noven's Expert Witnesses

22. Noven's expert witnesses testified live at trial.

[3] Certain fact witnesses testified by deposition. That is, the parties and Court agreed to admit portions of their deposition testimony, which became part of the trial record. (*See, e.g.*, Trial Tr. 530-31; D.I. 174)

23. Dr. Richard Guy has over 30 years of experience in drug delivery research, focusing on topical and transdermal drug delivery across the skin and other membranes. (D.I. 169 Ex. 6 at 3) Dr. Guy has published more than 350 peer-reviewed papers, written a number of book chapters, has many patents relating to drug delivery, and has been elected a fellow by a number of professional organizations, including the Controlled Release Society – which recognized him as its first recipient of an award for work in the area of transdermal drug delivery. (Guy Tr. 13-18; PTX-1; D.I. 169 Ex. 6 at 3)

24. Dr. Daniel F. Heitjan is a professor and Chair of Statistical Science at Southern Methodist University. (Heitjan Tr. 475-79) Dr. Heitjan teaches, directs graduate student research, and serves as a collaborating biostatistician on medical research projects. (*Id.*) He has published over 200 peer-reviewed articles, including around 80 in statistical journals. (*Id.*) Dr. Heitjan is an elected Fellow of the American Statistical Association (1997), the Institute of Mathematical Statistics (2012), and the Society for Clinical Trials (2017). (*Id.*) Dr. Heitjan has served in numerous appointed and elected offices in professional associations, including as President of the Eastern North American Region of the International Biometric Society (2013) and Chair of the Biometrics Section of the American Statistical Association (2009). (*Id.*)

B. Amneal's Expert Witnesses

25. Amneal's expert witnesses testified live at trial.

26. Dr. Kenneth Walters is the Director of Research and Development at An-eX Analytical Services, Ltd., a contract research lab that researches *in vitro* skin permeation, mucosal permeation, skin permeation, and formulation development for both transdermal and transmucosal systems. (Walters Tr. 313-19) Dr. Walters has over 50 years of experience in the pharmaceutical drug industry, including involvement with the development of transdermal and transmucosal drug delivery systems. (Walters Tr. 315; D.I. 169 Ex. 7.1) Dr. Walters has

authored numerous publications, including more than 40 book chapters, nine books, and 40-plus research publications in the field of skin transport, including transdermal drug delivery. (Walters Tr. 318)

27. Dr. Rogerio Lobo is a professor and former Chairman of the Department of Obstetrics and Gynecology at Columbia University. (Lobo Tr. 170-74; D.I. 169 Ex. 7.1) Dr. Lobo is a trained physician in obstetrics and gynecology and teaches medical students, residents, and fellows. (Lobo Tr. 171) He also carries out medical research and clinical trials, many of which involve transmucosal estradiol products. (Lobo Tr. at 173) Dr. Lobo has over 500 peer-reviewed publications in the field of obstetrics and gynecology. (Lobo Tr. 172)

28. Dr. M. Laurentius Marais is a consultant, with areas of expertise in mathematical and statistical techniques, including the techniques of biostatistics and epidemiology. (Marais Tr. 247-48) Dr. Marais earned a Ph.D. from Stanford University, concentrating in mathematical and statistical analysis. (*Id.*) He is a member of multiple professional organizations, including the American Statistical Association and the Royal Statistical Society. (*Id.*) Dr. Marais has performed statistical analyses as part of numerous projects over the course of 30 years and has testified in more than 50 cases. (*Id.*)

29. Dr. Alekha Dash is the Associate Dean for Research at the School of Pharmacy and Health Professions at Creighton University. (Dash Tr. 28-30; D.I. 169 Ex. 7.4) Dr. Dash is the Gilbert F. Taffe Endowed Chair for the School of Pharmacy, an award given for outstanding contribution in research. (Dash Tr. 28-30) Dr. Dash has over 30 years of experience in teaching about dosage forms and drug delivery systems. (*Id.*) Dr. Dash has more than 60 peer-reviewed publications, many of which are related to transdermal or topical drug delivery systems. (*Id.*)

C. Fact Witnesses

30. Dr. Jay Audett is Amneal's Executive Director of Product Development Commercialization. (D.I. 169 Ex. 6 at 8) Dr. Audett testified by deposition. (Audett April 10, 2019 deposition transcript ("Audett"); Audett II)

31. Mr. Juan Mantelle is a former employee of Noven. He held the position of Chief Scientific Officer from 2001 until he left Noven in 2009. (D.I. 169 Ex. 6 at 8) Mr. Mantelle testified by deposition. (Mantelle July 18, 2018 deposition transcript ("Mantelle"); Mantelle March 27, 2019 deposition transcript ("Mantelle II"))

32. Mr. Viet Nguyen is Noven's Principal Engineer, Research and Development. (Nguyen Tr. 542-43)

33. Mr. Kapil Gupta is an employee of Amneal Pharmaceuticals LLC and holds the position of Director of Portfolio Manager. Mr. Gupta testified by deposition. (Gupta)

VI. Person Of Ordinary Skill In The Art

34. A person of ordinary skill in the art ("POSA") in regard to the Asserted Patents would have a scientific degree (e.g., Ph.D., M.D., M.S., or B.S.) in a field related to drug delivery (such as pharmacy, organic chemistry, medicinal chemistry, transdermal drug delivery, biology, biochemistry, pharmacology, medicine, or chemical engineering), and at least two to three years of experience researching, developing, or working with transdermal formulations and transdermal drug delivery. This person may also work in collaboration with other scientists and/or clinicians who have complementary experience in making, developing, or working with transdermal systems. For example, a pharmaceutical formulator may work with a clinician, medical doctor, or other person having complementary skill. (UF ¶ 27; Guy Tr. 25-26)

VII. Claim Construction

35. The asserted claims of the '419 patent all require "a coat weight greater than 10 mg/cm^2," for which the Court determined no construction is required. (DTX-113 at 3; JTX-3 at 15:49-50) The parties' experts agreed that this term should be given its plain and ordinary meaning to a POSA. (Dash Tr. 37-38; Guy Tr. 63)

36. To a POSA, a "coat weight of greater than 10 mg/cm^2" simply means a coat weight value of more than 10 mg/cm^2, such as 10.01, 10.02, etc. (UF ¶ 27; Guy Tr. 64-66; Marais Tr. 293; Walters Tr. 464; PTX-1)

37. The asserted claims of the '900 and '310 patents recite "a coat weight of greater than about 10 mg/cm^2," which the Court construed as "having a coat which weighs more than 110% of 10 mg/cm^2." (UF ¶ 28) In other words, the Court's construction requires a coat weight of greater than 11 mg/cm^2.

38. By agreement of the parties, the Court adopted the definition of "flux" recited in the specification: "the absorption of a drug through skin or mucosal tissue." (JTX-1 at 5:24-26; D.I. 113 at 2)

VIII. Amneal's ANDA Product And In-Process Coat Weight Measurements

39. Amneal's ANDA describes Amneal's ANDA Product as "comprised of three layers:" (1) a backing layer, (2) "an adhesive formulation containing estradiol, USP, acrylic adhesive, silicone adhesive, oleyl alcohol, NF, povidone, USP and dipropylene glycol," and (3) "a polyester release liner which is attached to the adhesive surface and must be removed before the system can be used." (Guy Tr. 53-54; PTX-77.14-15; PTX-79.5; PTX-80.3)

40. "Coat weight" refers to the weight per unit area of the adhesive polymer matrix layer of a TDDS, which contains the active ingredient. (UF ¶ 28; Guy Tr. 54; PTX-73; PTX-

84.6; PTX-87.40-44, 61-85; PTX-88.41-45, 63-90; PTX-89.40-44, 57-70; PTX-90.35-38, 49-61; DTX-157 at 12105)

41. Amneal uses the following process steps to manufacture the Amneal ANDA Product: (1) dispensing, (2) mixing, (3) coating, (4) drying, and (5) laminating. (Guy Tr. 44-45, 57; PTX-84.6-12, 23; DTX-158 at 13378-79)

42. The adhesive polymer matrix layer containing estradiol is created by pumping an adhesive mix onto the release liner and then drying and evaporating excess solvent. (Guy Tr. 53-54, 58-59; Audett II 139-40, 150-51; PTX-65.6; PTX-77.15; PTX-79.5; PTX-80.18; PTX-80.3; PTX-82; PTX-84.6; PTX-87)

43. The adhesive material is deposited onto the release liner in two discrete lanes, the "Operator" side and the "Machine" side. (Guy Tr. 58-59; PTX-84.6)

44. During the manufacturing process, Amneal conducts in-process tests to control the production of its ANDA Product and keep the product within certain guidelines. (Dash Tr. 45-47; Guy Tr. 57-58; Audett 77-79; PTX-83.8; PTX-84.23; DTX-157 at 12105, 12181; DTX-158 at 13482) One such in-process test evaluates and measures coat weight of the coated laminate. (Dash Tr. 45-47; Guy Tr. 57-58; Audett 77-79, 136-37; PTX-83.8; PTX-84.23)

45. The procedures Amneal uses to measure the coat weight of the adhesive polymer matrix used to make its ANDA Product are described in the batch records. (Guy Tr. 58-59; Audett 139-40, 142-51, 160-62; PTX-81; PTX-87.40-44; PTX-88.41-45; PTX-89.40-44; PTX-90.35-38; DTX-157 at 12104-05; DTX-158 at 13482)

46. Amneal laminates a 2-mil protective film ("slip sheet") to the adhesive polymer matrix layer formed on the release liner, uses a die to cut 7.55 cm^2 "coupons" from the protected laminate, removes the laminate coupons from the release liner, weighs the coupons, and records

individual and average weights of the laminate coupons (adhesive polymer matrix layer + 2-mil film). (Guy Tr. 58-59; PTX-87.40-44, 61-85; PTX-88.41-45, 63-90; PTX-89.40-44, 57-70; PTX-90.35-38, 49-61; DTX-158 at 13482)

47. Ten 7.55 cm^2 coupons are cut out from the "machine side" and the "operator side." The backing film and adhesive, which is laminated to it, are stripped away from the release liner and weighed. The individual weights of the ten "machine side" coupons and ten "operator side" coupons are recorded and the "machine" and "operator" side averages are calculated. (Guy Tr. 58-59, 65-66; PTX-87.40-44, 61-85; PTX-88.41-45, 63-90; PTX-89.40-44, 57-70; PTX-90.35-38, 49-61; DTX-158 at 13482)

48. The average "machine side" coat weight is calculated by subtracting the average "machine side" backing film from the average "machine side" coupon weight. The average coat weight for the "operator side" is similarly calculated. The individual highs and lows are similarly calculated. (Guy Tr. 58-59, 65-66; Audett 150-51, 160-62; PTX-87.40-44, 61-85; PTX-88.41-45, 63-90; PTX-89.40-44, 57-70; PTX-90.35-38, 49-61; DTX-158 at 13482)

49. Separately, Amneal determines an average weight of 7.55 cm^2 coupons of the 2-mil film (only). (Guy Tr. 58-59, 65-66; *see also* Audett 150-51, 160-62; PTX-87.40-44, 61-85; PTX-88.41-45, 63-90; PTX-89.40-44, 57-70; PTX-90.35-38, 49-61; DTX-158 at 13482)

50. Finally, Amneal calculates average and individual coat weights for the adhesive polymer matrix layer of the laminate coupons by subtracting the average weight of the 2-mil film (only) coupons from the average and individual weights of the laminate coupons. (Guy Tr. 58-59, 65-66; Audett 150-51, 160-62; PTX-87.40-44, 61-85; PTX-88.41-45, 63-90; PTX-89.40-44, 57-70; PTX-90.35-38, 49-61; DTX-158 at 13482)

51. While Amneal measures coat weight in-process by the above procedures, it does not measure the coat weight of its finished product. (Guy Tr. 62; Audett 79, 180-83, 193; Audett II 59-60, 63; PTX-87 to PTX-90; PTX-93 to PTX-97; PTX-570; DTX-158 at 13482)

IX. Vivelle-Dot® Manufacturing Processes

52. A POSA would not have known (from the Patents-in-Suit or any publicly-available information) the Vivelle-Dot® coat weight guidelines or in-process coat weight measurements, or the manufacturing guidelines and ranges, all which were (and still are) confidential. (Dash Tr. 39-40; Guy Tr. 73; Dash Tr. 137-40, 147-48, 243-45; DTX-172; DTX-173)

53. A POSA would not compare the Amneal ANDA Product final coat weights to the Vivelle-Dot® in-process coat weight guidelines to determine whether the Amneal ANDA Product has a coat weight greater than 10 mg/cm^2. (Guy Tr. 73-74) A POSA would, instead, compare the in-process Amneal coat weights with the coat weights of the limitations of the Patents-in-Suit in order to determine whether Amneal's ANDA Product infringes. (Guy Tr. 63-65)

54. Dr. Walters testified that the in-process sampled coat weight will not change from the time that it is sampled to the time that it is packaged because the residual solvents have been driven off; the estradiol content is also stable during this period. (Walters Tr. 387)

X. Facts Relating To Infringement Of The '419 Patent

55. Amneal's coat weight guidelines identify a target coat weight of 10 mg/cm^2 (stated as 75.50 mg/7.55 cm^2) with a permitted range around that target. (Dash Tr. 46-47; Guy Tr. 60; PTX-65.20; PTX-67.9-10; PTX-82.97; PTX-83.8; PTX-85.2; DTX-158 at 13482)

56. Amneal has received tentative approval to make the Amneal ANDA Product with in-process controls that permit a coat weight in the range of 69.84 to 81.16 mg/7.55 cm^2 (or 9.25 to 10.75 mg/cm^2) for individual coat weights, and 71.73 to 79.28 mg/7.55 cm^2 (or 9.50 to 10.50 mg/cm^2) for average coat weights. (Dash Tr. 48-49; Guy Tr. 60-61; Gupta 21-22; PTX-68; PTX-82.97, PTX-83.8; PTX-85.2; DTX-157 at 12105; DTX-159)

57. Amneal submitted an unsolicited amendment on April 26, 2019 proposing to change the individual and average upper limits of the in-process coat weight guidelines. (Dash Tr. 48-49; Guy Tr. 61; Audett II at 16-31; PTX-85.2; DTX-159) Specifically, Amneal's proposed amendment seeks an upper limit for individual coat weight of 78.90 mg/7.55 cm^2 (or 10.45 mg/cm^2) and an upper limit for average coat weight of 78.52 mg/7.55 cm^2 (or 10.40 mg/cm^2). (Dash Tr. 48-49; Guy Tr. 61; Audett II 16, 26-27, 31; PTX-85.2; DTX-159)

58. Amneal's ANDA provides a range of coat weight values because it is impossible to consistently produce patches that have exactly the same coat weight. (Dash Tr. 47, 126; Guy Tr. 61-63)

59. Amneal's manufacturing process for the tentatively-approved and proposed-amended ANDA Product permits coat weights greater than 10 mg/cm^2, including coat weights between 10 and 10.75 mg/cm^2. (Dash Tr. 48-49; Guy Tr. 60-61, 64; PTX-82.97; PTX-83.8; PTX-85; DTX-157 at 12105; DTX-159)

60. Amneal made four exhibit batches of intermediate laminate during production of its ANDA Product: PW-ST-15032, PW-ST-15033, PW-ST-15034 and PW-ST-17031. (Guy Tr. 65-68; Audett 139-40, 142-43; PTX-81; PTX-82.35; PTX-87; PTX-88; PTX-89; PTX-90)

61. The batch records for each of the four exhibit batches of intermediate laminates report multiple instances in which individual and average polymer matrix adhesive coat weight

measurements were greater than 10 mg/cm^2. (Guy Tr. 65-68; PTX-87.61-82; PTX-88.63-88; PTX-89.57-68; PTX-90.49-59)

62. Batch PW-ST-15032 reported the highest actual individual coat weight measurement documented in Amneal's exhibit batches, which was taken on the operator side of Roll #4: 78.33 mg on a 7.55 cm^2 sample, which is equal to 10.37 mg/cm^2. Operator side Roll #4 also reported the highest average coat weight measurement: 77.62 mg on a 7.55 cm^2 sample, which is equal to 10.28 mg/cm^2. (Guy Tr. 68-69; Dash Tr. 136; PTX-67.9; PTX-87.67-68)

63. The average coat weight measurements in two of Amneal's exhibit batches, PW-ST-15032 and PW-ST-17031, are 75.63 mg/7.55 cm^2 (10.02 mg/cm^2) and 75.72 mg/7.55 cm^2 (10.03 mg/cm^2), respectively, which are both greater than 10 mg/cm^2. (Guy Tr. 70-73; PTX-85.7, 10; PTX-87; PTX-90)

64. A POSA would look at the ranges in the Amneal in-process coat weight guidelines as demonstrating the coat weight of the ANDA Product that Amneal will be permitted to sell upon final approval of its ANDA. (Guy Tr. 64-65)

65. In assessing whether the Amneal ANDA Product has a coat weight of greater than 10 mg/cm^2, as required to practice the Asserted Claims of the '419 patent, a POSA would consider actual coat weight measurements of the Amneal ANDA Product and not the target coat weight guidelines, and also not the average coat weight across all batches. (Guy Tr. 62, 69-74)

66. A target coat weight is a theoretical value, as it is impossible to consistently produce patches that have an exact coat weight, such as 10 mg/cm^2. (Dash Tr. 47-48, 126; Guy Tr. 62)

67. Neither the target coat weight, nor the average coat weight, necessarily represents the actual coat weight of any particular ANDA Product that will be sold. (Guy Tr. 62, 66-70;

Dash Tr. 47, 135, 148-51; PTX-85; PTX-87.61-82; PTX-88.63-88; PTX-89.57-68; PTX-90.49-59)

68. Amneal uses its in-process coat weight guidelines to identify and discard laminate that falls outside the coat weight guidelines. Amneal does not discard laminate having a coat weight that falls within its coat weight guidelines; instead, such laminate is used to make the Amneal ANDA Product. (Dash Tr. 126, 133-34, 154-57; *see also* Audett 160-62; Audett II 10-11, 63-64, 67-68)

69. The Amneal ANDA Product literally infringes the asserted claims of the '419 patent because it has actual measurements and permitted coat weight ranges that are greater than 10 mg/cm^2, as required by the '419 patent. (UF ¶ 32; Guy Tr. 63-64, 74; JTX-3)

XI. Facts Relating To Infringement Of The '900 And '310 Patents

A. Prosecution History

70. All asserted claims of the '900 and '310 patents require a coat weight of greater than about 10 mg/cm^2 – that is, as construed by the Court, greater than 11 mg/cm^2. (D.I. 112 at 4-7) Noven alleges that Amneal's ANDA Product infringes these claims under the doctrine of equivalents.

71. The prosecution histories of the '900 and '310 patents parallel one another and are materially the same for purposes of prosecution history estoppel.[4]

72. In response to an April 12, 2013 restriction requirement in connection with the '972 application (which became the '900 patent), the patent applicant filed a preliminary

[4] For simplicity, the recitation of the prosecution history in this Opinion cites to the '900 patent, with parallel cites to the '310 file history. (*See* JTX-4) Other than the difference in application number, claim numbers, and dates, this recitation should be understood to apply to both patents.

amendment on May 9, 2013, which cancelled claims 1-13 and 16-20. Claims 14-15 remained and new claims 21-30 were added.[5] (JTX-4.50-55; JTX-5.118-121)

73. The sole independent claim at that point, claim 14 – which ultimately issued as claim 1 – did not contain a coat weight limitation and read as follows:

> A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system consisting of (i) a backing layer and (ii) a single polymer matrix layer defining an active surface area and comprising a polymer matrix comprising estradiol as the only drug, wherein the polymer matrix includes greater than 0.156 mg/cm² estradiol and achieves an estradiol flux that is greater than 0.0 1 mg/cm²/day, based on the active surface area.

(JTX-5.119; *see also* JTX-4.52)

74. On May 5, 2015, the United States Patent and Trademark Office ("PTO") issued an office action rejecting all pending claims (claims 14, 15, and 21-30 of the '972 application) under 35 U.S.C. § 103.[6] (JTX-4.95-103; JTX-5.319-329) Specifically, the PTO rejected claims 14, 15, 21-26, and 28-30 as being unpatentable over Kanios (U.S. Patent No. 6,638,528) in view of Nuwayser (U.S. Patent No. 4,624,665) (JTX-4.98; JTX-5.323); and claims 14, 15, and 21-30 as being unpatentable over Kanios and Nuwayser in further view of Miller (U.S. Published Patent App. No. 2009/0041831). (JTX-4.100; JTX-5.325)

75. In connection with this rejection, the Examiner stated that "Kanios and Nuwayser do not teach that the polymer matrix has a coat weight of greater than about 10 mg/cm²." (JTX-

[5] The applicant filed a preliminary amendment for the '985 application (which became the '310 patent) on April 7, 2014, which cancelled claims 10, 12, 14-20, and amended claims 1-9, 11, and 13. (JTX-4.54-55) Independent claim 1 of the '985 application did not recite a coat weight limitation. (JTX-4.52)

[6] On May 25, 2015, the Examiner rejected claims 1-9, 11, and 13 of the '985 application. (*See* JTX-4.95-104)

5.325; *see also* JTX-4.100) The Examiner, however, stated that "it would have been obvious to a person of ordinary skill in the art at the time that the invention was made to utilize a coat weight of 90-110 g/m^2 (9-11 mg/cm^2) as taught by Miller et al. in the patch of Kanios and Nuwayser." (JTX-4.101; *see also* JTX-5.326)

76. On June 10, 2015, in an interview, the Examiner discussed with the applicant "possible claim amendments such as an adhesive polymer matrix or the addition of a coat weight." (JTX-5.396; *see also* JTX-4.179)

77. On June 12, 2015, in response to the May 5, 2015 office action, the applicant canceled claim 27 and amended claim 14 of the '972 application, adding for the first time a coat weight limitation of "greater than about 10 mg/cm^2," as follows:

> A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system consisting of (i) a backing layer and (ii) a single **adhesive** polymer matrix layer defining an active surface area and comprising [[a]] **an adhesive** polymer matrix comprising estradiol as the only drug, wherein the polymer matrix **has a coat weight greater than about 10 mg/cm^2** and includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux that is greater than 0.01 mg/cm^2/day, based on the active surface area.

(JTX-5.337-339; *see also* JTX-4.118-119)

78. As a further part of its June 12, 2015 response, the applicant argued that the prior art did not disclose the claimed coat weight limitation, stating as follows:

> As discussed during the patent Office Interview, none of the cited references teach or suggest that the amount of drug per unit area of a monolithic polymer matrix-type transdermal drug delivery system as claimed is a result-effective variable for drug flux (e.g., drug delivery rate).

(JTX-5.341; *see also* JTX-4.121)

79. The applicant added in the response that, prior to the invention, increasing coat weight was thought to provide delivery over a longer period of time, but the discovery that increasing coat weight resulted in an increased flux was surprising and unexpected. (JTX-5.341-347; *see also* JTX-4.121-126)

80. On October 2, 2015, the PTO issued a Notice of Allowance and Allowability, for pending claims 14-17, 21-26, and 28-30 of the '972 application, and pending claims 1-9 and 13 of the '985 application. (JTX-5.398-405; JTX-4.181-187) In doing so, the Examiner expressly found that "Applicant's arguments of unexpected results based on the coat weight of the polymer to achieve the claimed flux of the drug delivery are persuasive." (JTX-5.404; *see also* JTX-4.186)

81. The "greater than about 10 mg/cm^2" coat weight limitation added during prosecution was a narrowing amendment, made for reasons related to patentability, and not tangential to the accused coat weight in Amneal's ANDA Product.

B. Facts Relating To Application Of Function, Way, Result Analysis To Amneal's Coat Weight

82. Noven argues that, applying the function, way, result analysis ("FWR"), Amneal's coat weight is equivalent to a coat weight of greater than 11 mg/cm^2. The evidence presented at trial demonstrated, instead, that the coat weight of Amneal's ANDA Product does not perform substantially the same function, way, and result as a coat weight of greater than 11. (Dash Tr. 128-33; DTX-158 at AMNMIN13372, -13377, -13382)

83. The "function" of the coat weight limitations of the asserted claims is to increase flux. (*See* JTX-1 at 3:58-60) (stating "increasing the coat weight . . . resulted in an increased flux") At trial, however, Noven argued that the difference in coat weight between the Amneal ANDA Product and the claimed coat weight of greater than 11 mg/cm^2 is insubstantial because

the driving force for flux is the concentration gradient of estradiol across the skin. (Guy Tr. 82-84; D.I. 192 at 19) According to Noven, Amneal's ANDA Product achieves the same function by providing the appropriate level of estradiol "flux." (Guy Tr. 83-84; Dash Tr. 127-29) Noven's doctrine of equivalents theory cannot be squared with the stated function of coat weight in the patents, which is the alleged discovery at the heart of the alleged invention: that "increasing the coat weight . . . resulted in an increased flux." (JTX-1 at 3:58-60)

84. Amneal used different formulation parameters, not coat weight, to modulate flux. (Dash Tr. 130; DTX-158 at AMNMIN13377) Amneal's product development report ("PDR"), which it submitted to the FDA, explicitly identified the formulation parameters used to modulate flux in Amneal's product, and those parameters do not include coat weight. The PDR stated: "[b]ased on initial development, the key attributes were found to be the choice of the acrylate and the silicone adhesives, their ratios, the levels of Povidone, dipropylene glycol and the levels of oleyl alcohol. These properties affected the flux of the API . . . ." (DTX-158 at AMNMIN13382) The PDR also noted that "[t]he ratio of the two adhesives would . . . influence the flux of the API through human skin," adding the "level of oleyl alcohol directly influences the flux of estradiol as it is a permeation enhancer in the system." (*Id.*) Further, "[t]he aim was also to optimize the levels of Oleyl alcohol to ensure equivalent clinical performance as that of the RLD [reference listed drug]." (*Id.*)

85. Amneal selected the coat weight of its ANDA Product not to achieve any given flux or delivery rate, but instead to reduce residual drug left over after use. (Dash Tr. 130-33; DTX-158 at AMNMIN13377 (PDR stating: "[a]nother aspect of the formulation development was to minimize the initial drug load in the patch by keeping the patch size as similar to the innovator as possible. This would help minimize the residual drug remaining in the patch after

its use. An effective way to accomplish that without affecting the patch's pharmacokinetic performance and safety aspect was to reduce the coat weight of the system."))

86. When Amneal's patch formulation failed to pass bioequivalence testing, Amneal increased the size of the patch, not its coat weight. (Dash Tr. 131-33; DTX-158 at AMNMIN13437-38) Specifically, Amneal's 6.6 cm^2 patch failed bioequivalence testing, and Amneal's response was to increase the size of its patch to 7.55 cm^2, without changing the coat weight. (Dash Tr. 131-32; DTX-158 at AMNMIN13437-38, 13439)

C. Facts Relating To Application Of Insubstantial Differences Analysis To Amneal's Coat Weight

87. Amneal allows for manufacturing tolerances based on the die used to make coupons for in-process coat weight measurements ("in-process coupons") and patches in connection with its ANDA Product. The 7.55 cm^2 die used for the in-process coupons and the 0.1 mg/day patch has a diameter of 1.221 inches with a tolerance of ± 0.005 inches. Thus, the in-process coupons cut with this die have a diameter that can range between 1.216 and 1.226 inches. (Guy Tr. 77-78; PTX-108 to PTX-112) This is equal to a diameter of 3.09 to 3.11 cm. (Guy Tr. 77-78; PTX-112)

88. Accounting for the tolerance of Amneal's 7.55 cm^2 die cut, the in-process coupons and the 0.1 mg/day patch have a permissible area of 7.49 to 7.62 cm^2. (Guy Tr. 77-78; PTX-112)

89. Dividing the upper limit of the tentatively-approved guidelines (81.16 mg) by the smallest possible surface area of the die (7.49 cm^2) leads to a maximum coat weight of 10.83 mg/cm^2. (Guy Tr. 78)

90. Applying the same calculation to Amneal's proposed amended guidelines, the individual upper limit (10.45 mg/cm^2) could be as high as 10.53 mg/cm^2. (*Id.*)

91. If any actual measurement of Amneal's ANDA Product exceeds the in-process coat weight limits – all of which are less than 11 – Amneal will discard the entire batch. (Dash Tr. 126, 133-34; Audett 161-63; Audett II 10-11, 63-64, 67-68; DTX-159 at AMNMIN143507-08)

92. The table below displays the differences between the upper limit coat weights of 10.75, 10.83, 10.45, and 10.53 mg/cm^2, on the one hand, and 11 mg/cm^2, on the other hand.

Coat Weight Measures for ANDA Product	Individual	Average	% Increase to 11 mg/cm^2
Highest Actual	10.37	10.28	6.1%
Upper Limit (Tentatively-Approved)	10.75	10.50	2.3%
Upper Limit (Tentatively-Approved) + Tolerance	10.83	–	1.6%
Upper Limit (Proposed)	10.45	10.40	5.3%
Upper Limit (Proposed) + Tolerance	10.53	–	4.5%

(Guy Tr. 78-79; PTX-83.8; PTX-85.3; PTX-87; PTX-112)

93. The differences between Amneal's coat weights and the claimed coat weight range of greater than 11 mg/cm^2 are substantial.

XII. Facts Relating To Invalidity

A. Facts Relating To Enablement And Written Description

1. Transmucosal Embodiments

94. All mucosa are lined by fluid or mucous, and in that respect (among others) are all different than skin. (Lobo Tr. 183)

95. As of the priority date of July 10, 2008, the specifications of the Patents-in-Suit would not have conveyed to a POSA that the inventor actually invented or possessed any oral, buccal, nasal, rectal, or vaginal mucosal patch system. (Lobo Tr. 205-06; Walters Tr. 333-38, 361)

96. The specification does not address transmucosal estradiol flux or even transmucosal flux in general. (Lobo Tr. 177, 179-80, 203, 205-06; Walters Tr. 333-38; Guy Tr. 627)

97. The specification does not describe or provide any example of a transmucosal estradiol system, or discuss mucoadhesion or coat weight, flux, or estradiol content of any transmucosal system. (Lobo Tr. 177, 179-80, 203, 205-06; Walters Tr. 333-38)

98. The specification does not identify any excipients as being useful for a transmucosal system. It does not identify which excipients in which combinations or in what amount would cause an estradiol patch having the claimed coat weight and estradiol content to achieve the claimed flux values. (Walters Tr. 335-38)

99. The specification does not disclose that the alleged surprising relationship between coat weight and transdermal flux holds true for transmucosal flux. (Walters Tr. 336-38)

100. The specification lists many "acrylic polymers," including "copolymers, terpolymers, and multipolymers," and "[c]ombinations of acrylic-based polymers based on their functional groups," with different amounts of each type of monomer, and identifies more than two dozen potential monomers and functional groups that might adorn the acrylic polymer. (JTX-1 at 7:28-29, 43-45, 49-50, 7:57-8:36) The listing of acrylic polymers in the specification would not convey to a POSA possession of the claimed transmucosal estradiol patch systems. (Walters Tr. 336, 354-56)

101. The Asserted Patents use the term "bioadhesive" in reference to application to the skin, not mucosa. (JTX-1 at 5:56-58) ("polymer matrix comprises a pressure-sensitive adhesive or bioadhesive, and is adopted for direct application to a user's (e.g. a subject's) skin") The use

of the term "bioadhesive" would not convey to a POSA possession of the claimed transmucosal estradiol patch systems. (Walters Tr. 336-37, 339-41)

102. Inventor Juan Mantelle never attempted to develop a transmucosal estradiol patch of any kind. (Mantelle 110-13; JTX-1 at 15:7–47 (Example 1)) He did not perform mucosal flux testing and did not intend (nor test) for application of his invention to oral, buccal, nasal, rectal, or vaginal mucosal tissue. (Mantelle 118-21) He did not regard the formulations of Example 1 in the specification to be formulations that could be applied to mucosa. (Mantelle II at 239) He was unaware of any way to predict or correlate transmucosal flux with transdermal flux, and further unaware of any standard way to measure transmucosal flux. (Mantelle II at 231-35)

103. All of Noven's development work was directed solely to making a transdermal patch system, not a transmucosal system. (Nguyen Tr. 548) All of Noven's flux studies were performed on skin. (*Id.* at 548-49) Noven is not aware of any way to use the results of such transdermal studies to predict transmucosal flux. (*Id.* at 549)

104. Although Dr. Guy opined that Mr. Mantelle "possessed" the claimed mucosal inventions, purportedly because he had "the tools required to make that happen," his opinion was not persuasive, for reasons including his failure to identify what "tools" he was referring to, and his failure to identify where the specification teaches the use of such tools to make the claimed transmucosal estradiol patch systems. (Guy Tr. 626-29)

2. Facts Relating To Enablement And Possession Of Transmucosal Patch Systems

105. The Asserted Claims are broad, covering not just patch systems for application to the skin, but also systems for application to any mucosal tissue, including oral, buccal, nasal, rectal, and vaginal mucosal tissue. (JTX-1 at 5:24-32, 37-43 (defining "transdermal" to refer to

"delivery, administration, or application of a drug by means of direct contact with skin or mucosa;" "dermal" as "includ[ing] skin and mucosa, which includes oral, buccal, nasal, rectal and vaginal mucosa;" and "transdermal drug delivery system" as a system that "releases estrogen upon application" to skin "or any other surface noted above," listing "oral, buccal, nasal, rectal and vaginal mucosa"); D.I. 113 at 2 (construing "flux" as "the absorption of drug through skin or mucosal tissue" and all numerical flux limitations in Asserted Claims as referring to absorption of estradiol "through skin or mucosal tissue"))

106. Other than the definitional language, the only references to "mucosa" in the specification are the following:

> In accordance with some embodiments, there is provided a method for administering estradiol, comprising ***applying to the skin or mucosa*** of a subject in need thereof a transdermal drug delivery system comprising a drug-containing layer defining an active surface area and comprising a polymer matrix comprising estradiol, wherein the system includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux that is greater than 0.01 $mg/cm^2/day$, based on the active surface area.

(JTX-1 at 2:57-65) (emphasis added)

> In some embodiments, there is provided a method of effecting transdermal drug delivery of estrogen, such as estradiol, ***by applying a system as described herein to the skin or mucosa of a subject in need thereof.***

(JTX-1 at 14:50-58) (emphasis added)

107. Drs. Lobo and Walters explained persuasively that neither of the specification's two references to transmucosal systems provides any guidance on how to make or use any of the various claimed transmucosal systems. (Lobo Tr. 179-80, 205-06; Walters Tr. 333-34) Dr. Guy provided no persuasive opinion – or even any opinion – to the contrary. (Guy Tr. 590, 595-96, 607-10, 626-27)

108. The specification indicates that the inventor surprisingly discovered that increasing coat weight increases estradiol flux. (JTX-1 at 3:58-4:2)

109. The specification notes that flux is also impacted by concentration of drug in the polymer matrix. (JTX-1 at 5:13-32)

110. The specification does not contain any working examples of a transmucosal patch system. (Lobo Tr. 179; Walters Tr. 335; Guy Tr. 590, 627)

111. The specification does not contain any discussion of transmucosal flux, or how to achieve the claimed estradiol flux values across any mucosal tissue. (Lobo Tr. 205-06; Walters Tr. 333-34)

112. The specification contains a long list of potential excipients and potential adhesives, but does not identify which ingredients, combinations of ingredients, or amounts of ingredients would be useful for making any of the claimed transmucosal systems, and does not indicate how those substances might interact with mucosal tissues. (Walters Tr. 335-36)

113. The specification does not teach what concentration of estradiol or what coat weights should be used in any of the transmucosal systems to obtain the claimed flux across mucosal tissue. (Walters Tr. 337)

114. The specification does not teach how to make or use any system that will achieve the claimed flux values across oral, buccal, nasal, rectal, or vaginal mucosa. (Walters Tr. 336-37)

115. There was no known correlation between flux across the skin and flux across any of the various claimed mucosal tissues. (Mantelle 231-33, 239; Nguyen Tr. 549; Walters Tr. 585, 624)

116. The specification explains that passage of estradiol through skin was the rate-limiting step in estradiol drug delivery through skin (JTX-1 at 11:52-53) – but there is no similar explanation in the specification (nor was such knowledge possessed by a POSA) with respect to passage through mucosal tissues (Walters Tr. 337-38; Guy Tr. 584-85, 611, 624).

117. The specification's disclosures about formulation of a skin patch did not provide useful guidance to a POSA about how to make or use the claimed transmucosal patch systems. (Lobo Tr. 179, 182, 205-06; Walters Tr. 338)

118. Under the agreed-upon definition of a POSA, which the Court adopts, a POSA had training and experience in transdermal delivery but did not necessarily have any education, training, or experience in the design and development of transmucosal drug delivery systems. (UF ¶ 27)

119. Mucosal drug delivery is its own separate field of delivery, having its own thought leaders and treatises, distinct from transdermal delivery. (Guy Tr. 632, 634-35; DTX-3567; DTX-3570; DTX-3600 at xi-xii; DTX-5046 at ix-xi; DTX-5047; DTX-5048; DTX-5049 at v-xii; DTX-5050 at ix-x; DTX-5051)

120. As of 2008, no one had developed an adhesive patch for application to vaginal, rectal, or nasal mucosal tissue for delivery of any drug. (Guy Tr. 340)

121. Although several transmucosal estradiol products were described in prior art literature, those products did not provide meaningful guidance on how to make and use transmucosal estradiol patch systems with the claimed features. These products were not patch systems, but rather an immediate release nasal spray, a buccal film, an oral tablet, and a vaginal cream; accordingly, none of these were adhesive, had backing layers or coat weights, or were regarded as having a measurable flux. (Walters Tr. 340-42) Dr. Guy did not address these

differences from the claimed transmucosal adhesive patch systems nor explain how these other products would have guided development of the claimed systems. (Guy Tr. 571)

122. Although Dr. Guy testified that prior art U.S. Patent No. 5,047,244 (the "'244 patent") discloses a working example of a transmucosal estradiol formulation shown to exhibit sustained release (Guy Tr. 581-83, 610; DTX-1089), the Court was persuaded by Dr. Walters' opinion that the '244 patent would not have provided meaningful guidance to a POSA on how to make a transmucosal patch system with the claimed coat weight, estradiol content, and flux (Walters Tr. 345-46). Dr. Guy points to a bilaminate tablet, not a monolithic patch. (Walters Tr. 433-34; DTX-1089) Even for this tablet, the '244 patent does not report any coat weight, mucoadhesive properties, or flux testing. (DTX-1089 at 14:26-15:5 (Example 7), 17:30-18:2 (Example 10))

123. Noven also asserts that van der Bijl (1998) "reflects a POSA's understanding" that the same formulation can be used on the different mucosal surfaces, despite the physiological differences among the various mucosae, and further describes the flux of a transmucosal estradiol formulation. (Guy Tr. 585-86; PTX-521) van der Bijl described an *in vitro* flux study of estradiol used through human vaginal and buccal mucosal tissue. (Guy Tr. 585-86) Dr. Walters testified that van der Bijl was "certainly not a formulation paper" and did not describe a patch system, let alone a mucoadhesive patch system; nor did it report flux data in terms of weight. (Walters Tr. 344) Noven further relies on van der Bijl (2003), which describes an *in vitro* flux study of two non-steroidal anti-inflammatory drugs across human vaginal and buccal mucosal tissue. This reference does not teach a POSA how to design an *in vitro* flux study on a transmucosal system using mucosal tissue samples. (Guy Tr. 583-85, 607-09; PTX-371)

124. The prior art provided no meaningful guidance on how to select the types and amounts of excipients to make a monolithic adhesive estradiol patch meeting the coat weight, estradiol, and flux limitations. (Walters Tr. 342-46) There were hundreds or thousands of acrylates and a broad range of molecular weights and grades of PVP identified in the prior art and in the specification of the Patents-in-Suit. (Guy Tr. 342-43, 441-42; JTX-1 at 7:18-8:64)

125. The prior art U.S. Patent No. 6,562,363 ("'363 patent") – on which Juan Mantelle is the named inventor – discloses "bioadhesive compositions" but does not provide guidance to a POSA on how to formulate transmucosal estradiol patches. (Walters Tr. 342-44; Guy Tr. 574-75; DTX-987) It does not contain any examples using estradiol; nor does it discuss in any of its examples the site of application, coat weight, flux, or duration of release. (Guy Tr. 343-44) The focus of the '363 patent is mucoadhesives designed for adhesion for minutes or hours, not days. (*Id.*)

126. The challenge faced by the inventor of the Patents-in-Suit was how to increase flux across the ***skin***. The surprising discovery was that increasing the coat weight resulted in higher estradiol flux, a relationship which the inventor discovered by testing flux across the skin. (JTX-1 at 1:56-2:7, 3:58-4:2, 15:7-47 (Example 1); JTX-5 at 1074, 1080-82)

127. A POSA seeking to make a claimed transmucosal embodiment would have faced the added challenge of obtaining the claimed flux values while keeping the estradiol concentration in the claimed range of above 0.156 mg/cm^2 and the coat weight in the claimed range above 10 or 11 mg/cm^2. The specification is silent as to how to do this in the context of a transmucosal adhesive patch. (Lobo Tr. 177-80, 203; Walters Tr. 335-38)

128. Different mucosal tissues and environments were known at the priority date to present unique formulation challenges. (Walters Tr. 336-37, 354-55, 358-60; DTX-1073 at

ACTESTRA00060962 ("The unique properties of the oral mucosa have also imposed unique drug delivery challenges for formulation scientists . . . ."); DTX-1046 at ACTESTRA00060940 ("The vagina has unique features in terms of microflora, pH and cyclic changes, and these factors must be considered during the development and evaluation of vaginal delivery systems."))

129. The physiology and drug absorption characteristics of oral, buccal, nasal, rectal, and vaginal mucosae differ from one another, and from those of skin (which is the focus of the Patents-in-Suit's specification). (Lobo Tr. 182-88) Skin is an impervious barrier, mostly due to a protective outer layer (the "stratum corneum"), which has a "bricks and mortar" cell structure. (Lobo Tr. 180-82; DTX-477 at ACTESTRA00059562-63) Because mucosae, unlike skin, lack a stratum corneum – which is a significant barrier to drug permeation – it is much easier to get a drug to pass through mucosae than through skin. (Lobo Tr. 182, 218; Guy Tr. 569; *see also* DTX-447 at ACTESTRA00059515)

130. Estradiol, specifically, was known to be deliverable across the skin over multiple days through matrix and reservoir patches. (Lobo Tr. 192-93; DTX-445 at ACTESTRA00059437 (Figure 6)) By contrast, estradiol delivery across mucosae generally exhibits a burst effect, in which very high levels of drug are delivered immediately, followed by a precipitous drop off within hours. (Lobo Tr. 194-96; *see also* DTX-459; DTX-463) Such burst effect delivery would have been known or expected to occur through the nasal, vaginal, and rectal mucosae. (Lobo Tr. 196-98; DTX-445 at ACTESTRA00059442)

131. Dr. Walters explained that the materials used to make the two formulations disclosed in Example 1 of the specification of the '900 patent could not be used to make the claimed transmucosal systems, because mucosae are so different from skin. (Walters Tr. 335)

132. As Dr. Walters credibly testified, the art of transmucosal formulation was unpredictable, and the amount of experimentation needed to make and use the claimed transmucosal patch systems was extensive. (Walters Tr. 346-58)

133. While Dr. Guy testified, unpersuasively, that transmucosal drug delivery was more predictable than transdermal drug delivery (Guy Tr. 593), even he agreed that transmucosal flux is unpredictable (*id.* at 611, 624). The Court was persuaded by Dr. Walters, who explained that even if drug releases more quickly across mucosae than skin, that does not make it easier to achieve the claimed flux values across mucosae. (Walters Tr. 358)

134. The patents acknowledge that several parameters must be considered when developing a transdermal system, and that this reality presented a "daunting" challenge even with respect to delivery across the skin. (JTX-1 at 1:34-55; *see also* Walters Tr. 347-48, 357; DTX-976 at ACTESTRA00059517)

135. Making a transmucosal embodiment of the claimed invention for even one of the several mucosae within the scope of the claims would have required a POSA to address and test, in trial and error fashion, many interrelated and unpredictable formulation variables, constraints, and tradeoffs. (Walters Tr. 346-58)

136. The flux achieved by a patch system is unpredictable, and may depend on the composition of the blend, including how much estradiol is present and the solubility and stability of estradiol in the blend. (Walters Tr. 349-50, 352) The relationships between blend properties and flux were not predictable for a transmucosal system. (Walters Tr. 353)

137. The amount of experimentation required to make a transmucosal embodiment of the claimed invention could be extensive and could take years, although the amount of time it would take is itself unpredictable. (Walters Tr. 346-47, 351-52, 360-61) Dr. Guy did not

analyze the amount or type of experimentation that would need to be undertaken. (Guy Tr. 590-96; *see also id.* at 607-10 (stating it "would involve some formulation work" and "some experimental work," involving iterative process that "would take some time"))

138. Transdermal and transmucosal delivery are distinct fields in pharmaceutics, with different thought leaders and texts. (Guy Tr. 632)

139. Dr. Lobo explained that there was no precedent for getting a patch to stick to mucosal tissue for multiple days, and that patches adhering to the various mucosal tissues would interfere with (and be disrupted by) normal bodily functions, such as sneezing, defecating, and vaginal intercourse. (Lobo Tr. 199-201)

B. Facts Relating To On-Sale Bar Of 35 U.S.C. § 102

1. Supply Agreement

140. On April 1, 1999, prior to the July 10, 2007 critical date, Noven agreed to the Amended and Restated Supply Agreement ("Supply Agreement") with Novartis. (Walters Tr. 380-81; DTX-1002) Pursuant to Section 4.1 of the Supply Agreement, Novartis agreed to "purchase from Noven and make payment for a minimum of [redacted] of finished products ('Annual Purchase Minimum')." (DTX-1002 at NOV-MINI-A-0207353-354)

141. Section 1.4 of the Supply Agreement defined "Finished Products" as including "the 17β-estradiol single active ingredient in a dot matrix currently being marketed by Novartis (or the LLC as the case may be) under the trademark 'Vivelle-Dot®' ('Vivelle-Dot®') . . . manufactured by Noven in accordance with the Specifications (as defined herein) . . . ." (DTX-1002 at NOV-MINIA- 0207348-349)

142. The Supply Agreement required that the Vivelle-Dot® product would be made and tested according to the Vivelle-Dot® NDA, which is attached to the Supply Agreement. (Walters Tr. 380; DTX-1002 at 207381-83) The Supply Agreement defined the product that was being offered for sale to Novartis as FDA-approved Vivelle-Dot® in its "finished packaged form," not lots of Vivelle-Dot®. (DTX-1002 at 207348-49)

143. The Vivelle-Dot NDA was approved by the FDA on January 8, 1999, which was a few months prior to the execution of the Supply Agreement. (Walters Tr. 382–83; DTX-742 at NPCMNV-007446)

2. Impossibility Of Direct Measurement Of All Claimed Features In A Single Patch

144. The finished product specification for Vivelle-Dot® includes acceptance criteria for estradiol content (potency), coat weight, *in vitro* flux, or *in vivo* flux. (DTX-1002 at 207381-83; *see also* Walters Tr. 453-54; Nguyen Tr. 552; Guy Tr. 597)

145. It is not possible to measure the estradiol content, coat weight, and flux of any single Vivelle-Dot® patch and then sell that patch, given the impact of the testing on the patch. (Walters Tr. 407-08) Hence, the Vivelle-Dot® NDA does not report the estradiol content, coat weight, and flux of any single Vivelle-Dot® patch. (*Id.*)

146. Likewise, Amneal did not – and could not – present direct evidence of any single Vivelle-Dot® patch offered for sale or sold before the critical date meeting all of the claim limitations of the Asserted Claims, since no single patch that was sold or offered for sale could have been measured for estradiol content, coat weight, and flux. (Marais Tr. 280-81; Walters Tr. 460-61; Heitjan Tr. 502-03)

3. Dr. Marais' Statistical Analysis

147. Instead, Amneal relied on statistical analysis, presented through its expert, Dr. Marais. To arrive at an estimate of how many individual Vivelle-Dot® patches were sold or offered for sale that met the limitations of the Asserted Claims, Dr. Marais first estimated the fraction of Vivelle-Dot® patches that satisfied the estradiol limitation; then he estimated the fraction of Vivelle-Dot® patches that satisfied the coat weight limitation; and finally he estimated the fraction of Vivelle-Dot® patches that satisfied the various flux limitations. (Marais Tr. 249-52, 254-68, 270-78; Heitjan Tr. 502) Then Dr. Marais multiplied these three probabilities together and by the total number of Vivelle-Dot® patches shipped to Novartis before the critical date. (Marais Tr. 249-52, 254-68, 273-78; Heitjan Tr. 503)

148. The reliability of Dr. Marais' analysis depends on (among other things) whether estradiol content, coat weight, and flux are statistically independent of one another. (Heitjan Tr. 523) Only if they are independent events does Dr. Marais' multiplication of the three probabilities of each event yield a fair estimate of the probability that any single patch sold or offered for sale met all three limitations of the Asserted Claims. (Heitjan Tr. 523)

149. Dr. Heitjan opined, persuasively, that there is no way to determine (on the record before the Court) whether satisfaction of the three particular claim limitations are statistically independent events. (Heitjan Tr. 523)

150. The lots of Vivelle-Dot® Dr. Marais used to arrive at his estimates of the number of patches that met the estradiol and coat weight limitations are not the same as the lots of Vivelle-Dot® that he used to estimate the number of patches that satisfied the flux limitations. (Marais Tr. 308)

4. Manufacturing Process And Batch Records

151. The manufacturing process for Vivelle-Dot® consists generally of three parts: the blend or wet stage, the laminate or dry stage, and the package or final product stage. (Guy Tr. 596-97; DTX-1043) During the blend stage, the ingredients are mixed to make a homogenous blend. (Guy Tr. 596-97; DTX-1043) During the laminate stage, the blend is deposited onto coating lanes of release liner on a conveyor system, then dried, and then the exposed side is laminated to a backing film. (Guy Tr. 596-97) During the packaging step, patches of specified sizes are cut from the laminate using a die, the patches are placed into pouches, and the pouches are placed into cartons for shipping. (*Id.*)

152. During manufacture, as part of its quality control process, Noven removes sections of the intermediate laminate at periodic intervals and samples of laminate are punched from them to take in-process measurements. (Marais Tr. 257-58, 301; Heitjan Tr. 488-89; DTX-172; DTX-1029; DTX-2002; DTX3005; DTX-3007)

153. The sections of laminate from which test samples are taken for in-process testing are always discarded and never used to make finished Vivelle-Dot® patches. (Guy Tr. 598-99; DTX-3007 at 6661-73)

154. The test samples that are used for the in-process estradiol testing are different than the test samples that are used for the in-process coat weight testing. (Guy Tr. 597-98; PTX-454; PTX-486; PTX-487; DTX-997) Noven does not do in-process testing for estradiol flux. (Guy Tr. 596)

155. If the coat weight measurements fall out of the acceptable range at a given sample point, the coating bar is adjusted to be brought within the guidelines of 9.5 to 10.5 mg/cm^2. (Heitjan Tr. 488-89; Guy Tr. 596-99) If the estradiol content falls outside of the acceptable

range, the entire section of laminate back through to the previously-approved sampling point is discarded. (Guy Tr. 598-99)

5. Exhibit Batches Submitted With The Vivelle Dot® NDA

156. Part of the Vivelle-Dot® NDA Noven submitted in 1996 consisted of manufacturing batch records for Lot Nos. 6G1201-E, 6L2001-M, and 7A0801-E. (DTX-1044 at 3878-906; DTX-1045 at 4457-75, 4518-58)

157. Lot number 6G1201 was used in the *in vitro* flux study and residual drug study reported in the Vivelle-Dot® NDA. (Walters Tr. 459-60; DTX-942 at 4916, 5271)

158. Lot number 6G1201 does not have an in-process test sample with a measured coat weight over 11 mg/cm^2. (Walters Tr. 460-61; DTX-1044 at 3878-87)

159. Lot number 6L2001-M was an experimental lot that used a different release liner than Vivelle-Dot®, a release liner that was not approved by FDA to be sold as Vivelle-Dot®. (Nguyen Tr. 543-44; DTX-1045 at 4307)

160. Lot number 6L2001-M was not a lot of Vivelle-Dot® and was not part of the offer for sale to Novartis (as the Supply Agreement was limited to product that complied with the specifications of the Vivelle-Dot® NDA). (Nguyen Tr. 543-44; DTX-1045 at 4307)

161. There is no evidence in the record as to the flux of any patches or samples taken from Lot numbers 7A0801 or 6L2001. (Walters Tr. 459-60; DTX-942 at 4916, 5271)

6. Manufacturing Batch Records From Commercial Product

162. Between November 14, 2001 and the critical date of July 10, 2007, Noven manufactured and provided to Novartis 236 commercial lots of Vivelle-Dot® for which manufacturing records are available. (Marais Tr. 290-91)

163. Out of all in-process coat weight measurements taken for the 236 lots over the six-year manufacturing period, three individual test samples had a coat weight of more than 11 mg/cm^2. (Marais Tr. 293-94, 296-97; Heitjan Tr. 483-84, 487-88) Lot 20956 had one individual coat weight value over 11 mg/cm^2 while Lot 7120 had two. (DTX-172; DTX-2002) The two from Lot 7120 were both rejected by Noven's quality control process. (Heitjan Tr. 489-90; DTX-3005 at 306648; DTX-3007 at 306669)

164. Of the 1,020 manufacturing batch coat weight measurements considered by Dr. Marais, 27 tested samples had a coat weight of more than 10.5 mg/cm^2, and five of these (i.e., 18.5%) were rejected; the quality control process also rejected seven of the 356 (2%) of the samples with a coat weight over 10 mg/cm^2. (Heitjan Tr. 490)

7. Estimating Parameters Of Vivelle-Dot® Sold Or Offered For Sale

165. The Vivelle-Dot® specification includes a permitted range for estradiol potency of finished patches to be sold, but it does not include similar parameters for coat weight. (Walters Tr. 453-54; Nguyen Tr. 552; Guy Tr. 597; DTX-1002 at 207381-83) Noven does not test, measure, or calculate the coat weight of any finished Vivelle-Dot® product or patch before it is released for sale. (Walters Tr. 453-54; Nguyen Tr. 552; Guy Tr. 597; DTX-1002 at 207381-83) The same is true of estradiol flux: Noven does not test, measure, or calculate the estradiol flux of any Vivelle-Dot® product or patch before it is released for sale. (Walters Tr. 453-54; Nguyen Tr. 552; Guy Tr. 597; DTX-1002 at 207381-83)

166. Dr. Marais estimated the number of Vivelle-Dot® patches that met the coat weight limitations of the Asserted Claims by sampling lots from the universe of the 236 lots of Vivelle-Dot® for which he had manufacturing records containing in-process coat weight measurements. (Marais Tr. 290-91; Heitjan Tr. 483-84)

167. Specifically, Dr. Marais selected the one lot that was used in the experimental *in vitro* flux studies and went through each of the individual coat weight measurements for the in-process test samples for all of the 236 lots. He then selected the ten lots that had the highest individual test samples with the highest coat weight measurements (the "heavy lots"). Dr. Marais then selected a stratified random sample of 12 lots out of the remaining 225 lots (the "light lots"). (Marais Tr. 293-94; Heitjan Tr. 483-84)

168. The two test samples having the highest coat weights ever measured by in-process testing – 11.4 mg/cm^2 and 12.3 mg/cm^2 – were rejected by Noven's quality control process. (Heitjan 487-88; DTX-3005 at 306648; DTX-3007 at 306669) Dr. Heitjen criticizes Dr. Marais for not accounting for the rejection rate of the samples based on Noven's quality control process. (Marais Tr. 300; Heitjan Tr. 490) Dr. Marais testified in response to this criticism that he "considered what came out of the manufacturing process with all of its wrinkles and complications, including the fact that there is quality control embedded in the process." (Marais Tr. 301; *see also* Walters Tr. 386-87 (describing Noven's Vivelle-Dot® NDA in-process coat weight sampling technique as yielding representative results))

8. *In Vitro* Flux Studies Using Vivelle-Dot® As Control

169. Noven used *in vitro* flux studies to evaluate performance of a test formulation relative to a control. (Heitjan Tr. 493-94; Nguyen Tr. 561-62; Guy Tr. 600-02)

170. Noven did not use *in vitro* flux studies to assign absolute numerical flux values to a test subject or to the control used in the study. (Nguyen Tr. 561-62; Guy Tr. 600-02)

171. Dr. Guy opined that, due to variability of the skin, it is not possible to determine from an *in vitro* flux study an absolute numerical flux of a TDDS. (Guy Tr. 600-04)

172. All *in vitro* flux studies relied on by Amneal in this litigation used human cadaver donor skin. (Heitjan Tr. 493-94; Nguyen Tr. 548-49)

173. No *in vitro* flux study included any patches from any Vivelle-Dot® lot for which there was an in-process coat weight measurement greater than 11 mg/cm^2. (Walters Tr. 460; Guy Tr. 606-12)

174. Amneal presented evidence of 27 experimental *in vitro* flux studies in which Vivelle-Dot® was used as a control. (Marais Tr. 264-65, 302; Heitjan Tr. 493) The purpose of each of these flux studies was to test or evaluate the flux of various developmental formulations of patches, not to measure the flux of Vivelle-Dot®. (Heitjan Tr. 493-94; Nguyen Tr. 561-62) Of the six lots of Vivelle-Dot® used in the *in vitro* studies, three were manufactured after the critical date. (Marais Tr. 305-06; DTX-728; DTX-729; DTX-737; DTX-2617; DTX-3524; DTX-3544) Specifically, Vivelle-Dot® Lot No. 40283 was manufactured in 2009 (DTX-3544), and Vivelle-Dot® Lot Nos. 2988511 and 2988611 were manufactured in 2008 (DTX-728; DTX-729).

175. To calculate absolute flux values from the experimental *in vitro* flux studies, Dr. Marais used a linear regression method on raw data measured during the *in vitro* flux studies at different time points. (Marais Tr. 265; DTX-667)

176. The values calculated by Dr. Marais vary from 0.0033 mg/cm^2/day to 0.0262 mg/cm^2/day, values which are equivalent to about 1/3 to about 2.5 times the flux exhibited by Vivelle-Dot® as taught in the Patents-in-Suit. (Heitjan Tr. 498; JTX-1 at 4:9-13)

9. *In Vivo* Residual Drug Studies

177. Amneal presented evidence of a residual drug study conducted in 1996 that was included as part of the Vivelle-Dot® NDA. (Heitjan Tr. 500-01; PTX-942 at 4916-32)

178. The residual drug study included 12 human female patients. (Walters Tr. 398; Heitjan Tr. 501) It used developmental patches that were not commercially available Vivelle-Dot® patches. (Heitjan Tr. 501)

179. Noven relied on the residual drug study as qualitative support for dose proportionality between different patch sizes of Vivelle-Dot® and to demonstrate bioequivalence to Vivelle. (Guy Tr. 602-03)

180. The conclusions drawn from the study were that "the 10 cm^2 [Vivelle-Dot® patch] was comparable to the reference 29 cm^2 [Vivelle®] patch" (DTX-942 at 4918), such that "[t]he new 10 cm^2 [Vivelle-Dot® patch] is capable of producing comparable serum estradiol profiles to those obtained with the 29 cm^2 [Vivelle® patch]". (DTX-942 at 4918, 4932)

181. In the residual drug study, the initial estradiol content was calculated from an average of unworn patches. (Guy Tr. 603) This assumed initial estradiol content was not the actual initial estradiol content of any individual patch used in the study. (*Id.*)

182. When an adhesive patch is removed after the predetermined wear period, some of the adhesive can be left on the skin of the patient. (*Id.*)

183. Measurement of the residual amount of drug in a worn patch does not accurately reflect the amount of drug that left the patch, as the initial amount is based on an average of patches that are not worn by the patient while the residual amount is based on an actual measurement of the particular patch worn. Also, some of the drug-containing adhesive will remain on the patient's skin when the patch is removed, and some drug will remain on the patient's skin and not reach her bloodstream (and so not be available for measurement). (Guy Tr. 603-04)

184. A POSA would not use the residual drug study to assign a numerical flux to Vivelle- Dot®. (Heitjan Tr. 501; Guy Tr. 602-03)

185. Amneal did not present any evidence as to the coat weight or estradiol content of the Vivelle-Dot® patches used in the residual drug study; for this study Amneal only presented evidence of flux. (Walters Tr. 457; *see also* Guy Tr. 606 (opining there is no evidence any patches used in residual drug study had in-process coat weights of greater than 11 mg/cm^2))

10. *In Vitro* Flux Study Submitted To FDA With Vivelle-Dot® NDA

186. Amneal presented evidence of one *in vitro* flux study involving Vivelle-Dot® that was included as part of the Vivelle-Dot® NDA. (DTX-942 at 5269-85)

187. Noven relied on this *in vitro* study to confirm that the Vivelle-Dot® patch was bioequivalent to Vivelle®, based on the flux ratio. The study found that the normalized flux of Vivelle-Dot® relative to Vivelle® was 0.01 mg/cm^2/day. (*Id.* at 5274-75)

188. The ratio between the observed values for Vivelle-Dot® and Vivelle® was 2.9, which is the same ratio as the corresponding surface area of Vivelle-Dot® to Vivelle®. (*Id.*)

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). 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).

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, 1552 (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.

A. Literal Infringement And Doctrine Of Equivalents

A patent owner may prove infringement under two theories: literal infringement or the doctrine of equivalents. Literal infringement occurs when "every limitation set forth in a claim [is] found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995). Infringement under the doctrine of equivalents occurs when 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).

"[T]he 'all elements' rule informs a DOE analysis by requiring that equivalence be assessed on a limitation-by-limitation basis, rather than from the perspective of the invention as a whole, and that no limitation be read completely out of the claim." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1017 (Fed. Cir. 2006). A determination of infringement under the doctrine of equivalents is a question of fact. *See Crown Packaging Tech., Inc. v. Rexam Beverage Can Co.*, 559 F.3d 1308, 1312 (Fed. Cir. 2009).

B. Prosecution History Estoppel

"The doctrine of equivalents, however, is subject to the doctrine of prosecution history estoppel, which acts to limit infringement by otherwise equivalent products or processes." *Insituform Techs., Inc. v. CAT Contracting, Inc.*, 99 F.3d 1098, 1107 (Fed. Cir. 1996); *see also Loral Fairchild Corp. v. Sony Corp.*, 181 F.3d 1313, 1322 (Fed. Cir. 1999) ("The touchstone of prosecution history estoppel is that a patentee is unable to reclaim through the doctrine of equivalents what was surrendered or disclaimed in order to obtain the patent."). "The application of prosecution history estoppel is a question of law." *Insituform Techs.*, 99 F.3d at 1107.

"Estoppel arises when an amendment is made to secure the patent, and the amendment narrows the patent's scope." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 736 (2002). Thus, "[t]he first question in a prosecution history estoppel inquiry is whether an amendment filed in the patent and Trademark Office ('PTO') has narrowed the literal scope of a claim." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1366 (Fed. Cir. 2003) (en banc). "[A] narrowing amendment may occur when either (1) a preexisting claim limitation is narrowed by amendment or (2) a new claim limitation is added by amendment." *Honeywell Int'l, Inc. v. Hamilton Sundstrand Corp.*, 370 F.3d 1131, 1140 (Fed. Cir. 2004); *see also Festo*, 344 F.3d at 1366 ("[A] 'voluntary' amendment may give rise to prosecution history estoppel."). "If the amendment was not narrowing, then prosecution history estoppel does not apply. But if the accused infringer establishes that the amendment was a narrowing one, then the second question is whether the reason for that amendment was a substantial one relating to patentability." *Festo*, 344 F.3d at 1366.

A court must look to a patent's prosecution history to determine if an amendment was "made for a reason related to patentability." *Honeywell Int'l*, 370 F.3d at 1141; *see also Pioneer*

Magnetics, Inc. v. Micro Linear Corp., 330 F.3d 1352, 1356 (Fed. Cir. 2003) (holding that "[o]nly the public record of the patent prosecution, the prosecution history, can be a basis" for determining reason for amendment to claim). If the amendment was made for a reason related to patentability, a court may presume that prosecution history estoppel applies. *See Sulzer Textil A.G. v. Picanol N.V.*, 358 F.3d 1356, 1368 (Fed. Cir. 2004). Conversely, "if the claims were amended for a reason that was not 'related to patentability,' prosecution history estoppel does not apply absent a 'clear and unmistakable surrender' of certain subject matter." *Sextant Avionique, S.A. v. Analog Devices, Inc.*, 172 F.3d 817, 828 (Fed. Cir. 1999) (quoting *Warner-Jenkinson Co.*, 520 U.S. at 31-33). "Finally, if the patent prosecution record does not disclose the reason for an amendment, a court must presume that the amendment was made for purposes of patentability and that prosecution history estoppel applies." *Id.*; *see also Honeywell Int'l, Inc. v. Hamilton Sundstrand Corp.*, 523 F.3d 1304, 1315-16 (Fed. Cir. 2008) ("If the prosecution history reveals no reason for the narrowing amendment, the presumption is not rebutted. . . . Silence does not overcome the presumption.") (internal citation omitted).

A patentee may rebut the presumption of prosecution history estoppel by establishing one of three exceptions to estoppel: "the equivalent [was] unforeseeable at the time of the application; the rationale underlying the amendment [bore] no more than a tangential relation to the equivalent in question; or there [was] some other reason suggesting that the patentee could not reasonably be expected to have described the [equivalent]." *Festo*, 535 U.S. at 740-41.

If the result of the foregoing analysis is that prosecution history estoppel applies, then "the patentee has surrendered all territory between the original claim limitation and the amended claim limitation" and cannot "rely[] on the doctrine of equivalents for the accused element." *Festo*, 344 F.3d at 1367. However, if prosecution history estoppel does not apply, "the question

[of] whether the accused element is in fact equivalent to the limitation at issue [may be] reached on the merits." *Id.*

Two frameworks are available for analyzing application of the doctrine of equivalents: (1) the "function-way-result test," which involves assessment of whether the accused product performs "'substantially the same function in substantially the same way to obtain the same result'" as the patented invention; and (2) the "insubstantial differences test," which asks "whether the accused product or process is substantially different from what is patented." *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858, 866-67 (Fed. Cir. 2017) (quoting *Graver Tank & Manufacturing Co., Inc. v. Linde Air Products Co.*, 339 U.S. 605, 608 (1950)).

II. Invalidity

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. U.S. Int'l Trade Comm'n*, 946 F.2d 821, 830 (Fed. Cir. 1991) (internal quotation marks omitted; first alteration in original).

A. Enablement

Section 112 sets out separate requirements for written description and enablement. *See Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1344 (Fed. Cir. 2010) (holding that written description and enablement requirements are separate). Yet these requirements "often rise and fall together." *Id.* at 1352.

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

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

B. Written Description

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

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

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

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

C. Anticipation – On-Sale Bar

A claim is invalid as anticipated, under 35 U.S.C. § 102(a) or (b),[7] if:

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

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

Whether a claim is anticipated is a question of fact. *See Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006). "Application of the on-sale bar

[7] The pre-AIA version of 35 U.S.C. § 102 applies because the patents-in-suit have effective filing dates before March 16, 2013. *See* 35 U.S.C. § 100 (Note) (2015).

under section 102(b) is a question of law based on underlying issues of fact." *Robotic Vision Sys., Inc. v. View Eng'g, Inc.*, 112 F.3d 1163, 1167 (Fed. Cir. 1997).

DISCUSSION

I. Infringement

A. '419 Patent

1. Literal Infringement

Noven alleges that Amneal's ANDA Product has a coat weight of greater than 10 mg/cm^2 and, therefore, literally satisfies the coat weight limitation of the Asserted Claims of the '419 patent. (D.I. 192 at 3-14) The coat weight limitation is the only disputed limitation of these claims. The Court finds that Noven has proven, by a preponderance of the evidence, that Amneal's ANDA Product literally infringes claims 1-9, 11, and 15 of the '419 patent because Defendant's product has actual and permitted coat weight values that are greater than 10 mg/cm^2 (and all other claim limitations are, indisputably, met). (FF ¶ 68)

The Court held (and both parties' experts agreed) that no construction was required for the claim term "coat weight of greater than 10 mg/cm^2." (FF ¶¶ 35-36) Thus, the Court applies the plain and ordinary meaning of the term to a POSA, which means that any coat weight above 10 mg/cm^2 meets this claim limitation.

The infringement analysis "must focus on what the ANDA applicant will likely market if its application is approved." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997). Amneal's ANDA Product – in both its tentatively-approved form and as modified under its unsolicited proposed amendment – is permitted, by the terms of Amneal's ANDA, to have in-process coat weights above 10 mg/cm^2. (FF ¶¶ 56-58) Specifically, the upper limits of the coat weight in the tentatively-approved product are 10.75 mg/cm^2 for any individual coat weight value and 10.5 mg/cm^2 for the average coat weight value. (FF ¶ 56) Similarly, the upper limits

under Amneal's proposed amended ANDA for individual and average coat weights are 10.45 and 10.40 mg/cm^2, respectively. (FF ¶ 57) Consistent with these tolerances, each of the four exhibit batches of Amneal's ANDA Product show repeated instances of actual, in-process coat weight values greater than 10 mg/cm^2, with an individual coat weight measurements as high as 10.37 mg/cm^2 and average coat weights as high as 10.28 mg/cm^2. (FF ¶¶ 60-62) During production, Amneal does not discard products having a coat weight that falls within its permitted ranges. (FF ¶ 68) There is no evidence that the in-process coat weight decreases after measurement and before manufacture of the final product is complete. (FF ¶¶ 51, 54) It follows, then, that the ANDA Product Amneal seeks to sell (whether it be the tentatively-approved product or the proposed amended product) will include patches with coat weights of greater than 10 mg/cm^2 and, thus, Amneal's product infringes the asserted claims of the '419 patent. (FF ¶¶ 61-69; *see generally Sunovion Pharma., Inc. v. Teva Pharma. USA, Inc.*, 731 F.3d 1271, 1278 (Fed. Cir. 2013) (stating that where alleged infringer "is asking the FDA to approve for sale [a product that] falls within the scope of [the patents-in-suit], a judgment of infringement must necessarily ensue").

Amneal's defense to infringement of the '419 patent is based on its meritless contention that the plain and ordinary meaning construction the Court has given to "having a coat weight greater than 10 mg/cm^2" is contrary to the intrinsic and extrinsic evidence. Amneal argues that a POSA would understand that a single-value coat weight refers to a "target weight" in manufacturing, citing the manufacturing tolerances of the prior art Vivelle-Dot®, which describe a single-value coat-weight (10 mg/cm^2) while tolerating greater coat weights. (Nguyen Tr. 551-52; D.I. 195 at 20) As further support, Amneal points to the specification's guidance that "coat weight greater than 10 mg/cm^2" refers to the target coat weight of the Vivelle-Dot® (D.I. 195 at

19-20) and references to the exemplary target coat weights of 12.5 mg/cm^2 and 15 mg/cm^2 coat weights used to make the patches of Examples 1 and 1a (JTX-1 at 15:21-22, Fig. 1), as well as Noven's advocacy during the claim construction process of a view that understands coat weight to be a target coat weight (relative to a target coat weight for Vivelle-Dot®) (*see, e.g.*, D.I. 83 at 34 ("[T]his term covers a coat weight of greater than – i.e., not less than or equal to 10 mg/cm^2, the target coat weight for the Vivelle-Dot® product."). Amneal also relies on the opinion of its expert, Dr. Dash. (*See, e.g.*, Dash Tr. 127, 135-37, 147)

The Court continues to agree with Noven that the plain and ordinary meaning to a POSA of the claim term "coat weight of greater than 10 mg/cm^2" refers to the actual, measured coat weight of a patch, and not to a target coat weight. (FF ¶¶ 65, 67, 69) While the specification of the '419 patent references Vivelle-Dot®, it nowhere expressly states that the Vivelle-Dot® coat weight is 10 mg/cm^2; nor does it disclose the invention's coat weight in a context relative to Vivelle-Dot®. (JTX-1 at 2:46-47 ("In some embodiments, the polymer matrix has a coat weight of greater than about 10 mg/cm^2."); *id.* at 3:17-19, 13:45-57; *see also* Dash Tr. 47-48, 164-66; Guy Tr. 62; D.I. 83 at 27-28; D.I. 84 at ¶¶ 44-45)[8]

2. Doctrine Of Equivalents

Because Noven has proven that Amneal's ANDA Product literally infringes the asserted claims of the '419 patent, the Court does not reach the issue of infringement under the doctrine of equivalents. Accordingly, the Court need not decide whether prosecution history estoppel applies to the '419 patent.

[8] Unlike a case on which Amneal relies, *Kaneka Corp. v. Xiamen Kingdomway Grp. Co.*, 790 F.3d 1298, 1303-05 (Fed. Cir. 2015), there is no express disclosure in the '419 patent to inform a POSA's understanding of whether the coat weight is the "target" coat weight. Nor, therefore, does the Court's construction read out of the claims a preferred embodiment.

B. '900 And '310 Patents

1. Prosecution History Estoppel

Noven does not allege that Amneal's ANDA Product literally infringes the Asserted Claims of the '900 and '310 patents. Instead, it alleges infringement under the doctrine of equivalents ("DOE"). Noven cannot prevail on its claim of infringement under the DOE, however, due to the doctrine of prosecution history estoppel. (FF ¶ 81)

Specifically, Noven relies on DOE in an effort to show that Amneal's ANDA product infringes, by equivalents, the disputed claim limitation of a coat weight "greater than about 10 mg/cm^2," which the Court construed to mean "having a coat weight which weighs more than 110% of 10 mg/cm^2" (D.I. 112 at 4); that is, a coat weight of more than 11 mg/cm^2.

As originally filed, claim 14 of the '972 application that later became the '900 patent, and claim 1 of the '985 application that later became the '310 patent, had no coat weight limitations. (FF ¶ 73; *compare* JTX-5.119, JTX-5.158-19, JTX-5.337, JTX-4.52, JTX-4.118) Then, on May 5 and 20, 2015, respectively, office actions in the '900 and '310 patent prosecutions issued rejections based on obviousness. (FF ¶ 74; JTX-5.319-329; JTX-4.95-103) Specifically, the office actions rejected claims 14 of the '900 patent and 1 of the '310 patent as obvious over (1) Kanios in view of Nuwayser (JTX-5.323; JTX-4.98); and (2) Kanios and Nuwayser in view of Miller (JTX-5.325; JTX-4.100). (FF ¶ 75) This was based on the Examiner's express finding "that Kanios and Nuwayser do not teach the polymer matrix has a coat weight greater than about 10 mg/cm^2," but "it would have been obvious to a person of ordinary skill in the art at the time that the invention was made to utilize a coat weight of 90-110 g/m^2 (9-11 mg/cm^2) as taught by Miller et al. in the patch of Kanios and Nuwayser." (FF ¶ 75)

On June 10, 2015, in an interview following the rejection, the Examiner discussed with the applicant "***possible claim amendments such as*** an adhesive polymer matrix or ***the addition of a coat weight.***" (FF ¶ 76; JTX-5.396; JTX-4.179) (emphasis added) Two days later, on June 12, 2015, Noven amended the claims to add the emphasized language, which includes the coat weight limitations:

> A method for administering estradiol, comprising applying to the skin or mucosa of a subject in need thereof a monolithic transdermal drug delivery system consisting of (i) a backing layer and (ii) a single ***adhesive*** polymer matrix layer defining an active surface area and comprising a polymer matrix comprising ***an adhesive*** polymer matrix comprising estradiol as the only drug, wherein the polymer matrix ***has a coat weight of greater than about 10 mg/cm^2 and*** includes greater than 0.156 mg/cm^2 estradiol and achieves an estradiol flux that is greater than 0.01 mg/cm^2/day, based on the active surface area.

(JTX-5.337 (emphasis added), *see also* JTX-4.118-19; FF ¶ 77)

In connection with the amendment, Noven noted that "the Examiners suggested amending the claims to recite embodiments regarding the coat weight of the polymer matrix. Such amendments are reflected in the foregoing claim amendments, which incorporate the subject matter of claim 27 into claim 14, and make parallel amendments to the other claims." (FF ¶ 78; JTX-5.340-41; *see also* JTX-4.120-21)

Noven further explained to the PTO that "none of the cited references [on which the obviousness rejections were based] teach or suggest that the amount of drug per unit area of a monolithic polymer matrix-type transdermal drug delivery system as claimed is a result-effective variable for drug flux (e.g., drug delivery rate)," where "drug per unit area" depended on drug concentration and "coat weight." (JTX-5.341-43; JTX-4.121; FF ¶ 79; *see also* D.I. 195 at 8 n.2; D.I. 208 at 12)

The Court agrees with Amneal that these amendments give rise to a presumption that prosecution history estoppel applies here, a presumption which Noven has not succeeded in rebutting.

First, the amendments to add the coat weight limitations were narrowing. Because claim 14 of the '972 application and claim 1 of the '985 application did not have a coat weight limitation prior to the obviousness rejection in the May 2015 office actions (JTX-5.158-159; JTX-4.52), the addition of the coat weight limitation narrowed the scope of the claims, making certain embodiments that were previously within the scope of the claims no longer so (FF ¶ 77).

Second, the reason for the amendment is "a substantial one relating to patentability." *Festo*, 344 F.3d at 1366-67. The purpose of the amendment was to avoid an obviousness rejection based on Kanios, Nuwayser, and Miller, and highlight the "unexpected results based on the coat weight of the polymer to achieve the claimed flux of drug delivery." (JTX 5.404; JTX-4.186) As Amneal's expert, Dr. Dash, persuasively opined, the Examiner would not have granted the asserted claims of the '900 and '310 patents without the coat weight limitations, making the amendments substantial to patentability. (Dash Tr. 134-35) By contrast, Noven has failed to provide some other objectively apparent reason for the narrowing amendment and merely asserts the amendment was made for reasons unrelated to patentability. *See Ajinomoto Co., Inc. v. Int'l Trade Comm'n*, 932 F.3d 1342, 1351-52 (Fed. Cir. 2019).

Third, Noven has not rebutted the presumption that estoppel applies, because it has failed to show that the coat weight amendment is "tangential to the asserted equivalent in the Amneal ANDA Product." (D.I. 192 at 23) "The tangential relation criterion for overcoming the . . . presumption [of estoppel] is very narrow." *Honeywell Int'l*, 523 F.3d at 1315. "To rebut the estoppel presumption with tangentiality, a patentee must demonstrate that . . . the narrowing

amendment was peripheral, or not directly relevant, to the alleged equivalent." *Id.* Further, "th[e] reason [for the amendment] should be discernible from the prosecution history record, if the public notice function of a patent and its prosecution history is to have significance." *Festo*, 344 F.3d at 1369. Here, Noven has not "demonstrate[d] that an amendment required during prosecution had a purpose unrelated to patentability." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. at 40-41.

Noven contends that the claim amendment adding the limitation "greater than about 10 mg/cm^2" bore "no more than a tangential relation to the equivalent in question," *Festo Corp.*, 535 U.S. at 740, because the prior art reference, Miller, disclosed a coat weight range of 9 to 11 mg/cm^2 (D.I. 192 at 23). Noven also notes that Miller disclosed a system comprising fentanyl (not estradiol). (Guy Tr. 86; JTX-4.117-126; JTX-5.345[9]; D.I. 192 at 20-25) To Noven, then, the "greater than about 10 mg/cm^2" coat weight was already within the scope of Miller, so the Examiner could not have relied on the coat weight amendment to overcome Miller and must, instead, have relied on Noven's argument that Miller was irrelevant because it involves fentanyl, not estradiol. (D.I. 192 at 23) (citing JTX-4.117-126; JTX-5.336-46)

Noven further observes that the Examiner had initially rejected all claims, including claim 27, which included the limitation "a coat weight of greater than about 10 mg/cm^2," and stated that it would have been obvious to a POSA "to utilize a coat weight of 90-110 mg/cm^2 (9-11 mg/cm^2) as taught by Miller et al." (JTX-5.326; *see also* JTX-4.101; FF ¶ 75; Guy Tr. 85-86)

[9] In this portion of the prosecution history, the applicant stated: "Although Miller is cited for disclosing a transdermal system having a polymer matrix coat weight of greater than 10 mg/cm^2, Miller is largely irrelevant to the subject matter of the pending claims because its systems comprise fentanyl (not estradiol) suspended in solvated silicone adhesives." Notably, it was only after five pages of other reasoning that the applicant offered this attempted distinction of Miller. (*See* JTX-5.340-45; *see also* Guy Tr. 98-101)

Noven argues that, in its amendment, it simply moved the "coat weight of greater than about 10 mg/cm^2" limitation from rejected dependent claim 27 into rejected independent claim 14 (which later issued as claim 1 of the '900 patent), and distinguished Miller on grounds unrelated to coat weight (i.e., that Miller was a system involving fentanyl, not estradiol).[10] (Guy Tr. 86; JTX-4.117-126; JTX-5.336-345; D.I. 192 at 21) Noven adds that the amendment is tangential to the equivalent also because Noven "does not distinguish the coat weight manufacturing guidelines or measured coat weight values of the Amneal ANDA product (*e.g.*, 10.45 mg/cm^2), just like it did not distinguish Miller's coat weight range of 9-11 mg/cm^2." (D.I. 192 at 23)

Noven's is not a persuasive reading of the prosecution history. Notably, the applicant and Examiner both referenced the coat weight limitation repeatedly, while there is only one reference to the drug used in the Miller system. (FF ¶¶ 79-80) For instance, the Examiner expressly cited coat weight as a reason for allowing the claims: "***Applicant's arguments of unexpected results based on the coat weight of the polymer to achieve the claimed flux of delivery are persuasive.***" (JTX-5.404; JTX-4.186) (emphasis added) The applicant stressed the importance of coat weight, explaining that he was "surprised by the discovery that increasing the amount of estradiol per unit area[[11]] resulted an increased rate of drug delivery per unit area in the context of the claimed transdermal drug delivery systems. As explained in the specification,

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[10] While Noven tries to argue that the distinction between fentanyl and estradiol is so significant that it could have been the basis for the applicant's successful distinction of Miller from the '900 and '310 patents, Dr. Guy relied on his work with fentanyl as being pertinent to his qualifications to opine about the accused estradiol products. (*See* Guy Tr. 565)

[11] As Amneal observes, the phrases "drug per unit area" and "estradiol per unit area" are used interchangeably with "coat weight" in the June 12, 2015 office action response. (D.I. 195 at 8 n.2) Noven appears to disagree. (*See* D.I. 2018 at 12) (citing DTX-131 at 9) (stating that amount of drug per unit area "depends on both the concentration of the drug . . . and the coat weight") Even accepting Noven's view on this point, the pertinent point is that the applicant's focus was on the "surprising" result stemming from the coat weight limitation. (JTX-5.341)

prior to the invention, increasing coat weight was thought to provide delivery over a longer period of time, but it was not known that increasing the amount of drug per unit area could increase the drug delivery rate." (JTX-5.341-47; JTX-4.121-27) The applicant added that "[t]his result was surprising because coat weight is typically selected to control the duration of drug delivery, but was not understood to impact delivery rate (e.g., daily dose delivered)." (*Id.*) The applicant stressed the unexpected result of the coat weight limitation, explaining that TDDSs "already are formulated with much more drug than is delivered over intended periods of use . . . it was unexpected that increasing the amount of drug per unit area would impact drug delivery rate." (*Id.*) The applicant continued to describe why the prior art did not disclose the claimed coat weight limitation. (*Id.*) ("Although Nuwayser was cited for its statement that 'flux rates depend on the concentration of the applied substance in the vehicle,' a person of ordinary skill in the art would not have understood this statement to provide any guidance with regard to the subject matter of the instant claims, which recite . . . a coat weight of greater than about 10 mg/cm^2.")

The Examiner made no reference to the patentee's single statement distinguishing Miller based on the drug involved but, instead, focused on the unexpected result that that increasing the coat weight of the drug resulted in an increased flux per unit area (which the patentee repeatedly referenced). (*See* FF ¶ 80; JTX-5.398-405; JTX-4.181-87)

Moreover, as Amneal emphasizes, without the coat weight limitation in the claims, Noven "would not have been able to argue that the claimed invention embodied the 'unexpected result' of higher coat weight causing higher flux rates, to overcome the obviousness rejection." (D.I. 195 at 9-10; *see also id.* ("The centrality of coat weight to patentability shows that the amendment to claim 14 was related to patentability."); JTX-4.828-30; JTX-5.1049-51) (Noven's expert stating to PTO during prosecution that "the difference in coat weight is contributing to the

difference in flux between the Vivelle-Dot® system and the Example 1 and 1a systems [having coat weights of 12.5 and 15 mg/cm^2]"))

Like Amneal, the Court does not read the prosecution history as demonstrating that "the Examiner's suggestion of adding a coat weight limitation was not to distinguish prior art, but rather to encourage Noven to consolidate claim 27 into claim 14." (D.I. 195 at 10 (discussing D.I. 192 at 21-22); *see also generally Amgen, Inc. v. Amneal Pharm. LLC*, 945 F.3d 1368, 1381 (Fed. Cir. 2020) (affirming application of prosecution history estoppel even in context where added limitations were already present in previously-rejected claims))[12]

Finally, the Court turns to the question of "the scope of the subject matter surrendered by the narrowing amendment." *Festo Corp.*, 344 F.3d at 1367. Here, the original claim limitation did not have any coat weight limitation. The amended claim limitation added the requirement of "a coat weight greater than about 10 mg/cm^2." Accordingly, it is presumed under *Festo* that Noven has surrendered all coat weights that are not "greater than about 10 mg/cm^2," which, given the Court's construction, means Noven presumptively surrendered all coat weights that are not "greater than 11 mg/cm^2." That is, Noven cannot claim infringement by equivalents of an embodiment with a coat weight of 11 mg/cm^2 or less than 11 mg/cm^2.

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[12] Noven emphasizes that the during prosecution, the Examiner did not and could not apply the Court's claim construction, and, therefore, interpreted "greater than about 10 mg/cm^2" to encompass coat weight values between 10 and 11 mg/cm^2, under the "broadest reasonable interpretation standard." (D.I. 192 at 22-23) (citing DTX-129 at 6) Noven relies on the fact that the Examiner cited Miller, and its disclosure of "a coat weight of 90-110 mg/m^2 (9-11 mg/cm^2)" (DTX-129 at 6), as evidence that the Examiner did not apply the Court's construction (D.I. 112 at 4). This does not provide a basis for the Court to fail to apply prosecution history estoppel. The Court based its construction, in part, on the patentee's lexicography. (D.I. 112 at 6-7) (stating Court's construction of coat weight term "most accurately captures the patentee's lexicography and intent to avoid the coat weight of Vivelle-Dot®") As Amneal observes, "[s]uch lexicography is binding" under either the Examiner's then-applicable "broadest reasonable interpretation" or this Court's claim construction standard. (D.I. 195 at 13)

Noven has not met its burden to demonstrate that the asserted equivalent was not surrendered in the amendment. *See Festo Corp.* 535 U.S. at 740.[13] Because the coat weight of the Amneal ANDA Product that will be sold is no greater than 10.75 mg/cm^2 (as tentatively approved) or 10.45 (as set out in the proposed amendment) (*see* FF ¶¶ 56, 56), Noven has not – and cannot – prove that Amneal's ANDA Product infringes the asserted claims of the '900 or '310 patents under the doctrine of equivalents.

2. Function-Way-Result And Insubstantial Differences Analyses

Although Noven is estopped from asserting infringement of the '900 and '310 patents under the DOE, the Court will briefly address the evidence the parties presented with respect to Noven's claims. Even were Noven not estopped (which it is), Noven has failed to prove infringement by equivalents, whether the Court applies the function-way-result ("FWR") analysis or the insubstantial differences test. (FF ¶¶ 82, **Error! Reference source not found.**)

Noven contends that Amneal's ANDA Product infringes under the DOE because "the coat weight of the Amneal ANDA Product performs substantially the same function, in

[13] Noven argues that an amendment made for patentability does not necessarily surrender all claim scope, only that which was needed to avoid the prior art (*see* D.I. 192 at 20), relying on *Eli Lilly & Co. v. Hospira, Inc.*, 933 F.3d 1320, 1332 (Fed. Cir. 2019). Noven further explains that the context in which the amendment was made must be considered when determining whether the tangential exception applies. (D.I. 208 at 13) *Eli Lilly* expressly states: "[a]mendments are not construed to cede only that which is necessary to overcome the prior art." 933 F.3d at 1332; *see also generally Pharma Tech Sols., Inc. v. LifeScan, Inc.*, 942 F.3d 1372, 1382 (Fed. Cir. 2019) ("The fact that the inventors may have thought after the fact that they could have relied on other distinctions in order to defend their claims is irrelevant to discerning the objective reason for their amendment.") (internal quotation marks and citation omitted). *Eli Lilly* also says that "the tangential exception only exists because applicants over-narrow their claims during prosecution," and "the reasons for an amendment, where the tangential exception is invoked, cannot be determined without reference to the context in which it was made, including the prior art that might have given rise to the amendment in the first place." 933 F.3d at 1332. The Court has undertaken the required contextual analysis; it has considered the context in which the amendment was made and has determined that the amendment does not come within the tangential exception. The Court has further determined that Noven surrendered all claim scope between the original and amended claims.

substantially the same way, to achieve substantially the same result, as the coat weight claimed in the '900 and '310 Patents," that is, a coat weight of "greater than 11 mg/cm^2." (D.I. 192 at 15-20) The Court disagrees. (*See generally* FF ¶¶ 82-86)

In support of its position, Noven contends that the coat weight of the accused product and the claimed coat weight do not change the concentration gradient of estradiol across the skin. (Guy Tr. 82-84) Therefore, according to Noven, Amneal's ANDA Product will achieve the same appropriate level of estradiol flux as would a literal embodiment of the Asserted Claims. (Guy Tr. 84) Further, according to Noven, in both the claimed system and in Amneal's ANDA Product, "the flux will be achieved in substantially the same way, *i.e.*, by an adhesive polymer matrix coat weight that permits the claimed level of estradiol flux." (D.I. 192 at 19) (citing Guy Tr. at 84)

The Court agrees with Amneal that Noven has not met its burden. As Amneal correctly explains, Noven's FWR analysis would improperly "read the 'coat weight' limitation out of the claims . . . and entirely subsume it into the separate 'flux' limitation." (D.I. 195 at 14; FF ¶ 85) Moreover, "Noven simply disregards the evidence that Amneal achieved its flux levels ***despite*** lower coat weights than literally claimed, and by manipulating other formulation parameters (that is, other than coat weight) that were known in the field to modulate flux." (*Id.*; *see also id.* at 15 (citing evidence); FF ¶¶ 84-86)

Noven's failure of proof is evident also by considering the insubstantial differences test. Noven has failed to show that the difference between the coat weight of the Amneal ANDA product and the claimed coat weight of greater than 11 mg/cm^2 is insubstantial.

Noven's argument is inconsistent with the patents, which tout as the inventor's discovery the surprising relationship between coat weight and estradiol flux. (*See* JTX-1 at 3:58-4:2)

("Applicant surprisingly discovered that increasing the coat weight of the drug-containing adhesive layer resulted in an increased flux per unit area, and thus permitted the development of smaller transdermal drug delivery systems that achieve comparable daily dosages.") It is difficult to understand how the novel "surprising discovery" of the inventor could be significantly modified – including to a coat weight as low as 9.25 mg/cm^2 (the lowest individual coat weight permitted in Amneal's tentatively-approved manufacturing guidelines) (FF ¶ 56), which is 16% lower than the claimed more than 11 mg/cm^2 (11.0-9.25=1.75, and 1.75/11.0=.159) – and not substantially affect drug delivery. *See generally Rembrandt Patent Innovations, LLC v. Apple, Inc.*, 716 Fed. Appx. 965, 977 (Fed. Cir. 2017) (rejecting insubstantial differences argument that "would have [Court] ignore [a] clearly articulated purpose of the invention, as well as the specification's explanation of how the invention achieves this purpose"). Certainly, Noven did not present persuasive evidence to support such a finding.

Dr. Guy calculated the percentage differential between the claimed 11 mg/cm^2 coat weight and the highest actual individual coat weight values, the upper limit of the tentatively-approved coat weight guidelines (with tolerance), and the upper limit of the proposed amended coat weight guidelines (with tolerance). (Guy Tr. 77-79) Dr. Guy found that these percentage differences are only 1.6% to 5.3 %. (*Id.*; FF ¶¶ 87-90, 92) Because the FDA has permitted a 15% range in the tentatively-approved coat weight range of 9.25 to 10.75 mg/cm^2, Dr. Guy opined that a POSA would regard Amneal's ANDA Product to be insubstantially differently from patches embodying the small coat weight increases needed to reach a coat weight greater than 11 mg/cm^2. (Guy Tr. 79-82, 88; D.I. 192 at 17)

However, as Amneal points out, Noven improperly focuses on the highest possible individual measurements, as well as an inflated theoretical die "tolerance," rather than the target

coat weight. (D.I. 195 at 16) Furthermore, "bioequivalency and equivalent infringement are different inquiries," *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1298 (Fed. Cir. 2009), and the Court finds in the record no persuasive basis to conclude that the FDA's acceptance of a 15% range around a target of 10 mg/cm^2 for purposes of regulatory review is tantamount to a finding that all coat weights within that range perform identically (even if those coat weights are all delivering the same daily dose of estradiol). Noven has not presented evidence that an increase to greater than 11 mg/cm^2 would have an insubstantial effect on drug delivery.[14] The patents themselves teach that a change in coat weight to greater than 10 mg/cm^2 would result in increased flux. (*See* JTX-1 at 3:58-4:2)

Amneal's manufacturing practice further substantiates the Court's finding that the difference in coat weights falling within the range of 10 ± 0.75 is not insubstantially different (that is, the difference ***is*** substantial) from coat weights greater than 11 mg/cm^2. (*See, e.g.*, FF ¶ 91) As Dr. Dash explained, Amneal's manufacturing guidelines require Amneal to discard entire batches of the ANDA Product if the coat weight exceeds the permissible limit of 10.75 mg/cm^2 (tentatively approved) or 10.45 mg/cm^2 (as amended).[15] (Dash Tr. 126, 133-34; Audett 161-63; Audett II 10-11, 63-64, 67-68; FF ¶ 91; DTX-159 at AMNMIN143507-08) That is, Amneal "will necessarily throw away ***entire batches*** of its product if even one individual measurement in the batch is confirmed to exceed in-process limits, all of which are less than 11 (10.75 as tentatively-approved, and 10.45 under the proposed amendment" – which, as Amneal

[14] The Court did not find Dr. Guy's opinion on this point to be persuasive. (*See* Guy Tr. 82-88)

[15] There is no evidence that the in-process coat weight decreases after measurement and before manufacture of the final product is complete. (FF ¶¶ 51, 54)

rightly notes, reveals that "the difference is so substantial" as to render DOE infringement unproven (and unprovable). (D.I. 195 at 4)[16]

Accordingly, even if Noven were not estopped from proving infringement under the doctrine of equivalents, Noven has failed to meet its burden to prove such infringement by a preponderance of the evidence.

3. Indirect Infringement Of The '900 Patent

There can be no indirect infringement without direct infringement. *See Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 930 (2005). Because Noven has failed to prove direct infringement of the '900 patent, either literally or under the doctrine of equivalents, it follows that Noven has also failed to prove indirect infringement of claims 1-11 or 15 of the '900 patent.

II. Invalidity

A. Enablement

Amneal contends that all of the Asserted Claims of all three of the Patents-in-Suit are invalid because they fail to enable the full scope of the claims. Specifically, Amneal argues that the patents fail to enable the claimed transmucosal estradiol patch systems. The Court finds that Amneal has proven lack of enablement by the requisite clear and convincing evidence.

Application of the *Wands* factors, *see* 858 F.2d at 737, to the evidence credited by the Court leads the Court to conclude that a POSA would require undue experimentation to make and use the claimed transmucosal embodiments.

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[16] The Court further agrees with Amneal that its proposed amendment, which "was submitted merely to further tighten its coat weight specification more closely around its target of 10 mg/cm^2," "says ***nothing*** of whether a decrease from a coat weight of 10.75 to 10.45 mg/cm^2 would influence flux." (D.I. 195 at 17)

The asserted claims are broad; they cover not just estradiol patch systems for application to the skin but also estradiol patches to be applied to any mucosal tissue, including oral, buccal, nasal, rectal, and vaginal tissue. (FF ¶ 105; JTX-1 at 5:35-39) This breadth of the claims is particularly striking given the lack of any significant guidance in the specification as to how to make or use an estradiol patch system on any mucosa (let alone all mucosae). (FF ¶¶ 96-97) In fact, other than a few general references, the only references in the specification to mucosa are in the definitions of "transdermal" and "flux." (Lobo Tr. 179; Walters Tr. 335 (discussing JTX-1 at 2:57-65); FF ¶¶ 106-107)

The specification fails to disclose any working example of a transmucosal patch system. (FF ¶¶ 95, 96-100, 110) The specification is silent as to how much estradiol to include, or what coat weight should be used. (FF ¶¶ 96-100; Walters Tr. 336-37) The specification fails to identify which excipients or ingredients would be useful for making any (let alone all) of the claimed transmucosal systems. (FF ¶¶ 98, 112; Walters Tr. 334-36; JTX-1 at 2:57-65) While the specification identifies a list of bioadhesives for potential use, the patents provide no guidance as to which of these polymers would be specifically useful for making a transmucosal system. (FF ¶¶ 100-101; Walters Tr. 335-37) Dr. Guy did not explain why, for example, a POSA would have focused on PVP and acrylic adhesives, in particular, for a transmucosal estradiol patch; if so, which PVPs or acrylic adhesives; how many different kinds of each she would choose; or how much of each she would choose to obtain the claimed estradiol flux across any given mucosal tissue at the claimed estradiol concentration and claimed coat weight. (FF ¶ 124)[17] Instead, as Dr. Walters persuasively put it: "There are so many mucoadhesives that are

[17] The Court disagrees with Noven's contention that "Amneal has not and cannot show clearly and convincingly that a POSA with this extensive knowledge [from prior art patents and products] of bioadhesive polymers useful for transmucosal systems would not have understood

listed out there, that you just don't have any guidance as to which one would be the best one." (Walters Tr. 348; *see also* D.I. 216 at 12 ("Noven points to nothing in the specification indicating which of the many known adhesives a POSA would try, what amounts he would try, how long any given adhesive or mixture of adhesives would adhere to which of the several claimed mucosa, whether the adhesive or adhesive mixture will irritate any of those mucosae, which adhesives are physically and chemically compatible with estradiol, and what affect each will have on estradiol flux across the various mucosae either alone or in combination with other components of the adhesive matrix."))

Moreover, there is no mention in the specification of whether or how the central discovery of the patents – increasing coat weight to increase flux – would apply to the various mucosae. (FF ¶¶ 99, 126; Walters Tr. 336-38) This is perhaps not surprising, since the relationship was discovered by testing flux across skin, not mucosal tissue. (FF ¶¶ 102, 126; JTX-1 at 15:7-47 (Example 1)) The specification's example with respect to the flux achieved with various formulations pertained only to skin, not mucosae. (FF ¶ 111; Walters Tr. 335) This is significant because there was no known correlation between flux across the skin and flux across the various claimed mucosal tissues. (FF ¶ 113-115; Mantelle II 231-33, 239; Nguyen Tr. 549; Guy Tr. 585, 624) A POSA seeking to make a claimed transmucosal embodiment would have faced the added challenge of obtaining the claimed flux values while keeping the estradiol concentration in the claimed range of above 0.156 mg/cm^2 and the coat weight in the claimed range above 10 or 11 mg/cm^2. (FF ¶ 127) The specification is silent as to how to do this in the context of a transmucosal adhesive patch (and disclosed it was "daunting" to do so even in the

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the Specification's disclosure of embodiments made using bioadhesive polymers to describe and enable transmucosal embodiments of the Asserted Claims." (D.I. 215 at 13)

context of skin). (Lobo Tr. 177-80, 203; Walters Tr. 335-38, 347-48, 357; JTX-1 at 1:34-55) Similarly, the patents-in-suit teach that the rate-limiting step is the passage of estradiol through skin, but whether this is the rate-limiting step for any (or all) mucosal embodiments is not disclosed. (FF ¶ 116; Walters Tr. 337-38; JTX-1 at 11:53-54)

Dr. Lobo explained that the physiology and drug release characteristics of oral, buccal, nasal, rectal, and vaginal mucosa could vary greatly – not only from skin, but from one another. (FF ¶¶ 128-129; Lobo Tr. 182-89, 194) This is primarily because the skin has an impervious barrier due to a protective outer layer, known as the "stratum corneum," which is lacking in mucosae. (FF ¶ 129; Lobo Tr. 180-82; DTX-477 at -59562-63) Drug delivery across the skin is, therefore, constant and prolonged over days, while estradiol delivery across the mucosae was known to be rapid, sometimes exhibiting a burst effect. (FF ¶ 130; Lobo Tr. 191-94; DTX-447 at -59515) The patents provide a POSA no guidance about how to achieve the claimed daily flux when the drug is so rapidly absorbed over mucosa. (Lobo Tr. 180)

The state of the art of transmucosal patch designs further supports the Court's finding of lack of enablement.[18] In 2008, the prior art describing transmucosal patch design failed to provide meaningful guidance on how to make or use the claimed transmucosal estradiol patch

[18] Dr. Lobo testified that (1) it was not known how to get a patch to stick in a dynamic, fluid-laden mucosal environment, (2) there would be "all sorts of issues" with the act of using such a patch, including interference with or by normal bodily functions, and concerns over contamination, and (3) "there was nothing to say that it would be the right flux." (Lobo Tr. 199-206; *see also* FF ¶ 128)

The Court entirely disagrees with Noven's insistence that "[t]he fact that Dr. Lobo did not consider any patents renders his testimony not credible." (D.I. 215 at 2 n.3) While the disclosures of other patents can help the Court to understand the knowledge a POSA would have had and the state of the art, they cannot (as a matter of law) cure a non-enabling disclosure in the specification of the patent-in-suit itself. *See ALZA*, 603 F.3d at 941.

systems. (FF ¶ 120) At that point, no one had developed an adhesive vaginal, rectal, or nasal patch of any kind, for any drug. (FF ¶¶ 120-21; Lobo Tr. 201; Walters Tr. 340)

While Noven's Dr. Guy opined that the state of the art with respect to transmucosal systems was developed, and that a POSA would have understood that sustained release of estradiol could be delivered through oral, buccal, vaginal, rectal, and nasal mucosa, his opinion on these points was unpersuasive. (Guy Tr. 571-86, 592) Dr. Guy has essentially no experience with respect to transmucosal drug delivery systems.[19] (Guy Tr. 563-66) Further, the definition of a POSA adopted by the Court (which was proposed by Noven) does not require the POSA to have any experience or knowledge with respect to transmucosal embodiments. (FF ¶ 118) These facts further support a conclusion that a POSA would not understand the specifications to enable the claimed transmucosal embodiments.

Also, importantly, disclosures in the prior art cannot, as a matter of law, make up for deficiencies in a non-enabling specification. *See ALZA*, 603 F.3d at 941. "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." *Genentech*, 108 F.3d at 1366; *see also Enzo Life Sciences, Inc. v. Roche Molecular Systems, Inc.*, 928 F.3d 1340, 1348 (Fed. Cir. 2019). "[W]hen there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required." *Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1283-84 (Fed. Cir. 2007) (internal quotation marks omitted). Here, the specification provides "only a starting point, a direction for further research," which is not enabling. *Auto. Techs.*, 501 F.3d at 1284; *see also Genentech*, 108 F.3d at 1366.

[19] Dr. Guy's only clinical experience with actual mucosa compared pig buccal mucosa to pig esophageal mucosa, using a film, not a patch. (Guy Tr. 617-19)

In any event, the patents and publications Dr. Guy relies on in an effort to show that the state of the art was sufficiently advanced that a POSA would somehow have found in the specification of the Patents-in-Suit sufficient guidance to make and use a transmucosal embodiment of the claims (let alone embodiments with respect to each mucosa covered by the claims) do not suffice. Dr. Guy relies on publications reporting clinical studies that tested the immediate release of estradiol across different mucosal membranes as well as earlier patents on transmucosal systems on which Juan Mantelle (the inventor of the Patents-in-Suit) was the inventor. (*See, e.g.*, FF ¶¶ 122-125; Guy Tr. 571, 574-75; PTX-472; PTX-473; DTX-445 at 20-21; DTX-987; DTX-1091)

For example, Mantelle's '363 patent provides features of a "successful bioadhesive device," including being "sufficiently adhesive" to "maintain close or intimate contact with mucosa for prolonged periods of time" of up to 24 hours. (DTX-987 at 2:4-11) The device of the '363 was also able to "retain the active agent at a rate for sustained or controlled delivery under the conditions prevailing in wet and moist environments associated with mucosa," in addition to being "non-toxic" and not causing irritation. (DTX-987 at 2:12-19; *see also* Guy Tr. 576) The examples described in the '363 patent use the same types of polymers disclosed in the specification of the Patents-in-Suit. (Guy Tr. 589-90) Nevertheless, the '363 patent contains no working example of an estradiol system of any kind,[20] and makes no reference to coat weight, flux, delivery of any drug across any tissue, or duration of release. (*See* FF ¶ 125; Walters Tr. 343; D.I. 216 at 15) Further, the 80-plus examples in the '363 patent demonstrate the vast array of potential adhesive excipients that a POSA would need to evaluate in order to develop a

[20] The '363 patent does identify estrogens as one of the agents that can be topically applied to mucosa for delivery and identifies estradiol as a steroidal estrogen suitable for use with the disclosed bioadhesive compositions. (DTX-987 at 1:23-30, 26:11-12)

transmucosal patch. Even the Patents-in-Suit acknowledge that there were dozens of acrylates and several types and molecular weight variants of PVP – but there is a lack of guidance as to how to choose among them. (FF ¶ 125; Walters Tr. 343; JTX-1 at 7:18-8:64, 9:50-10:21)

Dr. Guy also points to the '244 patent, which describes an estradiol transmucosal system intended for controlled release for up to 24 hours. (Guy Tr. 583) But, as Amneal observes, the '244 patent claims a laminate tablet made in a tablet press, not a monolithic patch; the patent would not provide meaningful guidance to a POSA on how to make a transmucosal patch system. (Walters Tr. 345-46, 433-34; DTX-1089) Additionally, the '244 patent did not report coat weight, estradiol content, or flux, or any mucoadhesive property associated with its tablet. (FF ¶ 122; Walters Tr. 432-34; DTX-1089 at 14:26-15:5 (Example 7), 17:30-18:2 (Example 10))

The van der Bijl (1998 and 2003) references are no more helpful to Noven. Van der bijl 1998 did not test a transmucosal formulation, but instead "used radiolabeled estradiol, tritiated estradiol in solution, so it's not a patch, it's not a mucoadhesive." (Walters Tr. 344; FF ¶ 123) This paper fails to inform a POSA about the flux of a transmucosal estradiol formulation. (Walters Tr. 344-45) Similarly, van der Bijl (2003) does not guide a POSA as to how to design a transmucosal version of the claimed system to achieve the claimed flux. (Guy Tr. 590, 607-09; FF ¶ 123)

Dr. Guy also cited estradiol nasal sprays, buccal films, and vaginal creams, but they, too, would not have provided guidance to a POSA developing the claimed transmucosal adhesive patch systems. (FF ¶ 121; Guy Tr. 571) As Dr. Walters explained, these products were not adhesive, did not have backing layers, did not have coat weights, and would not have been regarded as having a measurable flux. (FF ¶ 121; Walters Tr. 340-42) Dr. Lobo explained that there was no precedent for getting a patch to stick to mucosal tissue for multiple days, and that

patches adhering to the various mucosal tissues would interfere with (and be disrupted by) normal bodily functions, such as sneezing, defecating, and vaginal intercourse. (FF ¶ 139; Lobo Tr. 199-201)

Turning to the quantity of experimentation, the "nature and predictability of the field," and the level of ordinary skill, the Court finds that the development and use of transmucosal patch systems constituted novel, highly unpredictable endeavors at the pertinent time. (*See, e.g.*, FF ¶ 137) Dr. Walters opined persuasively that it would take a lengthy, extensive, and unpredictable trial-and-error experimentation process, involving multiple interrelated formulation factors, to prepare the estradiol transmucosal patches of the claims. (FF ¶¶ 131-132; *see also* Walters Tr. 346-48 (citing JTX-1 at 1:33-49), 348-54, 357 (citing DTX-976 at ACTESTRA59517), 358-60 (citing DTX-1073 at ACTESTRA60962 and DTX-1046 at ACTESTRA60940)) According to Dr. Walters, formulating a transmucosal patch would have required a POSA to have evaluated a series of variables and tradeoffs, such as: (1) which of many known mucoadhesives to use and how much of each; (2) whether to use a solubilizer; (3) how much estradiol to include in the blend; (4) whether the resulting adhesive blend was physically and chemically stable; (5) whether the blend maintained a suitable viscosity; (6) whether the blend achieved the claimed flux; (7) whether the blend had suitable adhesive properties, including strength and duration of adhesion; (8) potential for irritation and for damage upon removal; and (9) what kind of backing to use. (FF ¶¶ 135-136; Walters Tr. 348-54) The amount of iterative trial-and-error experimentation to make the transmucosal version of the invention was unpredictable, and could have taken years – particularly given the different

physiologies of the five different mucosae specifically called out in the claims. (FF ¶ 137; Lobo Tr. 199-201; Walters Tr. 346-47, 351-52, 360)[21]

For his part, Dr. Guy did not analyze the amount of experimentation that would be needed, broadly concluding that it would be no different than the amount of experimentation a POSA would need in order to develop a delivery system for skin. (FF ¶ 133; Guy Tr. 591-96) Noven provided no persuasive reason for the Court to accept Dr. Guy's conclusory opinion. This is especially so because Dr. Guy did not contest Dr. Walters' evidence relating to experimentation, nor did he even opine that the required experimentation would be routine. (FF ¶ 137; Guy Tr. 608) In fact, Dr. Guy agreed with Dr. Walters that obtaining particular flux rates across mucosae would be unpredictable, requiring an unpredictable amount of iterative trial-and-error experimentation and measurement. (FF ¶ 133; Guy Tr. 584-85, 611, 624)

Noven's remaining arguments for enablement are unavailing. Noven cites Mr. Mantelle's successful development of Noven's Dentipatch, an oral transmucosal system designed to deliver lidocaine, which to Noven demonstrates that the inventor did not try and subsequently fail to make the claimed embodiments. (Mantelle II 226-27) The Court agrees with Amneal that DentiPatch did not "provide[] guidance for how to practice the claimed transmucosal patch with sustained delivery of estradiol for systemic administration," for reasons including that "DentiPatch was for the immediate (not sustained) local (not systemic) delivery of

[21] Noven contends that Dr. Walters opined it would only take six to twelve months to make a transmucosal embodiment. (D.I. 215 at 26, 33) As Amneal accurately points out in rebuttal (*see* D.I. 216 at 11), however, this is not a fair characterization of Dr. Walters' opinion, which was actually that ***if*** "just by chance, you're straight lucky and everything . . . falls into place on the first go-round," it would maybe take six to twelve months to develop an embodiment for one mucosa, but even that single embodiment could take double or triple that time "[i]f something goes wrong" and then "[y]ou've got no way of knowing how long that's going to take" (Walters Tr. 351-52).

lidocaine anesthesia during dental work (not estradiol or any kind of hormone)." (D.I. 216 at 16 n.6)

Noven also makes much of its belief that "both transdermal and transmucosal flux [are] quantitatively described and modeled according to Fick's 1st Law of Diffusion." (D.I. 215 at 5) But even accepting this general point as true, the specification is (as already explained) utterly devoid of the type of supporting and specific disclosure required to enable a POSA to apply scientific principles (including Fick's Law) to make and use a transmucosal embodiment.

For all of these reasons, the Court concludes that the Asserted Claims of the Patents-in-Suit are invalid for lack of enablement.

B. Written Description

Amneal has proven that all of the Asserted Claims of the Patents-in-Suit are invalid for failure to satisfy the written description requirement of 35 U.S.C. § 112. Amneal has shown, by clear and convincing evidence, that the patents fail to "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention" – here, a transmucosal patch system. *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) (internal citation omitted).

The Court agrees with Amneal's summary of its written description case:

> The shared specification of the '900, '310, and '319 patents . . . does not provide any example of a transmucosal estradiol system. It does not identify any excipients as being useful for a transmucosal system. It does not discuss mucoadhesion or the coat weight, flux, or estradiol content of any transmucosal system. It does not disclose that the alleged surprising relationship between coat weight and flux when applied to skin holds true for any transmucosal system. Nor does the specification disclose any formulation or design of any transmucosal patch that would achieve the specifically claimed numerical flux range.

(D.I. 191 at 9)

The specification lacks any description or example of a transmucosal estradiol system, including any description or example of any oral, buccal, nasal, rectal, or vaginal patch systems, even though such systems are within the scope of the claims. Aside from the specification's definition of "flux" and "transdermal" (JTX-1 at 5:29-39), the words "oral," "buccal," "nasal," "rectal," or "vaginal" mucosa do not appear in the specification. (JTX-1 at 5:24-39) That essentially the same language appears in the claims and specification does not alter the outcome. The Federal Circuit has "expressly rejected the 'argument that the written description requirement . . . is necessarily met as a matter of law because the claim language appears in *ipsis verbis* in the specification.'" *Nuvo Pharm. (Ireland) Designated Activity Co. v. Dr. Reddy's Laboratories Inc.*, 923 F.3d 1368, 1380 (Fed. Cir. 2019) (citing *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 968 (Fed. Cir. 2002)).

The Court found persuasive Amneal's expert, Dr. Walters, who opined that the specification fails to convey to a POSA the inventor's possession or invention of the claimed transmucosal estradiol patch systems. (FF ¶¶ 95, 100-101; Walters Tr. 333-38, 361) Persuasive, too, was Amneal's clinician, Dr. Lobo, who testified that the information disclosed in the four corners of the specification fails to adequately describe the transmucosal embodiments captured by the claims, and is particularly deficient with respect to transmucosal embodiments that meet the claimed flux range. (Lobo Tr. 177-78, 180, 203, 206)

Transmucosal delivery and formulation is a separate and distinct scientific field from transdermal formulation, each with separate bodies of specialized knowledge and separate technical literature and treatises. (FF ¶¶ 119, 138; Guy Tr. 632; DTX-3600; DTX-5046; DTX-

5049; DTX-5050)[22] Amneal's expert, Dr. Lobo, explained that a POSA would not understand the disclosures in the specification about embodiments for the skin to also relate to the claimed transmucosal systems. (Lobo Tr. 205-06) ("[I]t's totally different; right? So there's nothing to say it would stick, there is nothing to say that it would be the right flux, and there's nothing to say that would be tolerated.") Similarly, Dr. Walters analyzed the specification in detail and credibly explained, based on his significant experience and expertise in transmucosal formulation, that the specification fails to convey possession or invention of the claimed transmucosal estradiol patch systems. (Walters Tr. 333-38, 361)

"[I]t is the specification itself that must demonstrate possession." *Ariad*, 598 F.3d at 1352. Amneal has proven that "an objective inquiry into the four corners of the specification" from the perspective of a POSA results in a conclusion that the inventor did not possess the transmucosal embodiments of the claims. *Id.* at 1351. Accordingly, the Court finds that the specification of the Patents-in-Suit failed to convey with reasonable clarity to a POSA in July 10, 2008 that the inventor actually invented or possessed the oral, buccal, nasal, rectal, or vaginal transmucosal patch systems claimed as part of the Asserted Claims. (FF ¶¶ 95-97)

Noven contends that the specification's references to "bioadhesive polymer" and "adhesive polymer" convey to a POSA that the inventor possessed the claimed transmucosal invention. (D.I. 197 at 19-21 (citing JTX-1 at 5:63-65, 6:3-6; 13:11-13); *see also* Guy Tr. 575) In particular, Noven relies on Mantelle's '363 patent, which is listed on the face of the Patents-in-Suit, and discloses four polymers suitable for use in transmucosal systems that are also seen in the specification of the Patents-in-Suit. (*Compare, e.g.*, JTX-1 at 7:40-43, 7:48-49, 8:17-18,

[22] The Court does not agree with Noven's contention that "Amneal's eleventh hour assertion that transdermal and transmucosal drug delivery are separate fields of art does not merit serious consideration, and is not supported by direct evidence." (D.I. 215 at 31)

8:21-24 *with* DTX-987 at 5:62; JTX-1 at 7:29- 31 *with* DTX-987 at 5:63) These contentions are unavailing for at least all the same reasons they were unavailing in connection with lack of enablement. The term "bioadhesive" is not exclusively associated with mucosa. (*See, e.g.*, JTX-1 at 5:54-58) (disclosing embodiment of patch which "comprises a pressure-sensitive adhesive or bioadhesive, . . . adopted for direct application to a user's (e.g., a subject's) skin"); DTX-987 at 2:56-60 (Noven's '363 patent teaching "bioadhesive composition also serves as pressure-sensitive adhesive suitable for prolonged adherence to . . . dry surfaces, such as skin . . . . ") While the specification provides a broad list of potential bioadhesives, it does not explain what makes them effective or appropriate for transmucosal systems. (FF ¶¶ 100-01, 112; *see also* Walters Tr. 358; Guy Tr. 590) There is a lack of specificity or guidance in the specification relating to the use of any particular polymer or bioadhesive for developing a transmucosal embodiment of the claims. (*See, e.g.*, Walters Tr. 343) ("[I]f you've got a list of about several hundred, maybe even 1,000 different types of acrylate, it would be help[ful] to know which one would be the best one to use, if any.")

Dr. Guy effectively confirmed the invalidity of the patents-in-suit for lack of written description. On cross-examination, he testified that the inventor, Mr. Mantelle, purportedly "possessed" the claimed mucosal invention because he "had the tools required to make that happen" and "possessed all they needed to do that." (FF ¶ 104; Guy Tr. 628-30) However, a specification that conveys possession of nothing more than tools that may be useful to pursue a claimed invention does not convey the required possession of the invention itself. *See Ariad*, 598 F.3d at 1349.

Furthermore, "a description that merely renders the invention obvious does not satisfy the [written description] requirement." *Ariad*, 598 F.3d at 1352. Noven's response to the written

description defense appears to be largely directed to the proposition that a POSA would have found the Asserted Claims obvious[23] – but, even if so, this does not satisfy the written description requirement. *See id.*

Amneal also presented testimony from the inventor, Mr. Mantelle, and from Noven about its actual development work. Noven argues that this evidence is irrelevant. (*See, e.g.*, D.I. 215 at 15) The Court does not agree[24] – for reasons to be explained, the Court finds this evidence corroborates its conclusions – but, even if it did, Noven's argument would not change the outcome. Amneal has met its burden to prove the Asserted Claims invalid for lack of written description even without consideration of the inventor and development evidence.

Mr. Mantelle's testimony confirmed that his invention was never tested, by himself or anyone at or associated with Noven, on oral, buccal, nasal, rectal, or vaginal mucosa. (FF ¶ 102; Mantelle 110-13) Nor was his invention intended for application to any mucosal tissue. (FF ¶ 103; Mantelle 118-19) Mantelle agreed that the formulation of his Example 1 could not be

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[23] The Court agrees with Amneal's characterization of Noven's briefing on written description. As Amneal correctly writes: "Noven's written description argument begins not with the specification, but instead with a thirteen-page narrative of how twenty-two prior art references (only one of which appears in the patents) might possibly be cobbled together to make up for what is lacking in the specification. It reads like what it is – a prior art obviousness argument." (D.I. 216 at 1) (describing D.I. 215 at 3-15)

[24] Noven analogizes this case to *Streck, Inc. v. Research & Diagnostic Systems, Inc.*, 665 F.3d 1269, 1285-87 (Fed. Cir. 2012), in which the Federal Circuit found adequate written description for a claim with multiple embodiments even though the inventor had only reduced to practice one such embodiment. It is true that, in *Streck*, 665 F.3d at 1285, the Federal Circuit stated the written description requirement "does not demand either examples or an actual reduction to practice." However, the lack of an example in the specification "may be considered when determining whether the claimed invention is adequately described," *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011), and, as here, "the mere wish or plan" to obtain the claimed invention is not sufficient to support adequate written description, *Nuvo* 923 F.3d at 1381. Unlike in *Streck*, 655 F.3d at 1286-87, the specification here, which is devoid of meaningful guidance regarding a transmucosal embodiment, fails to demonstrate "a constructive reduction to practice that in a definite way identifies the claimed invention."

applied to mucosa, and he was unaware of any way to predict or correlate transmucosal flux with transdermal flux. (FF ¶ 102; Mantelle II 231-35, 239) Mr. Mantelle's testimony is consistent with that of Noven's 30(b)(6) witness, Mr. Nguyen, who testified that all development work on the project leading to the invention of the Patents-in-Suit was done on skin. (Nguyen Tr. 548-49) Mr. Nguyen, too, was not aware of any way to use the results of transdermal testing to predict transmucosal flux. (FF ¶ 103; Nguyen Tr. 549)

Noven points out that Mr. Mantelle never testified that the transmucosal embodiments of his claims could not be made (*see* Mantelle II 242-44) and focuses on evidence that there was no commercial demand for transmucosal estradiol patches (*see, e.g.*, Lobo Tr. 217; Guy Tr. 595), so the lack of development work may reflect market realities more than lack of possession of the invention. Again, even assuming these points are true, they only reduce the weight to be given to the Mantelle and Nguyen testimony, meaning those two witnesses help Amneal less than they otherwise would. But Noven's points do not come close to reducing Amneal's overall evidentiary showing to something less than clear and convincing evidence.

In sum, the Court concludes that the inventor did not provide a written description that would have demonstrated to a POSA that the inventor actually invented and possessed what he claimed. The record shows, instead, that, in light of everything a POSA would have known (and would not have known) about transmucosal drug delivery systems, a POSA reading the specification would not have understood the inventor of the patents-in-suit to be in possession of the transmucosal embodiments. Thus, the Asserted Claims are invalid.

C. Anticipation Due To On-Sale Bar

Amneal contends that the Asserted Claims are invalid under 35 U.S.C. § 102(b). Amneal's theory is that: (1) Noven offered to sell, and sold, its Vivelle-Dot® products prior to

the July 10, 2007 critical date of the patents-in-suit; and (2) at least one (and perhaps hundreds, thousands, or millions) of Vivelle-Dot® products sold or offered for sale met all the limitations of the Asserted Claims, given manufacturing variability and error tolerances. While there is much evidence to support Amneal's contentions, and most of Noven's criticisms lack merit, Amneal, ultimately, has failed to prove application of the on-sale bar by clear and convincing evidence, largely due to a failure of proof on a key component of Amneal's statistical analysis.

Noven's first response to Amneal's anticipation defense is a belated claim construction argument. Noven contends that the Court must construe "flux" to mean "nominal flux," such that it is the result of a calculation – dividing the daily dose by the active surface area – rather than a measurement. (*See, e.g.*, D.I. 215 at 37-40; Guy Tr. 604-05) As support for its position, Noven relies on the patent specification, the Court's construction of "flux" in prior litigation (*see* DTX-305 (citing *Noven Pharmaceuticals, Inc. v. Actavis Laboratories UT, Inc.*, C.A. No. 18-758-LPS D.I. 176 (D. Del. Aug. 20, 2018)), and Vivelle-Dot®'s label. To Noven, then, the flux of Vivelle-Dot® is and always was 0.01 mg/cm^2/day, which cannot anticipate the Asserted Claims, which require flux to be at least as high as 0.0125 mg/cm^2/day. (Guy Tr. 604-05)

Noven's claim construction position lacks merit. In this case, the Court construed "flux" consistent with the definition given in the specification: "absorption of a drug through skin or mucosal tissue." (D.I. 113 at 2) This was also the construction jointly-proposed by both parties during the claim construction phase of this case. (*See* D.I. 71 (Amended Joint Claim Construction Chart) at Appendix A) There is no basis to limit the concept of flux in relation to the Patents-in-Suit to only "nominal" flux. Instead, the flux limitations may be satisfied (both for purposes of infringement and invalidity) by nominal flux or by actual measured (*in vivo* or *in vitro*) data.

Turning to the evidence Amneal has presented for its anticipation defense, the Court finds that the first part of Amneal's on-sale bar theory is largely undisputed. (*See* FF ¶¶ 140-142) Noven did offer to sell and sold Vivelle-Dot® for years prior to July 10, 2007. Most prominently, in 1999, Noven entered into the Supply Agreement to sell Vivelle-Dot® products to Novartis. (UF ¶¶ 36-37) The inventions of the Asserted Claims of the Patents-in-Suit were ready for patenting prior to the July 10, 2007 critical date because the Vivelle-Dot® product sold and offered for sale under the Supply Agreement was fully described in the Vivelle-Dot® NDA, which the FDA approved a few months prior to the execution of the Supply Agreement with Novartis. (FF ¶ 143; Walters Tr. 382-83, 408-09; DTX-742 at -7446; *see also* DTX-1042 at -3298)

The real dispute for purposes of anticipation is whether, prior to July 10, 2007, any of the Vivelle-Dot® products offered for sale to Novartis and/or sold actually met the coat weight, flux, and estradiol content limitations of the Asserted Claims. If, as Amneal contends, at least one Vivelle-Dot® sold or offered for sale before July 10, 2007 met all three of these claim limitations (the only disputed limitations), that Vivelle-Dot® anticipates the Asserted Claims and the claims are invalid due to the on-sale bar. (D.I. 191 at 31-33) If, alternatively, there is not clear and convincing evidence that at least one such Vivelle-Dot® was sold or offered for sale, then the Asserted Claims have not been proven invalid by application of the on-sale bar.

It is undisputed that no single patch can be tested for estradiol content, coat weight, and flux, and then offered for sale or sold, due to the destructive impact of the tests. (*See, e.g.*, FF ¶¶ 145-146; Marais Tr. 252-53; Walters Tr. 419; Heitjan Tr. 505, 507-08)[25] Therefore, Amneal's

[25] In fact, other than a suggestion raised for the first time in Noven's post-trial briefing, it has always appeared to be agreed between the parties that no single patch could be tested for more than one of the disputed claim limitations: estradiol content ***or*** coat weight ***or*** flux. (*See, e.g.*,

anticipation claim relies on the statistical analysis of its expert, Dr. Marais, who analyzed multiple separate sources of data on the estradiol content, coat weight, and flux of Vivelle-Dot® patches manufactured over various years. (FF ¶¶ 156, 164, 166, 169, 174-77, 186; Marais Tr. 253-55, 258-60, 263-69, 290-91)[26] Then, making certain assumptions and calculations, Dr. Marais purported to calculate the likelihood that at least a single Vivelle-Dot® patch met all the disputed limitations prior to the critical date. (FF ¶ 147) In Dr. Marais' opinion, depending on the particular asserted claim, millions or hundreds of thousands of Vivelle-Dot® patches sold or offered for sale met all the limitations of the '419 patent, while hundreds or thousands of Vivelle-Dot® patches met all the limitations of the '900 and '310 patents. (*See, e.g.*, Marais Tr. 250-52, 277-79; Walters Tr. 410; DTX-1040; JTX-9 at 003)

Most of Noven's critiques of this approach are unpersuasive. Noven devotes a great deal of attention to identifying deficiencies in Amneal's claim of "inherent anticipation" (*see, e.g.*, D.I. 215 at 35-37, 52-54), but Amneal's theory is ***not*** one of inherent anticipation (*see, e.g.*, D.I. 216 at 25). Similarly, Noven contends that Amneal cannot prove anticipation through "probabilities" or "likelihood" (*see* D.I. 216 at 34, 43), but, again, that is not what Amneal is

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Guy Tr. 58-69 (Dr. Guy testifying that Amneal uses a standard coat weight testing procedure, that takes and averages multiple measurements on each of multiple 7.55 cm^2 coupons from each section of the laminate roll); Walters Tr. 386-87, 390-91 (Walters testifying that Noven uses a similar standard multi-coupon averaging approach); *see also* DTX 1045 at NPC-MNV-4529) Yet in its post-trial brief, Noven suggests that a single patch could be cut and different pieces of that single patch could each be tested for a different characteristic. (*See* D.I. 215 at 42 n.29) As Amneal correctly points out, however, there is no evidence in the record to support this contention. (*See* D.I. 216 at 23-24)

[26] The sources of data for the statistical analysis include Noven's Vivelle-Dot® batch records submitted as part of its NDA, 27 *in vitro* flux studies conducted by Noven (for purposes of calculating the flux of Minivelle®, for which Vivelle-Dot® was used as a control), and *in vivo* flux data Noven generated for Vivelle-Dot®. (*See, e.g.*, Marais Tr. at 264-65, 302; Walters Tr. 390-98; Heitjan Tr. 493-94, 501; Nguyen Tr. 548-52; DTX-667; DTX-1044 at -3870, -3880, -3900-01; DTX-1045 at -4475, -4480, -4460, -4518-58)

doing. Instead, Amneal aimed to prove, through statistical methods and probabilities, that it is ***certain*** at least one Vivelle-Dot® patch sold or offered for sale prior to the critical date did, in fact, meet all the disputed limitations of the Asserted Claims of the Patents-in-Suit. This is a legally permitted and reasonable approach. *See generally Atl. Thermoplastics Co. v. Faytex Corp.*, 970 F.2d 834, 836 (Fed. Cir. 1992) ("A single sale or offer to sell suffices to bar patentability."). The Court also agrees with Amneal that it was not inappropriate for Dr. Marais to consider data from Vivelle-Dot® lots manufactured after the critical date and lots that may not have been shipped to Novartis because the evidence shows that Noven never changed its formulation or manufacturing process for Vivelle-Dot®. (*See* D.I. 191 at 47) (citing evidence) Each lot appears to be representative of the Vivelle-Dot® actually sold and offered for sale. Also, the purported "heavy weighting" of Dr. Marais' analysis (*see, e.g.*, Heitjan Tr. 483-88) does not trouble the Court, as it seems to be an efficient way to approach the task of determining whether more than zero patches met all three disputed claim limitations. A "biased sample" might be a problem if it were necessary to determine the quantity of anticipating patches, but it is not a problem in answering the relevant question of whether at least one such patch was sold or offered for sale.[27]

The one criticism of Dr. Marais' analysis which the Court credits, and finds defeats Amneal's effort to prove anticipation by clear and convincing evidence, is the failure to prove that meeting each of the three disputed claim limitations – estradiol content, coat weight, and flux – are "independent events" from a statistical perspective. As Dr. Heitjan persuasively

[27] If, hypothetically, the record contained perfect measurements of the estradiol content, coat weight, and flux of each individual Vivelle-Dot® manufactured in a particular batch, it would be valid to say the Asserted Claims are anticipated if a single patch in that particular batch met all of those claims' limitations – regardless of whether that batch was representative of all Vivelle-Dot® patches sold or offered for sale.

testified, if estradiol content, coat weight, and flux are not each statistically independent of one another, one cannot determine the statistical likelihood of a single patch meeting all three requirements by simply multiplying together the estimated probabilities of each of these three events separately. (FF ¶¶ 147-150; Heitjan Tr. at 523)[28] On the record before the Court, there is no way to determine whether satisfaction of the estradiol content, coat weight, and flux limitations are all statistically independent of one another. (FF ¶¶ 147-50; *see also* D.I. 215 at 60) More to the point, Amneal has failed to prove by clear and convincing evidence that all three are independent of one another.[29] Therefore, Dr. Marais' opinions – which are based on multiplying the likelihoods of the three events times one another based on an unproven assumption they are statistically independent events – does not prove, by the required clear and convincing evidence, that at least a single Vivelle-Dot® patch meeting all three requirements was sold or offered for sale.

Thus, the Court finds that Amneal has failed to meet its burden of proving the Asserted Claims are invalid under 35 U.S.C. § 102(b) due to Noven's offer for sale and sale of Vivelle-Dot®.

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[28] Dr. Heitjan acknowledged that it could be possible to calculate the probability that a test sample with a given coat weight also met the required flux and estradiol limitations, but explained that "heroic assumptions [would be] involved" given the limitations of the data sets in the record. (Heitjan Tr. at 526)

[29] Indeed, to the contrary, the specification's disclosure that the inventor surprisingly discovered that increasing coat weight results in increased flux seems to suggest a lack of independence (at least between coat weight and flux). (*See* JTX-1 at 3:58-4:2; *see also* Dash Tr. 40 (Amneal's expert agreeing POSA would understand this relationship from specification))

CONCLUSION

Noven has met its burden to prove, by a preponderance of the evidence, that Amneal's proposed ANDA Product literally infringes the Asserted Claims of the '419 patent. However, Noven has failed to prove infringement of its '900 and '310 patents. For these latter patents, Noven only asserts infringement under the doctrine of equivalents, but prosecution history estoppel precludes Noven from prevailing on a DOE theory. In any event, Noven also failed to present evidence that would prove, by a preponderance of the evidence, that Amneal's ANDA Product meets the coat weight limitation by application of either the function-way-result test or the insubstantial differences test.

With respect to invalidity, Amneal has met its burden to prove, by clear and convincing evidence, that all of the Asserted Claims of the '419, '900, and '310 patents are invalid, both for lack of enablement and lack of adequate written description. Amneal has failed to prove that any of the Asserted Claims are also invalid due to anticipation and application of the on-sale bar.

An appropriate Order follows.