IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UCB, INC., UCB MANUFACTURING IRELAND LIMITED, UCB PHARMA GMBH, and LTS LOHMANN THERAPIE-SYSTEME AG,	:	
Plaintiffs,	:	
v.	:	C.A. No. 14-1083-LPS-SRF **REDACTED PUBLIC VERSION**
WATSON LABORATORIES, INC. and ACTAVIS LABORATORIES UT, INC.,	:	
Defendants.	:	

Jack B. Blumenfeld, Maryellen Noreika, Derek J. Fahnestock, Michael J. Flynn, and Eleanor G. Tennyson, MORRIS, NICHOLS, ARSHT & TUNNELL LLP, Wilmington, DE

James S. Trainor, Jr., Kevin X. McGann, Robert E. Counihan, and Silvia Medina, WHITE & CASE LLP, New York, NY

Attorneys for Plaintiffs.

Melanie K. Sharp, James L. Higgins, and Robert M. Vrana, YOUNG CONAWAY STARGATT & TAYLOR, LLP, Wilmington, DE

Leora Ben-Ami, Thomas F. Fleming, Christopher T. Jagoe, and Mark C. McLennan, KIRKLAND & ELLIS LLP, New York, NY

Alyse Wu, KIRKLAND & ELLIS LLP, Chicago, IL

Noah Frank, KIRKLAND & ELLIS LLP, Washington, DC

Attorneys for Defendants.

MEMORANDUM OPINION

November 14, 2017
Wilmington, Delaware

STARK, U.S. District Judge:

This patent infringement action is brought by Plaintiffs UCB, Inc., UCB Manufacturing Ireland Limited, UCB Pharma GMBH, and LTS Lohmann Therapie-Systeme AG (collectively, "UCB" or "Plaintiffs") under the Hatch-Waxman Act. Plaintiffs filed suit against Defendants Watson Laboratories, Inc. and Actavis Laboratories UT, Inc. (collectively, "Actavis" or "Defendants"), which submitted an Abbreviated New Drug Application ("ANDA") to market a generic version of Neupro®, a patch for transdermal delivery of rotigotine for treatment of Parkinson's disease. (D.I. 61 at ¶ 1) Plaintiffs assert U.S. Patent Nos. 6,884,434 and 8,232,414. The '434 patent is listed in the Orange Book and generally describes and claims transdermal systems containing rotigotine as a free base for treatment of Parkinson's disease. The '414 patent claims a certain polymorphic form of rotigotine.

This case began before the Honorable Sue L. Robinson, who is now retired. Before Judge Robinson, the parties stipulated to constructions for certain claim terms in the patents-in-suit. (D.I. 111) To resolve disputes as to the proper construction of any claim terms, the Court held a claim construction hearing on December 4, 2015 and issued a claim construction memorandum order on January 8, 2016. (D.I. 120) The case was then reassigned on December 21, 2016.

In June 2017, the Court held a four-day bench trial. (*See* D.I. 243-47 ("Tr.")) The parties submitted a Statement of Uncontested Facts ("SUF") (D.I. 211 Ex. 1) and competing versions of proposed findings of fact. (D.I. 236, 239, 255, 256) The parties also submitted extensive post-trial briefing. (D.I. 237, 238, 254, 257, 262, 263)

Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire record in this case and the applicable law, the Court concludes that: (1) Actavis infringes claims 1,

5, 7, 14, and 15 of the '434 patent; (2) claim 1 of the '434 patent is not invalid due to anticipation; (3) claims 1, 5, 7, 14, and 15 of the '434 patent are not invalid due to obviousness; (4) claims 1-3 of the '414 patent are not invalid due to derivation or inherent anticipation; and (5) claims 1-3 of the '414 patent are invalid under § 102(a) because the claimed invention was in use in the United States before its priority date.

FINDINGS OF FACT

This section contains the Court's findings of fact ("FF") on disputes raised by the parties during trial, as well as facts to which the parties have stipulated. Certain findings of fact are also provided in connection with the Court's conclusions of law.

A. The Parties

1. Plaintiff UCB, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 1950 Lake Park Drive, Smyrna, Georgia 30080. (SUF ¶ 1)

2. Plaintiff UCB Manufacturing Ireland Limited is a corporation organized and existing under the laws of Republic of Ireland, having an office and place of business at Shannon Industrial Estate, Shannon, Co. Clare, Ireland. (SUF ¶ 2)

3. Plaintiff UCB Pharma GmbH is an entity organized and existing under the laws of the Federal Republic of Germany, having a place of business at Alfred-Nobel-Strasse 10, Monheim, Germany. (SUF ¶ 3)

4. Plaintiff LTS Lohmann Therapie-Systeme AG ("LTS") is a corporation organized and existing under the laws of the Federal Republic of Germany, having an office and place of business at Lohmannstrasse 2, 56626 Andernach, Germany. (SUF ¶ 4)

5. Defendant Watson Laboratories, Inc. is a corporation organized and existing under the laws of the State of Nevada, having places of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, NJ 07054, and at 311 Bonnie Circle, Corona, CA 92880. (SUF ¶ 5)

6. Defendant Actavis Laboratories UT, Inc., formerly known as Watson Laboratories, Inc., is a corporation organized and existing under the laws of the State of Delaware, having places of business at 575, 577, and 579 Chipeta Way, Salt Lake City, Utah. (SUF ¶ 6)

B. Neupro

7. Plaintiff UCB, Inc. holds approved New Drug Application No. 0212829 ("NDA") for Rotigotine Transdermal System (1 mg/24 hours, 2 mg/24 hours, 3 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, and 8 mg/24 hours), which Plaintiffs sell under the trade name Neupro. (SUF ¶ 7)

8. Neupro is FDA-approved for the treatment of Parkinson's disease and moderate-to-severe primary Restless Leg Syndrome. (SUF ¶ 8)

9. The FDA first approved Neupro in May 2007 for the treatment of signs and symptoms of early stage idiopathic Parkinson's disease. Following manufacturing process changes and additional clinical trials, in April 2012, the FDA approved a new formulation of Neupro for the treatment of the signs and symptoms of advanced stage idiopathic Parkinson's disease and for the treatment of moderate-to-severe Restless Leg Syndrome. Multiple patents, including asserted U.S. Patent No. 6,884,434, are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to Neupro. (SUF ¶ 9)

C. Patents-in-Suit

i. The '434 Patent

10. The '434 patent issued on April 26, 2005 and is entitled "Transdermal therapeutic system which contains a d2 agonist and which is provided for treating Parkinsonism, and a method for the production thereof." (SUF ¶ 10) The '434 patent issued from U.S. Patent Application No. 09/647,290, filed on November 29, 2000. The '434 patent claims priority to German Application No. DE 198 14 084, through PCT/E99/01795, and claims a priority date of March 30, 1998. (SUF ¶ 14) The '434 patent names Walter Mueller and James V. Peck as inventors. (SUF ¶ 11) Plaintiffs UCB Ireland and LTS are assignees of the '434 Patent. (SUF ¶ 12)

11. Plaintiffs assert claims 1, 5, 7, 14, and 15 of the '434 patent against Defendants. (SUF ¶ 12) The asserted claims are reproduced below:

> 1. A transdermal therapeutic system comprising a self-adhesive matrix layer containing the free base (–)-5,6,7,8-tetrahydro-6-[propyl-1[2-(2-thienyl)ethyl]amino]-1-naphthalenol in an amount effective for the treatment of the symptoms of Parkinson's syndrome, wherein the matrix is based on a [sic] an acrylate-based or silicone-based polymer adhesive system having a solubility of 5% (w/w) for the free base (–)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol, all of said free base being present in the matrix in the absence of water; a backing layer inert to the components of the matrix layer; and a protective foil or sheet covering the matrix layer to be removed prior to use.
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> 5. The transdermal therapeutic system of claim 1 wherein the silicone-based polymer adhesive in the matrix layer further comprises additives to enhance the solubility of (–)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol in the form of hydrophilic polymers or glycerol or glycerol derivatives.
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> 7. The transdermal therapeutic system of claim 5 wherein the silicone-based polymer adhesive contains between 5 to 25% (w/w) (–)-5,6,7,8-tetrahydro[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol.

14. The transdermal therapeutic system of claim 5, wherein the hydrophilic polymer is selected from the group of polyvinylpyrrolidone, a copolymer of vinylpyrrolidone and vinylacetate, polyethyleneglycol, polypropylene glycol, and a copolymer of ethylene and vinylacetate.

15. The transdermal therapeutic system of claim 14 wherein the hydrophilic polymer is soluble polyvinylpyrrolidone, and wherein the soluble polyvinylpyrrolidone is present in the active substance-containing matrix layer at a concentration of between 1.5 and 5% (w/w).

ii. The '414 Patent

12. The '414 patent issued on July 31, 2012 and is entitled "Polymorphic form of rotigotine and process for production." (SUF ¶ 20) The '414 patent issued from U.S. Patent Application No. 12/324,166, which was filed on November 26, 2008 and claims a priority date of November 28, 2007. (SUF ¶ 24) The '414 patent names Hans Michael Wolff, Luc Quere, and Jens Riedner as inventors. (SUF ¶ 21) Plaintiff UCB Pharma is the assignee of the '414 patent. (SUF ¶ 22)

13. Plaintiffs assert claims 1-3 of the '414 patent against Defendants. (SUF ¶ 23) The asserted claims are reproduced below:

1. A polymorphic form of rotigotine characterized by at least one parameter selected from the group consisting of:

(a) a powder X-ray diffraction spectrum comprising at least one peak at the following ° 2θ angles (±0.2): 12.04, 13.68, 17.72, and 19.01;

(b) a Raman spectrum comprising at least one peak at the following (±3 cm-1): 226.2, 297.0, 363.9, 737.3, 847.3, 1018.7, and 1354.3 cm-1

(c) a DSC peak with a T_{onset} at 97° C.±2° C. measured with a heating rate of 10°/min; and

(d) a melting point of 97° C.±2° C.

2. The polymorphic form of rotigotine of claim 1, wherein the polymorphic form of rotigotine is characterized by at least the following powder X-ray diffraction peaks at ° 2θ angles (±0.2): 12.04, 13.68, 17.72 and/or 19.01.

3. A polymorphic form of rotigotine having a powder X-ray diffraction spectrum substantially as shown in FIG. 1.

D. Actavis' ANDA

14. On or around November 26, 2013, Watson (now Actavis) submitted Abbreviated New Drug Application No. 206348 ("Actavis ANDA") to the FDA, pursuant to 21 U.S.C. §§ 355(j), seeking approval to market a generic version of Rotigotine Transdermal System (1 mg/24 hours, 2 mg/24 hours, 3 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, and 8 mg/24 hours) ("ANDA products"). (SUF ¶ 35)

15. Actavis' ANDA refers to and relies upon the Neupro NDA and contains data that demonstrates that the ANDA products are bioequivalent to Neupro. (SUF ¶ 36)

16. Defendants included certifications in the Actavis ANDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that the '434 patent, among others, is invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of the ANDA products. (SUF ¶ 37)

17. On July 8, 2014, Actavis sent notice of its Paragraph IV certifications to Plaintiffs, providing its asserted factual and legal bases for its contentions that, among others, the '434 patent is not infringed and is invalid or unenforceable. (SUF ¶ 38)

18. Actavis' proposed ANDA products are Rotigotine transdermal systems designed to be a generic version of Neupro. Actavis' ANDA products come in six strengths – 1 mg, 2 mg, 3 mg, 4 mg, 6 mg and 8 mg – which are the same strengths as Neupro. Actavis seeks approval to

market its ANDA products for purposes set forth in Actavis' proposed label, which it has submitted to the FDA. (SUF ¶ 39)

19. The composition of Actavis' rotigotine patch is the same for all strengths. (SUF ¶ 41)

20. [redacted] (SUF ¶ 42)

E. Witnesses

i. Fact Witnesses

21. Dr. Hans-Michael Wolff testified by deposition. Dr. Wolff was a longtime scientist at Schwarz Pharma Monheim and is a named inventor on the '414 patent. (Wolff Tr. at 76)[1]

22. Dr. Johannes Leonhard testified by deposition. Dr. Leonhard is a scientist at LTS who worked on rotigotine transdermal patches with Dr. Mueller. (Leonhard Tr. at 97)

23. Dr. Marco Emgenbroich testified by deposition. Dr. Emgenbroich is a scientist at LTS and was designated as LTS' Rule 30(b)(6) witness. (Emgenbroich Tr. at 114)

24. Neal Hermanowicz, M.D., was called by Plaintiffs to testify at trial as a fact witness on Parkinson's disease. Dr. Hermanowicz is a neurologist and a professor of neurology at the University of California, Irvine. (Hermanowicz Tr at 233)

25. Dr. Luc Quere was called by Plaintiffs to testify at trial as a fact witness. Dr. Quere is employed at UCB and is a named inventor on the '414 patent. (Quere Tr. at 269)

26. Dr. Walter Mueller was called by Plaintiffs to testify at trial as a fact witness. Dr.

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[1]Trial testimony is cited as "([Witness last name] Tr. at [page number])."

Mueller is retired from his former employment at LTS, where he worked for 27 years. (Mueller Tr. at 311) Dr. Mueller is a named inventor on the '434 patent. (Mueller Tr. at 311)

27. Dr. James Peck testified by deposition. Dr. Peck is a named inventor on the '434 patent and was a scientist at Discovery Therapeutics, Inc. (Peck Tr. at 509)

ii. UCB's Experts

28. Dr. Allan Myerson, Plaintiffs' expert on validity, received a B.S. degree in chemical engineering from Columbia University in 1973, and a M.S. and a Ph.D. in chemical engineering from the University of Virginia in 1975 and 1977, respectively. (Myerson Tr. at 368) Dr. Myerson is a professor of chemical engineering at MIT. (Myerson Tr. at 368) Dr. Myerson was recognized as an expert in the fields of crystallization and crystallization of pharmaceutical solids, polymorphism, and pharmaceutical manufacturing. (Myerson Tr. at 371)

29. Dr. Majella Lane, Plaintiffs' expert on infringement and validity, received a bachelor's degree in pharmacy in 1992 and a Ph.D. in pharmaceutics at Trinity College Dublin. (Lane Tr. at 604) Dr. Lane is a senior lecturer at the University College London's School of Pharmacy and also the director of the Skin Research Group. (Lane Tr. at 605) Dr. Lane was recognized as an expert in the field of pharmaceutical formulations, including those for transdermal delivery. (Lane Tr. at 607)

30. Dr. Alexander Klibanov, Plaintiff's expert on infringement, received a master's degree in Chemistry in 1971 and Ph.D. in Chemical Enzymology in 1974, both from Moscow University in Russia. (Klibanov Tr. at 738) Dr. Klibanov is currently the Novartis Endowed Chair Professor of Chemistry and Bioengineering at MIT. (Klibanov Tr. at 738) Dr. Klibanov was recognized as an expert in chemistry and pharmaceutical formulation. (Klibanov Tr. at 739-

40)

iii. Actavis' Experts

31. Dr. Robin D. Rogers, Defendants' invalidity expert, received a B.S. degree in chemistry in 1978 and a Ph.D. degree in chemistry in 1982 from the University of Alabama. (Rogers Tr. at 134; DTX-659) He has conducted research in solid-state chemistry, x-ray crystallography, and spectroscopy to characterize solids. He has won numerous awards including the EPA, President Green Chemistry Award in 2005, and the ACS Award in Separations Science and Technology. (Rogers Tr. at 135; DTX-659) Dr. Rogers was recognized as an expert in the field of solid state chemistry, polymorphisms, and their applications to pharmaceutical products. (Rogers Tr. at 136)

32. Dr. Russell Potts, Defendants' invalidity expert, holds a Ph.D. in biochemistry and completed a post-doctoral fellowship in the Chemistry Department at Yale University. (Potts Tr. at 525; DTX-660) Dr. Potts has almost 30 years of experience in the pharmaceutical industry, specifically with transdermal drug delivery systems, including being involved in the development of commercial transdermal products. (Potts Tr. at 525) Dr. Potts was recognized as an expert in areas of chemistry, pharmaceutical formulations, pharmaceutical development, and transdermal drug delivery patches and devices. (Potts Tr. at 526)

33. Dr. George Gokel, Defendants' infringement expert, received a B.S. from Tulane University in 1968 and a doctorate from the University of Southern California in 1971. (Gokel Tr. at 795; DTX-302) He is a member of the Biophysical Society, the American Chemical Society, a Fellow of the American Association of the Advancement of Sciences, and Fellow of the National Academy of Inventors. (Gokel Tr. at 795-96) Dr. Gokel is currently a Distinguished Professor at

the University of Missouri, St. Louis, teaching courses including organic chemistry and drug delivery. (Gokel Tr. at 796) Dr. Gokel was recognized as an expert in the area of chemistry, bio-organic chemistry, supra-molecular chemistry, and pharmaceutical product development. (Gokel Tr. at 797)

F. Person of Ordinary Skill in the Art

34. The parties offered competing definitions of a person of ordinary skill in the art ("POSA") with respect to the '414 patent. (*See* D.I. 211 Ex. 2 at 14-15, Ex. 3 at 14-16) All experts stated that their opinions would not change if the other party's definition of a POSA were applied. (Potts Tr. at 537; Lane Tr. at 615; Rogers Tr. at 149; Myerson Tr. at 373) Therefore, while the Court lists below the parties' differing proposals, the Court need not make a finding as to whether Plaintiffs or Defendants are correct in their description of the POSA with respect to the '414 patent.

35. Plaintiffs define the POSA for the subject matter of the '414 patent as someone who "would have a B.S. in chemistry, chemical engineering, or a related discipline with three or more years of experience related to crystallization, polymorphism or pharmaceutical manufacturing . . . . One of skill also could be someone with an advanced degree (e.g., a Ph.D. or Masters) in these same fields with less experience." (D.I. 211 Ex. 2 at 14-15)

36. Defendants' definition of a POSA for the '414 patent is a person who "holds degrees in one of the pharmaceutical sciences, which includes chemistry, medicinal chemistry, or a related field. Their experience would depend upon their degree. A POSA would have an understanding of polymorphs and how they are important in the pharmaceutical industry. Techniques such as melting point, DSC, Raman spectroscopy, and XRPD were routine to a

POSA." (D.I. 236 at ¶ 13) (internal citations omitted)

37. With respect to the '434 patent, Plaintiffs use the POSA definition offered by Actavis' expert, Dr. Potts. (D.I. 239 at ¶ 3) Accordingly, the Court adopts the undisputed definition of a POSA for the '434 patent as being "someone with a background and experience in transdermal drug delivery devices, [as well as] a Ph.D. in this area with a few years of experience." (Potts Tr. at 537; Lane Tr. at 615)

G. Facts Relating to Validity of the '414 Patent

i. Inventorship

38. UCB's Neupro patch, a transdermal delivery system of rotigotine, was originally approved by the FDA in May 2007 and then launched in July 2007. (DTX-172 at 27; Rogers Tr. at 139)

39. In 2007, LTS manufactured Neupro under a supply agreement with UCB. (DTX-461 at 23; PTX-456 at 1; Quere Tr. at 304) LTS used rotigotine supplied by a third-party, Cambrex Karlskoga (Sweden) ("Cambrex"). (DTX-461 at 5; Mueller Tr. at 352) Each production run resulted in a large, dried laminate sheet from which individual Neupro patches of various sizes were punched out and packaged. (DTX-411 at 5-6; DTX-461 at 32; DTX-452 at 6)

40. As of August 2007, the manufacturing process for Neupro patches at LTS involved the initial step of dissolving rotigotine in ethanol at room temperature. (DTX-411 at 5; Wolff Tr. at 86)

41. On August 7, 2007, LTS was using Cambrex's rotigotine batch 16208652 (LTS lot 7769396). (DTX-391 at 2; PTX-231 at 1) During a Neupro manufacturing run a massive precipitation of rotigotine from ethanol occurred. (DTX-412 at 9; DTX-299 at 1; DTX-256 at 6-7;

DTX-408 at 2-3; Rogers Tr. at 180-83) This precipitation required LTS to stop the manufacturing process; the same process has never been used since then. (Mueller Tr. at 332-33)

42. LTS immediately informed Dr. Wolff at UCB of the event. (Wolff Tr. at 77-78; Mueller Tr. at 334) Dr. Wolff was a project leader at UCB and led UCB's investigation into the precipitation event. (Wolff Tr. at 78) Dr. Wolff began investigating and was at LTS almost every day. (Wolff Tr. at 91)

43. At the time of the precipitation event, LTS did not know what the precipitate was nor how it occurred. (Mueller Tr. at 332-34; Myerson Tr. at 392) LTS scientists began conducting laboratory tests on the precipitate on the afternoon of August 7, 2007 to determine whether the precipitate was rotigotine (DTX-408 at 8; DTX-256 at 6-7; DTX-299 at 1), which included making solubility observations (DTX-556 at 8-14) and taking a melting point (Emgenbroich Tr. at 116-17). LTS gave a sample of the precipitate to Dr. Wolff at UCB (Myerson Tr. at 493) and, in the following days, UCB also began conducting research on the precipitate. (Quere Tr. at 266-67; Wolff Tr. at 91)

44. On August 13, 2007, six days after the precipitation event, UCB and LTS had a meeting to discuss their findings. (DTX-145; Mueller Tr. at 335-37) By the time of the meeting, LTS had determined that the precipitate "is chemically identical to the Rotigotine base but [] has melting points that are higher by 20-25K" and has a lower solubility in ethanol than rotigotine Form I. (DTX-145 at 2) UCB "presented the results of the DSC testing on samples provided by LTS," which confirmed "the suspected existence of a new modification" of rotigotine, labeled Form II. (DTX-145 at 15) At that time, the scientists suspected that Form II was a polymorph or a solvate of rotigotine but did not know for certain. (Mueller Tr. at 355; Wolff Tr. at 78)

45. On August 22, 2007, UCB issued technical report No. 570/00, entitled "Investigations on a New Polymorph of Rotigotine," which contained results from differential scanning calorimetry ("DSC") testing and x-ray powder diffraction ("XRPD") analysis of the new polymorph. (DTX-409; PTX-231) UCB issued supplemental technical report No. 613/00 on September 21, 2007, which included Raman spectra of the new Form II. (PTX-295)

46. By September 23, 2007, Dr. Quere obtained a single crystal of Form II, from which he was able to use single crystal x-ray diffraction to determine the crystal structure of Form II. (PTX-239; Quere Tr. at 269-71) A theoretical XRPD spectrum was also calculated from this structure, and it matched the XRPD spectrum obtained earlier. (PTX-239) The single crystal x-ray study definitively confirmed, for the first time, that Form II was a pure polymorph of rotigotine, not a solvate or anything else. (Quere Tr. at 269-71; Myerson Tr. at 397)

47. By September 24, 2007, Jens Riedner Lynch at UCB conducted an experiment that allowed him to reproduce Form II rotigotine via prolonged storage inside an aluthene bag. (PTX-241; Myerson Tr. at 398) This experiment corresponds to "Preparation Example 1" of the '414 patent. (PTX-2 at col. 6 ll. 34-42) On or around October 30, 2007, Dr. Riedner Lynch made Form II of rotigotine using an ethanol slurry; this corresponds to "Preparation Example 2." (PTX-244; Myerson Tr. at 398; Wolff Tr. at 94; PTX-2 at col. 6 ll. 44-67) These were the first methods for making Form II that did not require starting with a Form II sample. (Myerson Tr. at 372; PTX-244) The work conducted by UCB culminated in the filing of a patent application on November 28, 2007 that would later issue as the '414 patent. (PTX-2)

48. Although LTS was involved in the initial experiments involving Form II, LTS did not perform the necessary characterization tests to determine the existence of a new polymorph of

rotigotine. (Wolff Tr. at 78-79, 93; Mueller Tr. at 334-35, 337)

49. Polymorphs are the same chemical compound with different crystal structures. (Rogers Tr. at 147; Myerson Tr. at 374-75) Solvates and hydrates are not considered polymorphs. (Myerson Tr. 376-77)

50. Visual melting point, DSC, XRPD, and HPLC do not permit one to identify definitively a new polymorphic form. (Myerson Tr. at 39295) For example, HPLC is a technique used to determine purity, but because a material is dissolved in a solution to perform an HPLC experiment, it cannot establish that the material in the solid form exists (or does not exist) as a solvate or a hydrate. (Myerson Tr. at 392-93) Therefore, HPLC cannot establish that a new solid form is a polymorph. (Myerson Tr. 392-93) Similarly, a visual melting point analysis does not distinguish solvates or hydrates from polymorphs. (Myerson Tr. at 393) Further, neither DSC nor XRPD can prove the existence of a new polymorphic form, as they cannot eliminate, for example, solvates. (Myerson Tr. at 394-95) Taking together all the data of the types described here allow a POSA to conclude if she has a new solid form, but not whether that new solid form is a polymorph or a solvate. (Myerson Tr. at 393)

51. The experiment that definitively characterizes a solid form is single-crystal x-ray diffraction, from which a three-dimensional model of the crystal structure can be built. (Myerson Tr. at 388, 397; Quere Tr. at 270-71)

ii. Use Before the Priority Date

52. According to Table 5 of UCB's Technical Report, "Batch Overview of Rotigotine Patches," laminate lots 47806, 47807, and 47808 were manufactured in June and July 2007 from Cambrex rotigotine batches 16208651 and 16208652. (DTX-457 at 19; Rogers Tr. at 176;

DTX-418 at 3-5) Cambrex batch 16208652 is also referred to as LTS batch 7769396. (PTX-231 at 1)

53. Cambrex rotigotine batches 16208650, 16208651, and four containers of 7769396 had a low chloride content, and Form II appeared in these batches. (DTX-384 at 24; Myerson Tr. at 475-76)

54. After observing "snow-flake like" crystals in Neupro patches in the U.K., UCB (then Schwarz Pharma) submitted an NDA Field Alert Report on November 12, 2007 to the FDA. (DTX-139 at 5) The Field Alert Report indicates that testing had confirmed on November 7, 2007 that the snowflakes were Form II crystals. (DTX-139 at 5; Rogers Tr. at 172) The Field Alert Report identified problems with Neupro lot numbers 108547 and 47808502. (DTX-139 at 5; Rogers Tr. at 172) In the Report, UCB told the FDA that "remaining inventory of the impacted lots has been placed on hold." (DTX-139 at 6; Myerson Tr. at 500)

55. In an attachment to the Field Alert Report, UCB further reported that "four batches of patches, manufactured from a common batch of API, . . . contain a polymorph variant (Form 2)." (DTX-139 at 7) In a separate attachment, UCB reported that "[t]he concerned batch number was produced from laminate batch number 47808" and that "[f]urther investigation has shown that the snowflake-like alterations in the titration kit patches have crystalline structures of a new polymorph (form 2) of the API rotigotine." (DTX-139 at 8; Rogers Tr. at 172-74) Using a visual inspection of patches, UCB consistently found crystals. (DTX-139 at 10) For batches specifically manufactured for distribution in the United States – lots 47808101, 47808117, and 47808501/502 (DTX-418 at 6) – a significant number of patches contained crystals. (DTX-139 at 10) For example, in finished product 47808501/502 (made from laminate batch 47808), snowflakes were

observed in 48 out of 50 patches examined. (DTX-139 at 10; Rogers Tr. at 173-74) Similarly, 50 out of 50 patches from lot 47808101 contained snowflakes, and 41 out of 50 patches from lot 47808117 did. (DTX-139 at 10) Third-party XRPD analysis also detected Form II rotigotine in a Neupro patch sold in Europe. (DTX-446 at 6-7; Rogers Tr. at 175-76)

56. Neupro patches from laminate lot 47808 were sold and used in the U.S. prior to November 28, 2007. UCB records list lot 47808501/502 as a commercial packing run for the U.S. (DTX-418 at 5-6) FDA records show that a female patient purchased Neupro lot 47808 (DTX-701 at 5-6) from a pharmacy in the U.S. in November 2007. (DTX-701 at 4) Her use of this lot led to problems described as "back-sliding," and she reported that an adverse event occurred on November 30, 2007. (DTX-701 at 4-5)

57. Dr. Rogers testified on the thermodynamics of rotigotine in Neupro and concluded that all patches made from laminate lot 47808 contained some amount of Form II rotigotine. (Rogers Tr. at 174; DTX-139 at 10) Even if visual inspection of patches did not find snowflakes, some smaller crystals were still present. (Rogers Tr. at 174)

58. In a Defective Product Report dated March 17, 2008, UCB reported to the European Medicines Agency that all finished products from laminate lots 47806, 47807, and 47808 were affected. (DTX-649 at 2; Rogers Tr. at 175) As with laminate lot 47808, laminate lots 47806 and 47807 were made from Cambrex rotigotine with low chloride content and then used to make patches in commercial packing runs for the U.S. (DTX-418 at 3-4)

59. On March 17, 2008, UCB informed the FDA that it was proposing "to initiate a recall of all remaining affected patch lots currently in commercial distribution." (DTX-172 at 11) UCB explained that the crystal growth of Form II in some patches from laminate 47807 resulted in

failure to meet drug release requirements and that product "manufactured from the same laminate (807) was distributed" in the U.S. (DTX-172 at 9)

60. According to UCB's 2008 FDA submission, Neupro patches were identified that "contain a crystal formation identified as polymorphic form 2 of rotigotine." (DTX-172 at 9) UCB put patches punched from laminate lots 47806, 47807, and 47808 through a three-month stability test. (DTX-172 at 13) After one month, 20 out of 20 examined patches from laminate 47808 had crystals. (DTX-172 at 14) For laminate 47807, 20 out of 20 patches had crystals at the start of the 3-month test on December 13, 2007. (DTX-172 at 13-14)

61. In its 2008 FDA submission, UCB also disclosed that some patients had complained about altered patch appearance of Neupro made with lot numbers 47806, 47808, and 108547 – lots for which inventory was placed on hold by November 12, 2007. (DTX-172 at 2, 19-20)

iii. Inherency

62. Two crystalline forms of rotigotine are known. Form I of rotigotine is not a disappearing polymorph. (Rogers Tr. at 196-97; Myerson Tr. at 410) Form I can still be made today and will not inevitably and necessarily convert to Form II. (Rogers Tr. at 221; Myerson Tr. at 409-10; PTX-170-184) Form II will not always crystallize from amorphous rotigotine. (Rogers Tr. at 202, 221; Quere Tr. at 273-81; PTX-254; PTX-255)

63. Form II is more thermodynamically stable than Form I. (Rogers Tr. at 145) But crystallization of Form II from amorphous rotigotine is not inevitable just because Form II is more thermodynamically stable. (Myerson Tr. at 374-75, 379-80) Many conditions can affect the appearance of one form or another, including but not limited to the level of impurities, viscosity,

and storage temperature. (Myerson Tr. at 380-83, 418-20)

64. Among other studies conducted by UCB, scientists studied the effect of adding polyvinylpyrrolidone ("PVP"), with or without acid binder, to rotigotine. (PTX-258 at 14; PTX-254; PTX-255; DTX-384) UCB observed less crystallization of Form II under certain conditions, including in the presence of acid. (Quere Tr. at 286; Myerson Tr. at 427)

a. Schacht Example 1

65. The Schacht patent application, U.S. Patent Application No. 10/623,864, which was published on April 14, 2005, is prior art under § 102(b). (DTX-336)

66. Schacht Example 1 describes a method for making patches, reciting in part:

> 252.6 g Rotigotine free base are dissolved in 587.8 g ethanol 100% w/w and mixed with 222.2 g ethanolic solution containing 25% w/w polyvinylpyrrolidone (Kollidon F 90), 0.11 % w/w aqueous sodium bisulfite solution (10% w/w), 0.25 % ascorbyl palmitate and 0.62% DL-α-tocopherol. To the homogenous mixture 1692.8 g BIO-PSA Q7 4301 (73% w/w), 1691.6 g BIO-PSA Q7 4201 (73% w/w) and 416.3 g petrol ether are added and all components are stirred for at least 1 hour to get a homogenous dispersion.

(DTX-336 at ¶ 68)

67. Schacht Example 1 describes a formulation that is substantially similar to the original commercial version of Neupro. (Myerson Tr. at 438-39; Rogers Tr. at 169) UCB used the formulation disclosed for Neupro batch WE11249. (DTX-416 at 1; Rogers Tr. at 168-69; Myerson Tr. at 466) UCB informed the FDA that WE11249 was the final formulation, and all ensuing batches had this formulation, including Neupro sold commercially in 2007. (DTX-419 at 14-15; Rogers Tr. at 169-70) The ingredients in patches made by Schacht Example 1 and the original Neupro are the same. (DTX-690 at 12594; Myerson Tr. at 491-92)

68. Specifically, both original Neupro and Schacht Example 1 have a rotigotine/PVP

ratio of 9:2. (DTX-690 at 12616; DTX-336 at ¶ 68)

69. U.S. Patent Publication No. 2012/0322845 ("Wolff"), assigned to Plaintiffs UCB and LTS, provides experimental data indicating that patches made with a rotigotine/PVP ratio of 9:2 results in crystallization of Form II crystals. (DTX-345 at ¶¶ 155-156; Rogers Tr. at 165-66; Quere Tr. at 303-04) This application describes solving the problem of formation of Form II crystals in commercial patches. (DTX-345 at ¶¶ 17-18; Rogers Tr. at 163-64) Table 3 shows that in 9:2 and 9:3 formulations, crystallization is observed.

70. Formation of Form II crystals is not the necessary and inevitable result of practicing Schacht Example 1. (Myerson Tr. at 373, 408-09, 430-31)

71. While very similar, Schacht Example 1 was not the commercial manufacturing process for Neupro, either before or after August 7, 2007. (Myerson Tr. at 412-13) In particular, Schacht Example 1 uses a different scale, solvent composition, and order of combining ingredients than the commercial process for Neupro. (Myerson Tr. at 416-18) These changes could influence whether a particular form appears or if it appears at all. (Myerson Tr. at 418; Rogers Tr. at 223)

72. Schacht Example 1 does not require any particular method for synthesizing the rotigotine free base starting material. (Rogers Tr. at 209, 213) Nor does the example specify an impurity limit for the starting material. (Myerson Tr. at 426) At most, Wolff states that when making rotigotine patches, it is preferable, but not required, to limit certain impurities:

> In some cases, however, traces of rotigotine hydrochloride may be contained in a rotigotine preparation but these traces typically do not exceed 5 wt-%, based on the amount of the free base. More preferably the content of hydrochloride impurities should be less than 2 wt-%, even more preferably less than 1 wt-% and most preferably the rotigotine used in the present invention contains less than 0.1 wt-% or no hydrochloride impurities at all.

(DTX-345 at ¶ 89)

73. A POSA would know that rotigotine free base can be made by starting with rotigotine hydrochloride salt. (Rogers Tr. at 207, 213) Rotigotine free base made from the hydrochloride salt can be isolated in advance or made in situ. (Rogers Tr. at 208-09; Emgenbroich Tr. at 121-22)

74. Rotigotine free base made from the hydrochloride salt is likely to contain hydrochloride impurities, whether the free base is isolated in advance or made in situ. (Myerson Tr. at 429-31) When creating the rotigotine free base in situ, it is likely that the prepared free base will have impurities in the form of residual rotigotine hydrochloride, even up to 10%. (Rogers Tr. at 212; Myerson Tr. at 426) On the present record, commercially-available rotigotine free base is known to have up to 0.3% rotigotine hydrochloride. (DTX-384 at 24; Myerson Tr. at 430)

75. Rotigotine hydrochloride acts as an inhibitor to the crystallization of Form II. (Rogers Tr. at 215; Myerson Tr. 427, 429-31) Trace amounts of hydrochloric acid (which will react with rotigotine free base to form rotigotine hydrochloride) can also inhibit the appearance of crystals. (PTX-258 at 13-14; DTX-384 at 17)

76. A patch made according to Schacht Example 1 will not necessarily and inevitably result in Form II crystals if the rotigotine free base starting material contains sufficient rotigotine hydrochloride impurities to inhibit crystal growth. Schacht Example 1 does not exclude such impurities, which are commonly present in rotigotine free base.

b. '434 Patent Example 2

77. The '434 patent was published on April 26, 2005 and is § 102(b) prior art to the '414 patent. (DTX-1) PCT WO 99/49852 has the same disclosure as the '434 patent and is

disclosed as prior art in the '414 patent's specification. (Rogers Tr. at 15; DTX-3 at col. 1 l. 60)

78. Example 2 of the '434 patent did not use the commercial manufacturing process used to make Neupro, either before or after August 7, 2007, but followed the process used to prepare Neupro patches on the lab scale. (Mueller Tr. at 332)

79. Example 2 of the '434 patent has a 9:3 ratio of rotigotine to PVP and no other crystallization inhibitor is taught. (Rogers Tr. at 171) Example 2 begins with rotigotine free base – i.e., the free base is not prepared in situ. (Rogers Tr. at 228, *compare* DTX-1 col. 5 l. 54 - col 6 l. 14, *with* col. 6 ll. 32-52)

80. Example 2 of the '434 patent does not specify how the starting material must be made and does not set forth any guidelines for the impurity profile of the starting material. (Rogers Tr. at 206-07) Thus, as with Schacht Example 1, rotigotine free base may be made from the hydrochloride salt and isolated in advance. (Rogers Tr. at 208-09) Rotigotine free base prepared in this manner is known to contain some rotigotine hydrochloride impurities that may, in sufficient amount, inhibit growth of Form II crystals. (Myerson Tr. at 430) Accordingly, a patch made according to Example 2 of the '434 patent will not necessarily and inevitably result in Form II crystals.

H. Facts Relating to Validity of the '434 Patent

i. Parkinson's Disease and Transdermal Drug Delivery

81. Parkinson's disease is neurodegenerative disorder that affects more than a million Americans. (Hermanowicz Tr. at 238-39) It is a progressive and debilitating disease that impacts motor control, with symptoms including tremors, difficulty moving and controlling bodily functions, and problems with balance and speech. (Hermanowicz Tr. at 238-39) It also causes

significant gastrointestinal dysfunction, which manifests as difficulty swallowing, delayed gastric emptying, and slow transit times through the intestines – all of which complicate oral treatment and interfere with reliable delivery of medicine on a 24 hour basis. (Hermanowicz Tr. at 239-41) There is no cure for Parkinson's disease, although there are treatments available, including several dopamine agonists. (Hermanowicz Tr. at 239, 243-44)

82. Rotigotine, the active ingredient in Neupro, is a dopamine agonist. (Hermanowicz Tr. at 244; PTX-100) Neupro is the only product available that delivers a dopamine agonist transdermally. (Hermanowicz Tr. at 248) It is also the only transdermal treatment available for patients with Parkinson's disease. (Potts Tr. at 563)

83. Transdermal delivery refers to delivering active ingredients across the skin for systemic distribution. (Lane Tr. at 610-12) An example of a transdermal delivery system is a self-adhesive patch that contains medicine within the adhesive, which delivers it through the skin in a controlled manner. (Lane Tr. at 609)

84. Transdermal delivery offers benefits over oral administration – it avoids gastrointestinal side effects, provides continuous longer-acting delivery that reduces dosing frequency, and improves patient compliance in taking medication regularly. (Hermanowicz Tr. at 248-50, 252)

85. Despite the benefits of transdermal patches, only about 20 drugs are available as patches, compared to thousands of oral formulations that currently exist. (Lane Tr. at 610) In 1998, there were about eight transdermally-delivered drugs. (Lane Tr. at 610)

86. Neupro is the first drug to be approved in transdermal patch form without first having been approved as a different type of formulation (e.g., as an oral formulation). (Lane Tr. at

613-14; DTX-41 at 1)

ii. The '434 Patent

87. The '434 patent, owned by LTS, is directed to transdermal systems containing rotigotine free base. (DTX-1) The transdermal systems claimed in the '434 patent use polymer adhesive systems having solubility of ≥5% (w/w) for rotigotine free base, and the matrix layer containing rotigotine is free of water. (DTX-1 at col. 7 ll. 56-67) The transdermal systems may include between 5 and 25% (w/w) rotigotine. (DTX-1 at col. 8 ll. 27-30) The transdermal systems also optionally contain solubility enhancers, including PVP at a concentration of between 1.5 and 5% (w/w). (DTX-1 at col. 8 ll. 17-22, 54-64)

iii. Cygnus Application

88. In the early 1990s, Cygnus Therapeutic Systems ("Cygnus") worked with Discovery Therapeutics Inc. ("DTI") to develop transdermal rotigotine patches. (DTX-41 at 2-3) Preliminary clinical trials using patches manufactured by Cygnus demonstrated proof of concept that transdermal delivery of rotigotine was sufficient to produce plasma levels in an appropriate range for treatment. (DTX-41 at 3) DTI then partnered with LTS to develop a commercial product, i.e., Neupro. (DTX-41 at 3)

89. Cygnus filed a patent application, WO 94/07468, titled "Two-Phase Matrix for Sustained Release Drug Delivery Device" ("Cygnus Application"), relating to its work with DTI. (DTX-334) Scientists from Cygnus also published a short article, "A Two-Phase Matrix for the Delivery of N-0923, a Dopamine Agonist," authored by Chiang et al. ("Chiang"), describing the results of the studies with DTI. (DTX-67)

90. Chiang describes the preparation of a two-phase matrix system:

> N-0923 was dissolved in a mixture of phosphate buffer, propylene glycol and benzyl alcohol. The dissolved N-0923 solution was then added to Micro-Cel E and mixed vigorously to form a viscous hydrophilic mixture. Tween 20, propylene glycol monolaurate and silicone adhesive were added to the hydrophilic mixture and resulted in a finely dispersed mixture. This mixture was then cast onto a release film and the solvent was evaporated. A polyester film was then laminated onto the casting film.

(DTX-67 at 1) N-0923 is rotigotine hydrochloride. (Potts Tr. at 550; PTX-37)

91. The Cygnus Application was published on April 14, 1994 and is prior art under § 102(b). (DTX-334 at 1)

92. The Cygnus Application is generally directed to "two phase" transdermal systems. (DTX-334 at 1) The Cygnus Application describes "a novel matrix composed of a continuous hydrophobic domain and a dispersed particulate hydrated silicate domain" – that is, a hydrated inorganic silicate in a polymer matrix – "which may be used to administer hydrophilic drugs in a sustained manner." (DTX-334 at 5) "The particulate hydrated silicate is dispersed uniformly throughout the matrix . . . ." (DTX-334 at 9) "The drugs that may be used in matrixes of this invention are hydrophilic and are dissolved in the aqueous component of the hydrated silicate." (DTX-334 at 9)

93. Example 15 of the Cygnus Application describes patches made using active ingredient S(–)-2-(N-propyl-N-2-thienylethylamine)-5-hydroxytetralin. (DTX-334 at 16, 8) Dr. Potts, Dr. Klibanov (Plaintiffs' expert), and Dr. Peck (co-inventor of the '434 patent) agreed that the drug named in Example 15 is rotigotine free base. (Potts Tr. at 542; Peck Tr. at 514, 516; Klibanov Tr. at 772)

94. Example 15 discloses formulations that include pH 6 phosphate buffer. (DTX-334 at 17) In phosphate buffer at pH 6, rotigotine is present primarily in the salt form. (Lane Tr. at

654-55)

95. The Cygnus Application discloses "[s]pecific examples of polymers that may be used as the continuous hydrophobic phase of the matrix are polysiloxanes, polyisobutylene, solvent-based hydrophobic polyacrylates, polyurethanes, plasticized ethylene-vinyl acetate copolymers, low molecular weight polyether block amide copolymers, styrene-butadiene polymers, and vinyl acetate-based adhesives." (DTX-334 at 7-8)

96. Example 15 uses Silicone 4201 Adhesive as the hydrophobic matrix. (DTX-334 at 17) This is the same silicone polymer that the '434 patent calls BIO-PSA Q7-4201. (DTX-1 at col. 6 ll. 10-12; Potts Tr. at 543)

97. The Cygnus Application also states that "[o]ther hydrophobic materials such as solvents or permeation enhancers may be included in the hydrophobic domain of the matrix," such as "fatty acids (oleic and stearic acid), isopropyl myristate (IPM), fatty acid esters (e.g., propylene glycol monolaurate, polyethylene glycol monolaurate (PEGML), methyl oleate, oleyl oleate), fatty alcohols (e.g., oleyl alcohol), and terpenoids (limonene, menthol, P-pinene, and geraniol)." (DTX-334 at 8)

98. The Cygnus Application's inorganic silicate is "hydrated," which, according to the application's disclosure, means that "the dispersed particulate material comprises all or a portion of its total absorptive capacity of absorbed aqueous phase (i.e. water and/or other polar solvent)." (DTX-334 at 7) The application states that "[i]n its hydrated form the material will normally contain about 15% to 600% of its own weight in absorbed water, more usually 100% to 500% of its own weight in water (measured at 25°C)." (DTX-334 at 8) However, "[o]ther hydrophilic polar solvents such as ethanol, propylene glycol, low molecular weight (200 to 400 mw)

polyethylene glycol, isopropyl alcohol, N-butanediol, m-pyrol and benzyl alcohol may be substituted for water or included in the hydrophilic domain of the matrix." (DTX-334 at 8)

iv. Lipp

99. Canadian Patent No. 2,120,599, entitled "Transdermal Therapeutic Systems Containing Crystallization Inhibitors," to Ralph Lipp et al. ("Lipp") teaches the use of crystallization inhibitors in transdermal systems. (DTX-338) Lipp specifically teaches the use of PVP as a crystallization inhibitor and the use of such inhibitors at 0.1 to 40% by weight. (DTX-338 at 6-7; Potts Tr. at 548-49) Lipp does not list anti-Parkinson's drugs generally, or rotigotine specifically, as drugs to be used in the described transdermal system. (DTX-338 at 8-10; Potts Tr. at 584)

v. Pfister

100. European Patent Application 0524776, entitled "Silicone pressure sensitive adhesive compositions for transdermal drug delivery devices and related medical devices," to William Richard Pfister et al. ("Pfister"), describes using PVP in transdermal drug delivery patches. (DTX-332; Potts Tr. at 549) Pfister is mentioned in the '434 patent. (DTX-1 at col. 4 ll. 26-27)

vi. Miranda

101. International Patent Application WO 95/18603, entitled "Transdermal Device Containing Polyvinylpyrrolidone as Solubility Enhancer," to Jesus Miranda ("Miranda") teaches transdermal systems based on adhesive polymer blends. (DTX-340) Miranda discloses that using and making transdermal patches with silicone, polyacrylate, or polyisobutylene-based polymer adhesives was "well known." (DTX-340 at 3, 16) Miranda describes using PVP as a solubilizer

in concentrations between 1 and 20%. (DTX-340 at 8) Miranda states that the invention is especially useful for drug uses in low concentrations, including between 3 and 10%. (DTX-340 at 15) Miranda discloses that suitable solvents to be used include various non-water solvents, such as ethanol, and that the solvents are removed during the laminate drying process. (DTX-340 at 36-37) Although Miranda does not specifically name rotigotine as a suitable drug, it does include a list of other drugs for treating Parkinson's disease. (DTX-340 at 25)

vii. Timmerman

102. A journal article published by Timmerman et al. ("Timmerman"), entitled "Microdialysis and striatal dopamine release: stereoselective actions of the enantiomers of N-0437," describes a study in which rats were treated transdermally with rotigotine free base in an ethanol, water, and polyethylene glycol solution. (DTX-6 at 2, 6; Potts Tr. at 589) Timmerman states that rotigotine is a potent dopamine agonist. (DTX-6 at 1) Timmerman also concluded that transdermal administration of rotigotine was superior to oral administration. (DTX-6 at 6)

viii. Yamanaka

103. European Patent Application 0 387 751, entitled "Medicated Plasters," to Akihito Yamanaka et al. ("Yamanaka") teaches fabrication of transdermal drug delivery patches, which it refers to as "medicated plasters," suitable for use with basic, amine drugs. (DTX-339 at 4) Yamanaka lists numerous drugs in salt form used in accordance with its medicated plasters, including eight anti-Parkinson's drugs, all in salt form. (DTX-339 at 5; Potts Tr. at 591-92) Yamanaka teaches that the adhesive may include PVP. (DTX-339 at 4)

ix. Secondary Considerations

a. Nexus

104. There have been three versions of Neupro: the original version launched in the U.S. in 2007, the version relaunched in the U.S. in 2012, and the current formulation. (Lane Tr. at 628; DTX-41 at 4; PTX-287 at 8 (current Neupro); PTX-280 at 2 (Neupro 2012); PTX-223 at 2 (Neupro 2007))

105. The claims of the '434 patent require "all of said free base being present in the matrix in the absence of water." (DTX-1 at col. 7 ll. 63-65)

106. Neupro is formulated not to have water in the matrix; the NDA states that there is no water present in the finished product. (Lane Tr. at 626-27; PTX-287 at 8 (water "[r]emoved during processing, not present in finished product"); PTX-280 at 2 (same for Neupro 2012); PTX-223 at 2 (same for Neupro 2007)) Water is only used as a solvent for sodium metabisulfite, an upstream ingredient, in the first manufacturing step, and the water is removed during processing. (PTX-287 at 9, 31) Water is also an impurity present in PVP. For example, Kollidon 90F, USP grade PVP, may contain up to 5% water. (PTX-180; Potts Tr. at 549)

107. Stability testing shows that Neupro laminate contains about 0.3% water. (Lane Tr. 726-35; DTX-690 at 18843; DTX-461 at 31; DTX-174 at 5-7)

b. Long-Felt but Unmet Need

108. In 1998, many oral medications were available for patients with Parkinson's disease, including levodopa/carbidopa and dopamine agonists, but each suffered significant drawbacks. (Hermanowicz Tr. at 243-47) The oral medications available were unable to control symptoms over a full 24 hours and patient compliance was made more difficult due to the "pill

burden." (Hermanowicz Tr. at 248) There was, thus, a need for a formulation to treat the symptoms of Parkinson's disease that avoided the known problems of oral medications. (Hermanowicz Tr. at 246-47)

109. Neupro satisfied this long-felt need because it is a transdermal patch that contains and delivers an effective dose of dopamine agonist over 24 hours, bypassing the gastrointestinal tract. (Hermanowicz Tr. at 248-53; PTX-131; PTX-83; PTX-79) Neupro was the first and remains the only transdermal patch available to treat Parkinson's disease. (Hermanowicz Tr. at 244, 248; Potts Tr. at 563)

c. Unexpected Results

110. Cygnus attempted systems without the separate aqueous phase but found that the "two phase" design was necessary in order to achieve adequate results, and further found that systems without the separate water phase resulted in only nominal skin flux. (DTX-67 at 2) The Cygnus patches used rotigotine hydrochloride as the active ingredient. (DTX-41 at 3)

d. Failure of Others

111. The Cygnus rotigotine patch was used in proof of concept clinical trials. (DTX-41 at 3; Potts Tr. at 543; Mueller Tr. at 362) In one study, the Cygnus patch was applied to healthy volunteers and produced plasma levels in a range useful for treatment. (DTX-41 at 3; Peck Tr. at 518-19) In a second study, nine patients with Parkinson's disease were given the Cygnus patch, resulting in reduction in severity of symptoms. (DTX-41 at 3) The Cygnus patches showed "promising results." (Peck Tr. at 521)

112. The Cygnus patches were not developed commercially because Cygnus' partner, DTI, opted to continue its development of a rotigotine transdermal delivery system with LTS.

(DTX-41 at 3; Peck Tr. at 521) The Cygnus patches were the "prototype" for Neupro (DTX-419 at 5; Potts Tr. at 539-40), and the Cygnus studies were submitted to the FDA when Plaintiffs sought approval for Neupro (Peck Tr. at 517; DTX-419 at 7).

I. Facts Relating to Infringement of the '434 Patent

113. The claims of the '434 patent are limited to patches "wherein the matrix is based on [] an acrylate-based or silicone-based polymer adhesive system having a solubility of ≥5% (w/w) for the free base (–)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol." (DTX-1 at col. 7 ll. 59-63) The parties agreed that this claim language means "wherein the matrix is a matrix layer containing an acrylate-based or silicone-based polymer adhesive system having a solubility of ≥5% (w/w) for the free base of rotigotine." (D.I. 111 at 3)

114. The claimed transdermal systems are prepared with two classes of polymer adhesive materials – acrylate-based and silicone-based adhesives – and the patent provides examples of such adhesives. (DTX-1 at col. 2 l. 56 - col. 3 l. 10) The terms "silicone" and "acrylate" refer to broad classes of polymers that are useful as adhesives and exhibit a wide range of physical properties, including solubilities. (Klibanov Tr. at 749-52; PTX-365; PTX-364)

115. The '434 patent discloses that the dissolving capacity of the adhesive polymer for active ingredients is "an important parameter for the development of matrix systems." (DTX-1 at col. 3 ll. 15-22) The patent teaches that acrylates have relatively high solubility for the rotigotine free base, whereas silicones have a lower solubility. (DTX-1 at col. 3 ll. 29-33 (acrylates 15–35%), ll. 56-60 (silicones 5%)) Dr. Klibanov testified that some silicone polymers have even lower solubility for rotigotine. (Klibanov Tr. at 766 (specific silicones with solubility <0.1%))

116. In the claimed inventions, solubility enhancers, such as PVP, may be admixed with

the silicone adhesive to raise the dissolving capacity of the system for rotigotine free base up to 40% (w/w) "without adversely affecting the physical properties of the matrix." (DTX-1 at col. 3 ll. 62-66) The patent provides that PVP dispersed in the adhesive increases the solubility for the free base in silicone adhesives. (DTX-1 at col. 4 ll. 6-19; Klibanov Tr. at 756-57)

i. Actavis' ANDA Products

117. Actavis' ANDA products are a matrix-type transdermal patch having three layers: (1) a backing layer composed of a flexible film; (2) a drug/adhesive matrix composed of rotigotine free-base, polyisobutylene adhesive (Duro-Tak 87-6908), and excipients including PVP and isopropyl myristate; and (3) a release liner. (PTX-336 at 1, 6; PTX-428 at 2-4)

118. The proposed label for Actavis' ANDA products indicates that, if approved, Actavis will sell its ANDA products for the treatment of the symptoms of Parkinson's disease and Restless Legs Syndrome. (PTX-416 at 1; Lane Tr. at C-7)

119. It is undisputed that Actavis' ANDA products meet each element of claim 1 of the '434 patent, except for the element: "wherein the matrix is based on [] an acrylate-based or silicone-based polymer adhesive system having a solubility of ≥5% (w/w) for the free base [of rotigotine]." (SUF ¶ 43)[2]

120. Actavis' ANDA products have a polyisobutylene-based polymer adhesive system having ≥5% (w/w) solubility for rotigotine free base. (Lane Tr. at 631) The only difference between the disputed element and Actavis' matrix is the use of a polyisobutylene-based polymer adhesive system instead of an acrylate- or silicone-based polymer adhesive system as literally

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[2]At the pretrial conference, the Court granted UCB's motion in limine to preclude Actavis from asserting a non-infringement defense on the basis of the "absence of water" limitation. (D.I. 229 at 25-26)

claimed.

121. With respect to dependent claims 5, 14, and 15, the Actavis ANDA products contain [redacted] PVP (w/w), a hydrophilic polymer, in the adhesive matrix. (Lane Tr. at C-14-15; PTX-336 at 3; PTX-428 at 3; Lane Tr. at 627)

122. PVP is present to inhibit crystallization and to assist in drug dissolution. (Lane Tr. at C-15; PTX-402 at 12) Internal Actavis documents describe PVP as a "drug solubilizer." (PTX-381; Lane Tr. at C-15) An indication that the drug is fully dissolved in the matrix is the absence of crystals. (Klibanov Tr. at 741) PVP is a crystallization inhibitor because it enhances the solubility of rotigotine in Actavis' polyisobutylene-based polymer adhesive system. (Klibanov Tr. at 759)

123. With respect to claim 7, the Actavis ANDA products contain [redacted] rotigotine (w/w) in the polymer adhesive system. (Lane Tr. at C-16; PTX-336 at 3; PTX-428 at 3)

ii. Doctrine of Equivalents

124. The purpose of the adhesive polymer in the disputed claim element is to act as a scaffold for the drug and to provide adhesion for the transdermal patch. (Klibanov Tr. at 747) Generally, the polymers suitable for transdermal patches are pressure-sensitive adhesives. (Klibanov Tr. at 747) As was true at the time the '434 patent was filed, silicones, acrylates, and polyisobutylenes are the most commonly used pressure-sensitive adhesives in transdermal patches. (Klibanov Tr. at 748; PTX-125 at 60; DTX-334 at 7)

125. A POSA would recognize that there are many different types of silicone and acrylate adhesives, having a wide range of varying properties – e.g., levels of solubility, hydrophobicity, tack, and viscosity – many of which overlap with the properties of

polyisobutylene. (Klibanov Tr. at 750-52; PTX-365; PTX-364)

126. Silicones, acrylates, and polyisobutylene also share common properties as pressure-sensitive adhesives – e.g., they are adhesive, biologically inert, non-irritating, and non-toxic. (Klibanov Tr. at 748-49; PTX-125 at 62-63) A POSA would recognize that polyisobutylene is not substantially different from the classes of adhesives literally within the scope of the claims. (Klibanov Tr. at 749)

127. Polyisobutylene is an organic polymer, consisting exclusively of carbon and hydrogen atoms, forming a non-polar backbone, without any functional groups. (Mueller Tr. at 344; Gokel Tr. at 804-05) Accordingly, polyisobutylene is non-polar and hydrophobic. (PTX-125 at 63; Gokel Tr. at 807)

128. A silicone polymer has a backbone made of polar heteroatoms silicon and oxygen. (Gokel Tr. at 804; Klibanov Tr. at 779) Silicones and polyacrylates, unlike polyisobutylene, may also contain functional groups that may be polar and/or reactive. (Gokel Tr. at 805)

129. Polyisobutylene, unlike silicone or acrylate polymers, does not allow for cross-linking agents to be used to increase adhesion or reduce cold-flow. (Gokel Tr. at 810-11; Mueller Tr. at 345; PTX-365) Additionally, polyisobutylene has substantially different adhesiveness compared to acrylate- and silicone-based adhesives, due to differences in polarity. (PTX-125 at 63, 68)

130. Rotigotine contains oxygen, nitrogen, and sulfur, heteroatoms that can interact with certain functional groups that can be present in silicone and acrylate polymers. (Gokel Tr. at 807-08) Rotigotine does not interact significantly with polyisobutylene. (Gokel Tr. at 808-09) For example, rotigotine can form hydrogen bonds with silicones and acrylates but not with

polyisobutylene. (Gokel Tr. at 809, 811-12)

131. Actavis started its development work by making Neupro and a formulation identical to Neupro but with polyisobutylene substituted for silicone ("PIB Neupro"). (*Compare* PTX-378 (formulation for PIB Neupro) *with* PTX-280 at 2 (formulation for Neupro); Lane Tr. at 641-42) Permeation results for Neupro and PIB Neupro were comparable in terms of transdermal delivery of rotigotine. (Lane Tr. at 642; DTX-170 at 3-4) Even at 24 hours, the intended wear time, the amount of rotigotine delivered by PIB Neupro was statistically indistinguishable from Neupro. (DTX-170 at 3; Lane Tr. at 642-43) These results show that the polyisobutylene-based polymer adhesive system did not alter the way rotigotine is transdermally delivered compared to a silicone-based polymer adhesive system.

132. Actavis' PIB Neupro testing demonstrates that the polyisobutylene-based polymer adhesive system allows for mobility of rotigotine through the matrix and its transfer to the skin in the same way as the claimed silicone-based adhesive system. (Lane Tr. at 642-43) That replacing polyisobutylene for silicone does not alter rotigotine transdermal delivery rates also shows that polyisobutylene is interchangeable with silicone in the claimed polymer adhesive system. (Lane Tr. at 642-43, 645-46) The polyisobutylene-based adhesive system is an insubstantial modification of the claimed invention.

133. Actavis selected polyisobutylene as the adhesive for its ANDA products after confirming that use of polyisobutylene in place of silicone yielded the comparable permeation rates. (Lane Tr. at 642-43; Klibanov Tr. at 752-54; PTX-436 at 6) Actavis chose to proceed with polyisobutylene as the adhesive based on prior experience – not because polyisobutylene produced any different or better results than silicone. (Klibanov Tr. at 75-54; PTX- 436 at 6 ("Based on

previous experience with PIB adhesives, PIB adhesive 87-6908 was selected to move forward and was optimized as discussed in the following subheadings."))

134. After deciding to proceed with polyisobutylene, Actavis began making minor changes in the excipients used in Neupro. (Lane Tr. at 643-45; PTX-383 (describing all formulations Actavis tested, by date); PTX-436 at 4-9) For example, Actavis changed the [redacted] (PTX-436 at 13; DTX-170 at 3) and changed [redacted] (PTX-436 at 13). These small changes in excipients did not result in substantial differences between the silicone and polyisobutylene formulations. (Lane Tr. at 645-46)

135. Actavis' ANDA products use PVP in their polyisobutylene-based polymer adhesive system as a solubility enhancer for rotigotine – in the same way as the claimed silicone-based polymer adhesive system. (Klibanov Tr. at 759; Lane Tr. at C-14-15; PTX-428 at 3; Mueller Tr. at 323-26) Actavis' stability testing confirms that [redacted] PVP was necessary in the polyisobutylene-based polymer adhesive system to fully dissolve the necessary amount of free base and prevent crystallization, and this amount is within the range of PVP disclosed in the patent. (Klibanov Tr. at 758-59; PTX-436 at 12)

136. Both Actavis' polyisobutylene-based polymer adhesive system and the claimed silicone-based polymer adhesive system use a hydrophobic adhesive with inherently low solubility for rotigotine free base in which rotigotine-PVP complexes are dispersed. (Klibanov Tr. at 756-5, 759, 768; DTX-120 at 5; Lane Tr. at 674; Mueller 325-26; PTX-267 at 6) In both systems, a small amount of free base is also dissolved in the adhesive itself. (Klibanov Tr. at 764, 767-69; PTX-267 at 6)

137. Rotigotine-PVP complexes in the polyisobutylene-based polymer adhesive allow

for the mobility of the free base through the matrix and its transfer to the skin. (Klibanov Tr. at 768-69; DTX-120 at 5) These complexes establish a dynamic equilibrium in the polyisobutylene-based polymer adhesive system that allows the free base to move through the adhesive and transfer to the skin. (Klibanov Tr. at 763-71) When the matrix is adhered to skin, the small amount of rotigotine free base that is dissolved in the adhesive itself is transferred to (and through) the skin and, when this happens, additional rotigotine dissociates from the PVP complexes and dissolves in the adhesive, thereby replenishing what was lost through transdermal delivery. (Klibanov Tr. at 763-71) These rotigotine-PVP complexes exist in the claimed silicone-based polymer adhesive system, in which the same dynamic equilibrium allows for rotigotine free base mobility and transfer to the skin. (Klibanov Tr. at 762-63, 766-67; Mueller Tr. at 324-26; PTX-287 at 15; PTX-267 at 1, 6)

138. That polyisobutylene has some different properties (e.g., lack of heteroatoms and functional groups, different polarity, etc.) does not change how the polymer adhesive system works. The polymer functions as a scaffold for the drug. (Klibanov Tr. at 747) Rotigotine-PVP complexes form in silicone polymers and polyisobutylene both to increase drug solubility and allow for drug mobility. (Klibanov Tr. at 762-64)

139. Actavis' ANDA products also contain isopropyl myristate, which Actavis indicates is a skin permeation enhancer. (PTX-428 at 3) The addition of isopropyl myristate does not result in Actavis' ANDA products working in a different way than the claimed invention.

140. Testing during development of Actavis' polyisobutylene-based polymer adhesive system shows that isopropyl myristate modestly improves permeation. Formulations with and without isopropyl myristate, but otherwise substantially the same as Actavis' final formulation,

yielded comparable permeation results with large margins of error. (Lane Tr. at C-4-5; PTX-395) [redacted] the amount of isopropyl myristate from [redacted] (Actavis' final formulation) similarly showed little statistical improvement in rotigotine permeation after 24 hours. (Lane Tr. at C-3-4; PTX-436 at 9) More importantly, even though isopropyl myristate is present at [redacted] (Gokel Tr. at 813-14; PTX-436 at 8), isopropyl myristate does not affect the formation of rotigotine-PVP complexes or the resulting dynamic equilibrium that allows for free base mobility and transfer to the skin. (Klibanov Tr. at 769-70)

141. Actavis also uses a [redacted] (PTX-336 at 7) This excipient does not change how rotigotine is delivered. (Lane Tr. at 645-46)

142. Polyisobutylene is interchangeable with silicone in the claimed polymer adhesive system, resulting in an insubstantially different system that also uses dispersed rotigotine-PVP to effect ≥5% solubility. (Klibanov Tr. at 752-55, 759)

iii. Prosecution History

143. The polymer classes recited in claim 1 (acrylates and silicones) were always included in the claims. (DTX-316 at 17) The original application had 17 claims, which were cancelled in a preliminary amendment prior to any Patent Office action. (DTX-316 at 28-31) Original claims 1-12 and new claims 18-33 all included an "acrylate-based or silicone-based polymer adhesive system having a solubility of ≥5% (w/w) for [rotigotine free base]." (DTX-316 at 17-18, 28) That claim language was never amended during prosecution.

144. Original claims 13-17 and new claims 34-40 were generally directed to processes for preparing a transdermal therapeutic system that included "an adhesive." (DTX-316 at 19, 31-32) The examiner issued a restriction requirement (DTX-316 at 291-93), and the patentee elected

to prosecute claims 18-33 (DTX-316 at 337-38).

145. The patentee referred to some of the systems disclosed in the Cygnus references as "two-phase matrix systems," as they were designated by Cygnus. (DTX-334) Applicants distinguished the particular two-phase systems of Cygnus, arguing that the Cygnus references were different because there "the drug is dissolved in an aqueous phase of a hydrated inorganic silicate." (*See, e.g.*, DTX-316 at 444) Applicants described the two-phase systems as follows: "the hydrophilic phase of the two phase system of CHIANG contains N-0923, the phosphate buffer, propylene glycol, benzyl alcohol, Micro-Cel E, Tween 20, and propylene glycol monolaurate, while the hydrophobic phase consists virtually solely of the silicone adhesive." (DTX-316 at 443) Applicants distinguished their invention from two-phase system containing an aqueous phase. (DTX-316 at 443-44)

J. Infringement of the '414 Patent

146. The importation into the United States, the use, or both, of the API in crystal form of ANDA No. 206348 for the commercial manufacture within the United States of the ANDA products would infringe claims 1-3 of the '414 patent, if those claims are valid and enforceable. (SUF ¶ 44; D.I. 93)

LEGAL STANDARDS

I. Infringement

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). Courts employ a two-step analysis in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). First, a court must

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

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

A patentee may be prevented from invoking the doctrine of equivalents by prosecution history estoppel. *See Festo*, 535 U.S. at 734-36. Applicability of prosecution history estoppel is a question of law. *See Panduit Corp. v. HellermannTyton Corp.*, 451 F.3d 819, 826 (Fed. Cir. 2006).

II. Presumption of Validity

An issued patent is presumed to be valid. *See* 35 U.S.C. § 282. Therefore, to invalidate a patent, a party must meet its burden of proof by "clear and convincing evidence." *See Procter &*

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

III. Anticipation

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

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

35 U.S.C. § 102.[3] A patent claim is anticipated if each and every limitation is found, either expressly or inherently, in a single prior art reference. *See Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Such disclosure in the prior art can be explicit or inherent. *See Cont'l Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). Mere disclosure of each and every limitation of a claim, however, is not enough for anticipation. "An anticipating reference must enable that which it is asserted to anticipate." *Abbott Labs. v. Sandoz, Inc.*, 544

[3]The Court will use the version of 35 U.S.C. § 102 in effect prior to passage of the Leahy–Smith America Invents Act; this prior version of § 102 applies to all patents with an effective filing date of on or before March 16, 2013, including the asserted patents. *See Solvay S.A. v. Honeywell Int'l Inc.*, 742 F.3d 998, 1000 n.1 (Fed. Cir. 2014).

F.3d 1341, 1345 (Fed. Cir. 2008). Furthermore, a single prior art reference must also disclose the limitations as arranged in the claim. *See Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) ("[U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102.").

To establish anticipation by inherent disclosure, the evidence must make clear that the reference discloses the unstated limitation. *See Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010); *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002); *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). "Inherency [] may not be established by probabilities or possibilities. The mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient." *Therasense*, 593 F.3d at 1332 (internal quotation marks and citation omitted).

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).

IV. Obviousness

A patent may not issue "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a). Obviousness is a question of law based on underlying factual findings concerning: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective

considerations of non-obviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

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

The use of hindsight is not permitted when determining whether a claim would have been obvious to one having ordinary skill in the art. *See id.* at 421 (cautioning against "the distortion caused by hindsight bias" and obviousness "arguments reliant upon *ex post* reasoning"). To protect against the improper use of hindsight when assessing obviousness, the Court is required to consider objective (or "secondary") considerations of non-obviousness, such as commercial success, failure of others, unexpected results, and long-felt but unmet need. *See, e.g., Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Objective considerations "may often be the most probative and cogent evidence in the record" relating to obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

V. Inventorship

An applicant is not entitled to a patent if "he did not himself invent the subject matter

sought to be patented." 35 U.S.C. § 102(f). Section 102(f) prohibits the issuance of a patent to a person who derived the conception of an invention from any other source. *See Price v. Symsek*, 988 F.2d 1187, 1190 (Fed. Cir. 1993). To prove derivation, the patent challenger must establish "prior conception of the claimed subject matter and communication of the conception" to the named inventor. *Id.*; *see also Cumberland Pharm. Inc. v. Mylan Institutional LLC*, 846 F.3d 1213, 1218 (Fed. Cir. 2017).

"Conception is the touchstone to determining inventorship." *Fina Oil & Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997). Conception is "the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Burroughs Wellcome Co. v. Barr Labs. Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994). "[W]ith regard to a claimed chemical compound, conception requires that the inventor be able to define the compound so as to distinguish it from other materials, and to describe how to obtain it." *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1063 (Fed. Cir. 2005) (internal quotation marks omitted).

"Because the issuance of a patent creates a presumption that the named inventors are the true and only inventors, the burden of showing misjoinder or nonjoinder of inventors is a heavy one and must be proved by clear and convincing evidence." *Bd. of Educ. v. Am. BioSci., Inc.*, 333 F.3d 1330, 1337 (Fed. Cir. 2003). The same standard applies in the derivation context. *See Cumberland*, 846 F.3d at 1218.

DISCUSSION

I. Infringement of the '434 patent

UCB alleges that Actavis' ANDA products infringe claims 1, 5, 7, 14, and 15 of the '434

patent. The only limitation in dispute is "an acrylate-based or silicone-based polymer adhesive system having a solubility of ≥5% (w/w) for the free base."[4] (DTX-1 at col. 7 ll. 60-62) Actavis' ANDA products do not contain an acrylate or silicone polymer. Instead, Actavis' products are based on a polyisobutylene polymer.

UCB does not assert that the ANDA products literally infringe the '434 patent. UCB contends, instead, that it has proven infringement under the doctrine of equivalents. As explained below, the Court agrees that UCB has proven, by a preponderance of the evidence, that Actavis' ANDA products infringe under the doctrine of equivalents. The Court also rejects Actavis' position with respect to two preliminary issues: a claim construction dispute and whether UCB is precluded from pursuing its theory of doctrine of equivalents infringement.

A. The "polymer adhesive system" includes PVP and other additives

The parties first dispute the meaning of the "polymer adhesive term." The Court views this essentially as a claim construction dispute. *See O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1361 (Fed. Cir. 2008) ("The parties presented a dispute to the district court regarding the scope of the asserted claims . . . . This dispute over the scope of the asserted claims is a question of law.").

Actavis contends that the polymer adhesive system is composed solely of the polymer adhesive. Actavis points to language in the specification stating that "[t]he adhesive's dissolving capacity for the active substance is an important parameter for the development of matrix

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[4]Actavis also contends that its ANDA product contains water, and therefore does not infringe because it does not meet the water-free limitation of the claims. (*See* D.I. 224) Before trial, the Court granted UCB's motion *in limine* to preclude Actavis from asserting this non-infringement position because Actavis failed to disclose it in a timely manner. (*See* D.I. 229 at 25-26) Accordingly, this issue is not presently before the Court.

systems." (DTX-1 at col. 3 ll. 15-17) The specification then discloses that the solubility of rotigotine free base in acrylate polymers is between 15-35% and the solubility of rotigotine in silicone polymers is about 5%. (DTX-1 at col. 3 ll. 27-33, 55-65) Actavis contends that the 5% solubility threshold refers to the solubility of rotigotine in the polymer adhesive itself.

UCB counters that polymer adhesive system includes additives, such as solubility enhancers. The Court agrees with UCB. The claim language is a strong indication that the limitation concerns more than just the polymer's solubility for rotigotine; the claim recites "an acrylate-***based*** or silicone-***based*** polymer adhesive ***system*** having a solubility of ≥5% (w/w) for the free base." (DTX-1 at col. 7 ll. 60-62) (emphasis added) If the claim were trying to communicate that the polymer ***without additives*** must have a threshold solubility for rotigotine, the claim could have more simply read "an acrylate or silicone polymer adhesive having a solubility of ≥5% (w/w) for the free base." In the Court's view, it is noteworthy that this is not what the claim states.

Moreover, the dependent claims support reading the polymer system to include additives. Claim 4 states that "the acrylate-based polymer adhesive in the matrix layer contains at least two monomers." (DTX-1 at col 8 ll. 7-16) Similarly, claim 5 adds that "the silicone-based polymer adhesive in the matrix layer further comprises additives to enhance the solubility of [rotigotine] in the form of hydrophilic polymers or glycerol or glycerol derivatives." (DTX-1 at col. 8 ll. 17-22) These dependent claims confirm that the polymer adhesive system contains the polymer as well as any additives.

Actavis contends that this understanding of the claims cannot be correct because it makes the matrix term coextensive with the polymer adhesive system. The Court disagrees. Again, the

claims provide helpful instruction. In particular, claim 2 – which claims "[t]he transdermal therapeutic system of claim 1 further comprising <0.5% (w/w) inorganic silicate particulates ***in the matrix layer***" – suggests that there are certain substances that, when added to the matrix layer, are not considered part of the polymer adhesive. (DTX-1 at col. 8 ll. 1-3) (emphasis added) The implication from claim 2, and similarly claim 3, is that if silicate particulates were present in the matrix layer, the matrix layer would be composed of the silicate and polymer adhesive. Thus, while the claims indicate that some additives, like PVP, are part of the polymer adhesive system, other components, like inorganic silicates, are not. That the polymer adhesive system and matrix may be coextensive in some embodiments, such as those not having silicates, does not alter the Court's conclusion.

Nor is the Court persuaded that the discussion of one-matrix versus two-matrix systems during prosecution should lead the Court to adopt Actavis' construction. In distinguishing the present invention from the Cygnus Application and Chiang paper, the applicants created a chart showing the differences between the two types of matrix systems. (*See* DTX-336 at 444) The chart includes the statement that "N-0923 as the **free base** dissolved in the hydrophobic polymer having a solubility ≥5%." (*Id.*) Actavis contends that this statement means that the polymer itself must have the noted solubility. However, the purpose of this chart was to emphasize the key differences between the prior art and the present invention – namely, that the polymer system had a solubility of at least 5% for rotigotine free base without a using separate aqueous phase. Hence, in context, this statement does not require the polymer adhesive itself – without additives – to have the claimed solubility properties.

Accordingly, the Court views the claims as requiring the polymer adhesive system – not

simply the polymer on its own – to have a solubility of at least 5% for rotigotine free base. Hence, in evaluating the accused product, the Court will consider the solubility of rotigotine in the polymer with additives.

B. UCB is not precluded from asserting an infringement theory under the doctrine of equivalence

Actavis contends that UCB is precluded from asserting infringement under the doctrine of equivalents to cover Actavis' ANDA products because: (1) UCB intentionally surrendered polyisobutylene polymers during prosecution; (2) UCB intentionally pursued narrow claims; (3) UCB's theory would vitiate claim limitations; and (4) a hypothetical claim based on UCB's doctrine of equivalents theory would ensnare the prior art. The Court disagrees with Actavis on each of these points.

1. Prosecution history estoppel is inapplicable

Prosecution history estoppel limits the doctrine of equivalents. *See Glaxo Wellcome, Inc. v. Impax Labs., Inc.*, 356 F.3d 1348, 1351 (Fed. Cir. 2004). There is a presumption that a narrowing amendment made for a reason of patentability surrenders the entire territory between the original claim limitation and the amended claim limitation. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1365 (Fed. Cir. 2003); *Cross Med. Prods. v. Medtronic Sofamar Danek, Inc.*, 480 F.3d 1335, 1341 (Fed. Cir. 2003). To rebut this presumption, "the patentee must demonstrate that the alleged equivalent would have been unforeseeable at the time of the narrowing amendment, that the rationale underlying the narrowing amendment bore no more than a tangential relation to the equivalent in question, or that there was some other reason suggesting that the patentee could not reasonably have been expected to have described the alleged equivalent." *Festo*, 344 F.3d at 1368. An amendment cannot reasonably be viewed as

surrendering a particular equivalent if the rationale underlying the amendment bears no more than a tangential relation to the equivalent. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 740-41 (2002). Thus, "[i]n determining whether an estoppel arose, and the scope of the estoppel, the analysis focuses on the claims as originally filed, the amendments made, and the reasons therefor." *Funai Elec. Co. v. Daewoo Elecs. Corp.*, 616 F.3d 1357, 1368 (Fed. Cir. 2010).

A restriction requirement does not necessarily invoke prosecution history estoppel. *See Bayer Aktiengesellschaft v. Duphar Int'l Research B.V.*, 738 F.2d 1237, 1243 (Fed. Cir. 1984). Like other amendments made during prosecution, whether a patentee's actions in the face of a restriction requirement gives rise to estoppel must be judged "from the viewpoint of a person of skill in the field of the invention, and when the issue includes consideration of formalities of patent practice, experience in patent law and procedures is presumed." *Merck & Co. v. Mylan Pharm., Inc.*, 190 F.3d 1335, 1340 (Fed. Cir. 1999). In *Merck*, the Federal Circuit determined that the patentee's actions limiting the claims to a certain subset – when the examiner issued a restriction requirement and rejected claims for obviousness – "were primarily in consideration of the patentability rejection under § 103." *Id.* at 1340-41. Thus, the Federal Circuit there concluded that Merck's actions gave rise to prosecution history estoppel.

Here, Actavis contends that the patentee's actions after the examiner issued a restriction requirement should prevent UCB from now asserting infringement under the doctrine of equivalents. In Actavis' view, the original application included broad claims that were not limited to silicone- and acrylate-based polymer adhesive systems. Because the patentee withdrew those claims, the patentee, in Actavis' view, gave up its broad claims to adhesives that are not silicones or acrylates, and should not be allowed to recapture that subject matter through the doctrine of

equivalents. The Court disagrees with Actavis' reading of the prosecution history.

The original application had 17 claims, which were cancelled in a preliminary amendment before any Patent Office action and replaced with 23 new claims. (*See* DTX-316 at 17-19, 28-31) Original claims 1-12 and new claims 18-33 all included an "acrylate-based or silicone-based polymer adhesive system having a solubility of ≥5% (w/w) for [rotigotine free base]." (*Id.* at 17-18, 28) That claim language was never amended during prosecution. Original claims 13-17 and new claims 34-41 were generally directed to processes for preparing a transdermal therapeutic system that included "an adhesive." (*Id.* at 19, 31-32, 145-46)

The examiner issued a restriction requirement, asking the patentee to elect to prosecute claims from Group I (claims 18-33) or Group II (claims 34-41). (*See id.* at 291-93) The examiner's restriction was not accompanied by any rejections based on prior art or otherwise. (*See id.*) The patentee elected to prosecute claims 18-33. (*See id.* at 337-38) The record is unclear as to whether the examiner or patentee understood claims 34-41 to cover a process using all types of adhesives. (*See id.* at 337) ("[T]he process of group II is only applicable on silicon[e]-based polymer and not on acrylate-based polymer.") Accordingly, the Court is not persuaded that the election to pursue claims 18-33 was an amendment made for purposes of patentability that would lead to prosecution history estoppel.

2. The patentee did not pursue narrow claims

Relatedly, Actavis contends that the patentee pursued narrow claims from the beginning, so should not be permitted to expand the scope of the claims through the doctrine of equivalents. Specifically, Actavis argues that Dr. Mueller, an inventor of the '434 patent, knew that polyisobutylene was a polymer that could be used in transdermal patches but intentionally did not

prosecute a claim broad enough to cover polyisobutylene. The Court disagrees.

In essence, Actavis contends that the inventor's awareness of polyisobutylene as a foreseeable equivalent to the claimed polymers should now bar application of the doctrine of equivalents. "There is not, nor has there ever been, a foreseeability limitation on the application of the doctrine of equivalents. It has long been clear that known interchangeability weighs in favor of finding infringement under the doctrine of equivalents." *Ring & Pinion Serv. Inc. v. ARB Corp.*, 743 F.3d 831, 834 (Fed. Cir. 2014) (citing *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 36 (1997); *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 609 (1950); *Abraxis Bioscience, Inc. v. Mayne Pharma (USA) Inc.*, 467 F.3d 1370, 1382 (Fed. Cir. 2006); *Interactive Pictures Corp. v. Infinite Pictures, Inc.*, 274 F.3d 1371, 1383 (Fed. Cir. 2001); *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1261 (Fed. Cir. 1989)). "Excluding equivalents that were foreseeable at the time of patenting would directly conflict with these holdings that 'known interchangeability' supports infringement under the doctrine of equivalents." *Id.* at 834. Hence, the Court concludes that Dr. Mueller's awareness of polyisobutylene as a suitable polymer for transdermal systems does not foreclose UCB from asserting infringement under the doctrine of equivalents.

The cases cited by Actavis do not persuade the Court otherwise. *See Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1366 (Fed. Cir. 2012); *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1297 (Fed. Cir. 2009). In *Wrigley*, the Federal Circuit affirmed the District Court's finding of no infringement because the patent "disclaimed all compounds other than N-substituted-p-menthane carboxamides." *Wrigley*, 683 F.3d at 1365. That "the claims themselves [were] narrow, not even claiming all N-substituted-p-menthane carboxamides, but only

a subset of those compounds" was additional support that the accused product was not an equivalent. *Id.* at 1366. Here, by contrast, the Court has not found any disclaimer and the claims are not directed to a narrow subset of compounds. Instead, the claims broadly recite the classes of silicone and acrylate polymers, which are known to contain a multitude of species. (*See, e.g.*, PTX-365, PTX-364)

Similarly, *Abbott* does not compel a different result. The patent in *Abbott* claimed a product designated Crystal A, and the plaintiff alleged that Crystal B was an equivalent. *See Abbott*, 566 F.3d at 1297. The Federal Circuit determined that the dedication doctrine "foreclose[d] invocation of the doctrine of equivalents." *Id.* The patentee "claimed and disclosed [Crystal B] in its Japanese priority application. Yet it declined to claim an embodiment expressly disclosed in its priority document, thus dedicating that embodiment to the public and foreclosing any recapture under the doctrine of equivalents." *Id.* Here, there is no argument that the patentee disclosed and dedicated embodiments using polyisobutylene to the public.

Accordingly, the Court will not prohibit UCB from asserting infringement under the doctrine of equivalents on the basis of Dr. Mueller's knowledge of polyisobutylene.

3. UCB's infringement theory does not vitiate any claim limitation

Actavis asserts that UCB's doctrine of equivalents infringement theory is improper because it vitiates the "acrylate-based or silicone-base polymer adhesive system" limitation. *See Akzo Nobel Coatings, Inc. v. Dow Chem. Co.*, 811 F.3d 1334, 1342 (Fed. Cir. 2016) ("Under the doctrine of equivalents, an infringement theory thus fails if it renders a claim limitation inconsequential or ineffective."). The Court is not persuaded that UCB's theory vitiates any claim element. *See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1018-19 (Fed.

Cir. 2006) ("A holding that the doctrine of equivalents cannot be applied to an accused device because it 'vitiates' a claim limitation is nothing more than a conclusion that the evidence is such that no reasonable jury could conclude that an element of an accused device is equivalent to an element called for in the claim, or that the theory of equivalence to support the conclusion of infringement otherwise lacks legal sufficiency.") UCB has demonstrated that polyisobutylene is equivalent to an acrylate or silicone polymer here, meaning that there is no vitiation of the claim element.

4. UCB's infringement theory does not ensnare the prior art

Actavis also contends that UCB's infringement theory is improper because it "ensnares" the prior art. *See Intendis GMBH v. Glenmark Pharm. Inc., USA*, 822 F.3d 1355, 1363 (Fed. Cir. 2016) ("A patentee may not assert 'a scope of equivalency that would encompass, or ensnare, the prior art.'"); *Wilson Sporting Goods Co. v. David Geoffrey & Assocs.*, 904 F.2d 677, 684 (Fed. Cir. 1990). "A helpful first step in an ensnarement analysis is to construct a hypothetical claim that literally covers the accused device." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1324 (Fed. Cir. 2009). "Next, the district court must assess the prior art introduced by the accused infringer and determine whether the patentee has carried its burden of persuading the court that the hypothetical claim is patentable over the prior art." *Id.* at 1325. "In short, [the Court] ask[s] if a hypothetical claim can be crafted, which contains both the literal claim scope and the accused device, without ensnaring the prior art." *Intendis*, 822 F.3d at 1363.

Actavis contends that a hypothetical claim not limited to silicone and polyacrylate polymers would encompass the prior art, including the Cygnus Application and other cited references. The Court disagrees. The bases for finding that the '434 patent is not invalid for

anticipation or obviousness in light of the prior art are wholly unrelated to the polymer used in the matrix. A hypothetical claim covering polyisobutylene-based polymer adhesive systems would not be anticipated by the Cygnus Application and would not have been obvious, for the same reasons discussed above. Thus, even though the prior art describes using polyisobutylene as a pressure-sensitive adhesive suitable for use in transdermal patches, UCB's equivalence theory does not ensnare the prior art.

C. Actavis infringes under the doctrine of equivalents

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

The Supreme Court has set out two frameworks for evaluating equivalency: (1) the function-way-result test, which asks whether an alleged equivalent performs substantially the same function in substantially the same way to obtain the same result; and (2) the substantial differences test, which asks whether the substitute element plays a role substantially different from the

claimed element. *See Graver Tank*, 339 U.S. at 608-09; *Warner-Jenkinson*, 520 U.S. at 40. The Federal Circuit recently advised that "the substantial differences test may be more suitable than [the function-way-result test] for determining equivalence in the chemical arts." *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858, 869 (Fed. Cir. 2017).

The Court agrees with Actavis that the substantial differences tests provides a more helpful framework for evaluating equivalency in the context of the '434 patent. However, the Court also agrees with UCB that, even applying the substantial differences test, UCB has proved infringement by a preponderance of the evidence.[5]

UCB contends that the role of polyisobutylene in the accused transdermal patch is insubstantially different from the role of a silicone or acrylate polymer in the claimed invention. Actavis counters that polyisobutylene is chemically very different from silicone and acrylate polymers.[6] Actavis focuses on differences at the molecular scale. In particular, Actavis has shown that polyisobutylene is an organic polymer that consists exclusively of carbon and hydrogen atoms, which form a non-polar backbone without any functional groups. (*See* Mueller Tr. at 344; Gokel

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[5]Under the function-way-result test, UCB contends that the "function of the polymer adhesive system is to enable the transdermal delivery of rotigotine free base." (D.I. 238 at 7) The way it does this is "by forming an adhesive matrix that dissolves (or contains) at least 5% (w/w) rotigotine free base, wherein the matrix allows for mobility of the free base and its transfer to the skin." (*Id.* at 7) This results in "the transdermal delivery of an amount of rotigotine free base effective to treat Parkinson's disease." (*Id.* at 9) The Court agrees with Actavis that UCB's proposed function and result are directed to the entire matrix, not the specific role of the polymer adhesive system within the matrix.

[6]Actavis also contends that Neupro is not an embodiment of the claimed invention, arguing that this is dispositive of the infringement question. As infringement requires a comparison of the accused product (the ANDA product) and the claims, it is not strictly necessary to resolve this dispute. Nevertheless, the Court is persuaded by UCB that Neupro is, in fact, an embodiment of the '434 patent.

Tr. at 804-05) As a result of this molecular composition, polyisobutylene is non-polar and hydrophobic. (*See* PTX-125 at 63; Gokel Tr. at 807) By contrast, the backbone of a silicone polymer consists of the polar heteroatoms silicon and oxygen. (*See* Gokel Tr. at 804; Klibanov Tr. at 779) Silicones and polyacrylates, unlike polyisobutylene, may also contain functional groups that may be polar and/or reactive. (*See* Gokel Tr. at 805) According to Actavis, these differences are material because rotigotine contains oxygen, nitrogen, and sulfur, which are heteroatoms that can interact with certain functional groups that can be present in silicone and acrylate polymers but not in polyisobutylene. (*See* Gokel Tr. at 807-08) Thus, in contrast to other polymers, rotigotine does not interact significantly with polyisobutylene. (*See* Gokel Tr. at 808-09) For example, rotigotine can form hydrogen bonds with silicones and acrylates but not polyisobutylene. (*See* Gokel Tr. at 809, 811-12)

Although polyisobutylene is chemically different from silicone and acrylate polymers, it is nonetheless the case that ***in the context of the asserted claims***, a polyisobutylene polymer is not substantially different from a silicone or acrylate polymer. As an initial matter, as the Court has concluded that the appropriate focus is on the polymer adhesive system, and not merely on the polymer adhesive, it follows that in assessing the substantiality of any differences the Court's focus is on the differences between the ***polymer adhesive system*** of the claims and the ***polymer adhesive system*** in the ANDA products. In the context of the claimed invention, the purpose of the adhesive polymer is to act as a scaffold for the drug and to provide adhesion for the transdermal patch. (*See* Klibanov Tr. at 747) Polymers suitable for use in transdermal patches are typically pressure-sensitive adhesives and, as was known at the time of invention, silicones, acrylates, and polyisobutylenes are the most commonly used pressure-sensitive adhesives in

transdermal patches. (*See* Klibanov Tr. at 747-48; PTX-125 at 60; DTX-334 at 7) Silicones, acrylates, and polyisobutylene share common properties that are relevant to their role as pressure-sensitive adhesives – they are adhesive, biologically inert, non-irritating, and non-toxic. (*See* Klibanov Tr. at 748-49; PTX-125 at 62-63) Moreover, a POSA would understand that there are many different types of silicone and acrylate adhesives, with a wide range of varying properties – e.g., levels of solubility, hydrophobicity, tack, and viscosity. (*See* Klibanov Tr. at 750-52; PTX-365; PTX-364) The properties of silicones and acrylates can be very different from each other, and they can also overlap with the properties of polyisobutylene. (*See* Klibanov Tr. at 750-52; PTX-365; PTX-364) Thus, although silicones, acrylates, and polyisobutylenes can have different chemical and physical properties, they also share key traits that make them interchangeable as pressure-sensitive adhesives in transdermal patches. (*See* PTX-125) (reviewing "the three most commonly used adhesives (polyisobutylenes, polyacrylates and silicones)" in transdermal drug delivery systems)

Despite the fact that the relevant art indicates that polyisobutylenes, polyacrylates and silicones can all be used in transdermal patches, Actavis contends that polyisobutylene is not interchangeable for the polymer classes named in the claims because it has inherently low solubility for rotigotine. However, both Neupro itself and the '434 patent in exemplary embodiments use silicones adhesives BIO-PSA-Q7-4301 and BIO-PSA-Q7-4201 that have a solubility for rotigotine of less than 0.1%. (*See* Klibanov Tr. at 766; PTX-287 at 10, 15) The patent explicitly teaches that certain substances, such as PVP, can be added to polymers to increase "the dissolving capacity for the free base." (DTX-1 at col 3. l. 62 - col. 4 l. 16) In both silicone- and polyisobutylene-based polymer adhesive systems with PVP added, PVP and

rotigotine form complexes (microspheres) that allow the free base to move through the matrix and transfer to the skin. (*See* Klibanov Tr. at 763-71; Mueller Tr. at 324-26; DTX-120 at 5; PTX-287 at 15; PTX-267 at 1, 6)

Moreover, the evidence demonstrates that polyisobutylene can be substituted for the silicone polymer with little impact. Actavis began developing its ANDA product by making Neupro and a formulation identical to Neupro but with polyisobutylene substituted for silicone ("PIB Neupro"). (*See* PTX-378; PTX-280 at 2) Actavis then performed permeation studies, which showed that Neupro and PIB Neupro were comparable in terms of transdermal delivery of rotigotine. (*See* DTX-170 at 3-4) The amount of rotigotine delivered by PIB Neupro was statistically indistinguishable from Neupro. (*See* DTX-170 at 3) These results, although on a preliminary product that is not the ANDA product, further support the Court's conclusion that polyisobutylene is interchangeable with silicone in the claimed polymer adhesive system, as replacing silicone with polyisobutylene in Neupro had no impact on transdermal delivery.

That Actavis' optimized ANDA products containing additional ingredients not found in Neupro is not persuasive evidence that polyisobutylene and silicone are not equivalent. In particular, Actavis' ANDA products contain isopropyl myristate, which Actavis indicates is a skin permeation enhancer. (*See* PTX-428 at 3) The Court is not persuaded that the addition of isopropyl myristate suggests that polyisobutylene is substantially different from the recited polymers. Claim 1 uses the term "comprising," which allows for additional ingredients such as permeation enhancers. (DTX-1 at col. 7 l. 55) The patent also explicitly discloses the use of permeation enhancers in the present invention. (*See* DTX-1 at col. 4 ll. 57-63; col. 8 ll. 31-38) Thus, the use of an additive specifically contemplated by the patent suggests that the role of the

polymer adhesive system is not changed by including a permeation enhancer. Further, isopropyl myristate does not affect the formation of rotigotine-PVP complexes, which allow rotigotine to move through the patch and transfer to the skin. (*See* Klibanov Tr. at 769-70) Nor is Actavis' selection of [redacted] evidence of non-infringement.

Having considered the purpose for which the polymer is used in the patent, the qualities it has when combined with the other ingredients, and the scaffold function that it is intended to perform, *see Graver Tank*, 339 U.S. at 609, the Court finds that polyisobutylene and the recited silicone and acrylate polymers are not substantially different in the context of these claims. Accordingly, the Court concludes that UCB has proven by a preponderance of the evidence that Actavis infringes claim 1 of the '434 patent.

D. Actavis' ANDA product infringes dependent claims 5, 7, 14, and 15

Having found Actavis' ANDA products to infringe claim 1 of the '434 patent, the Court further finds that the ANDA products also infringe the asserted dependent claims.

Dependent claims 5, 14, and 15 require a solubility enhancing agent, specifically PVP and more specifically at a concentration of 1.5 to 5% (w/w). The Actavis ANDA products contain [redacted] PVP (w/w), a hydrophilic polymer, in the adhesive matrix. (*See* Lane Tr. at C-14-15; PTX-336 at 3; PTX-428 at 3; Lane Tr. at 627) In the ANDA products, PVP inhibits crystallization and assists in drug dissolution, by acting as a "drug solubilizer." (PTX-381; *see also* PTX-402 at 12; Lane Tr. at C-15)

Dependent claim 7 requires the polymer adhesive to contain 5 to 25% rotigotine. Actavis' ANDA products contain [redacted] rotigotine (w/w) in the polymer adhesive system. (*See* Lane Tr. at C-16; PTX-336 at 3; PTX-428 at 3)

Accordingly, UCB has demonstrated by a preponderance of the evidence that Actavis infringes claims 5, 7, 14, and 15.

II. Validity of the '434 Patent

The '434 patent generally claims transdermal therapeutic systems containing rotigotine free base in an acrylate or silicone polymer for treatment of Parkinson's disease. As relevant to Actavis' invalidity arguments, claim 1 of the '434 patent recites: "a matrix is based on a [sic] an acrylate-based or silicone-based polymer adhesive system having a solubility of ≥5% (w/w) for the free base (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol, all of said free base being present in the matrix in the absence of water." Actavis contends that the asserted claims of the '434 patent are invalid because: (1) the claims are anticipated by the Cygnus Application and (2) the claimed invention would have been obvious in light of various prior art references. As explained below, the Court concludes that Actavis has failed to meet its burden to prove by clear and convincing evidence that the asserted claims are invalid for anticipation or obviousness.

A. The Cygnus Application does not anticipate claim 1 of the '434 patent

Actavis contends that the Cygnus Application anticipates claim 1 of the '434 patent. For the Cygnus Application to anticipate claim 1, the application must disclose "all elements of [the] claimed invention arranged as in the claim." *SynQor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1375 (Fed. Cir. 2013). Because the patent examiner considered the Cygnus Application during the course of prosecution, Actavis' burden here is "particularly heavy." *Impax Labs., Inc. v. Aventis Pharm., Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008). The Court concludes that Actavis has failed to meet that burden.

The Cygnus Application generally discloses controlled-release drug formulations that can be used with transdermal patches. (*See* DTX-334 at 3) The application describes "a novel matrix composed of a continuous hydrophobic domain and a dispersed particulate hydrated silicate domain." (*Id.* at 5) A hydrophilic drug can be at least partially dissolved in the aqueous phase of the hydrated silicate. (*See id.*) Overall, the drug is associated with the hydrated silicate phase, which is then dispersed within the hydrophobic matrix. In Example 15, the hydrophilic drug is rotigotine. (*See id.* at 16) In that example, skin flux studies are presented of patches containing: the drug, propylene glycol monolaurate, benzyl alcohol, propylene glycol, a pH 6 phosphate buffer, a calcium silicate called Micro-Cell E, an emulsifier, and Silicone 4201 Adhesive. (*See id.* at 17) Example 15 corresponds to the patches described by Cygnus in a short article authored by Chiang. (*See* DTX-67 at 1) ("Chiang")

UCB essentially contends that the teachings of the Cygnus Application are limited to the exemplary patches described in the application and Chiang. UCB argues that the described patches all use rotigotine hydrochloride and water, so the Cygnus Application does not anticipate the asserted claim. However, "[a] reference must be considered for everything it teaches by way of technology and is not limited to the particular invention it is describing and attempting to protect." *EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 907 (Fed. Cir. 1985). Therefore, the Court agrees with Actavis that the application's disclosure is broader than the particular preferred embodiments (i.e., the patches described in Chiang) that the Cygnus Application is meant to cover.

The parties particularly dispute whether the Cygnus Application discloses three elements of the asserted claim: (1) a polymer adhesive system having a solubility of $\geq 5\%$ for rotigotine free

base; (2) rotigotine free base present in the matrix in the absence of water; and (3) a patch containing rotigotine free base. The Court finds that Actavis has met its burden to prove that the Cygnus Application discloses the first two of these limitations, but has failed to meet its burden to prove that the anticipatory reference discloses the third disputed limitation.

The Court finds that the Cygnus Application teaches a polymer adhesive system having a solubility of 5% or greater for rotigotine free base. The Cygnus Application discloses a number of polymers that can be used in the hydrophobic phase of the matrix, including "polysiloxanes, polyisobutylene, solvent-based hydrophobic ***polyacrylates***, polyurethanes, plasticized ethylene-vinyl acetate copolymers, low molecular weight polyether block amide copolymers, styrene-butadiene polymers, and vinyl acetate-based adhesives." (DTX-334 at 7-8) (emphasis added) The '434 patent teaches that the solubility of rotigotine free base in polyacrylate polymers "lies in the range of between 15-35% (w/w)." (DTX-1 at col. 3 ll. 29-33) Accordingly, the Cygnus Application discloses using a polymer having a solubility of at least 5% for rotigotine free base.[7]

The Court also finds that the Cygnus Application discloses water-free systems. Although the application is generally directed to two-phase matrix systems, with one phase being a hydrated or aqueous inorganic silicate phase, and the patches described in Example 15 all contain water, the application also teaches replacing the water with other polar solvents. According to the Cygnus

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[7]Example 15 also uses the same silicone polymer as Example 2 of the '434 patent. (*See* FF ¶ 96) The Court, however, does not rely on this teaching, as other evidence shows that the solubility of rotigotine free base in this silicone polymer, without additives, is <0.1%. (*See* PTX-287 at 15; Lane Tr. at 659) Although the Court concludes, *infra*, that the claimed "polymer adhesive system" consists of more than simply the polymer, the Court finds it unnecessary to delve into these details at this time, given the Cygnus Application's disclosure of polyacrylate polymers.

Application, its invention contains "hydrated" inorganic silicate, which means that "the dispersed particulate material comprises all or a portion of its total absorptive capacity of absorbed aqueous phase (i.e. water and/***or*** other polar solvent)." (DTX-334 at 7) (emphasis added) The application states that "[i]n its hydrated form the material will normally contain about 15% to 600% of its own weight in absorbed water, more usually 100% to 500% of its own weight in water (measured at 25°C)." (*Id.* at 8) But the application then explains that "[o]ther hydrophilic polar solvents such as ethanol, propylene glycol, low molecular weight (200 to 400 mw) polyethylene glycol, isopropyl alcohol, N-butanediol, m-pyrol and benzyl alcohol ***may be substituted for water*** or included in the hydrophilic domain of the matrix." (*Id.* at 8) (emphasis added) Therefore, the Cygnus Application explicitly teaches that water may be replaced with other solvents; a patch made according to this teaching would not contain water if a polar solvent was fully substituted for water. Accordingly, the Cygnus Application discloses a matrix free from water.

With respect to the final disputed limitation, Actavis has not met its burden to show by clear and convincing evidence that the Cygnus Application discloses rotigotine free base in a patch. The Cygnus Application states the chemical name of rotigotine free base: S(–)-2-(N-propyl-N-2-thienylethylamine)-5-hydroxytetralin. (*See* DTX-334 at 16, 8; Potts Tr. at 542; Peck Tr. at 514, 516; Klibanov Tr. at 772) Rotigotine, however, is a basic drug that can exist as a neutral species (i.e., the free base) or in salt form, depending on the conditions. (*See* Lane Tr. at 654) Importantly, anticipation requires the Cygnus Application to describe the element of the asserted claim as "arranged as in the claim." *SynQor*, 709 F.3d at 1375. Here, claim 1 of the '434 patent requires the ***patch*** to contain rotigotine as a free base. Thus, to anticipate the claim element, the Cygnus Application must disclose conditions in which rotigotine would be in free

base form when made into a patch.

UCB presented evidence that under the conditions set forth for Example 15 of the Cygnus Application, rotigotine is present as a salt (i.e., in its protonated form). (*See* Lane Tr. at 654-55) In particular, Example 15 uses a water solution at pH 6. (*See* DTX-334 at 17) Taking into account this pH and rotigotine's pKa (a measure of its inclination to exist as a neutral or charged compound), rotigotine would primarily exist in salt form in patches formulated according to Example 15. (*See* Lane Tr. at 654-55) (applying Henderson-Hasselbalch equation to determine amount of neutral and charged rotigotine) Under these conditions, "only 1.28 percent of the rotigotine could be present in the free base." (*Id.* at 655)

As discussed above, the Cygnus Application's teachings are not limited to Example 15. Furthermore, and importantly, the patches of Example 15 are not water-free. Therefore, it is possible that in a patch in which all water is replaced with ethanol (which is necessary to meet the water-free limitation), rotigotine would be present primarily in its neutral, free base form. But Actavis has presented no evidence to that effect. Actavis merely relies on the fact that the Cygnus Application uses the chemical name of rotigotine in its neutral form but does not show that the neutral form would be present in a patch. In the absence of such evidence, the Court cannot conclude that merely providing the chemical name for the rotigotine free base is sufficient evidence that rotigotine free base is present in a patch that is water-free.

Accordingly, the Court concludes that Actavis has not proven by clear and convincing evidence that the Cygnus Application teaches every limitation of claim 1 of the '434 patent.

B. Obviousness

Actavis presents three obviousness combinations: (1) that claims 5, 7, 14, and 15 would

have been obvious in light of the Cygnus Application alone or with Lipp or Pfister; (2) that claims 1, 5, 7, 14, and 15 would have been obvious in light Miranda and Timmerman; and (3) that claims 1, 5, 7, 14, and 15 would have been obvious in light Yamanaka and Timmerman.

1. The claimed invention would not have been obvious in light of the Cygnus Application alone or with Lipp or Pfister

Actavis first contends that the Cygnus Application alone or in combination with Lipp or Pfister renders the asserted dependent claims invalid for obviousness. Specifically, claim 7 recites that the polymer adhesive contains 5 to 25% rotigotine, which Actavis argues would have been obvious in light of the Cygnus Application's teaching of 1 to 20% of a drug. (*See* DTX-334 at 9) Dependent claims 5, 14, and 15 cover embodiments with PVP present in a concentration of 1.5 to 5%. Prior art references Lipp (DTX-338) and Pfister (DTX-332) both disclose transdermal patches containing PVP. (*See* Potts Tr. at 548-49) Actavis contends that it would have been obvious to combine the Cygnus Application with Lipp or Pfister to achieve the claimed invention, perhaps requiring some routine experimentation to reach the claimed range of PVP.

Actavis' contention that claims 5, 7, 14, and 15 would have been obvious in light of the Cygnus Application are predicated on the Court finding that the Cygnus Application anticipates claim 1. That is, Actavis' obviousness arguments assume that the Cygnus Application teaches all elements of claim 1; Actavis then identifies other teachings of the Cygnus Application, Lipp, or Pfister to satisfy additional limitations present in the dependent claims, such as the amount of rotigotine or the presence and concentration of PVP as a solubility enhancing again. Actavis does not meaningfully develop an alternative argument that claim 1 would have been obvious in light of the Cygnus Application. (*See* Potts Tr. at 526-27) (outlining invalidity arguments) Having found that the Cygnus Application does not anticipate claim 1 because it does not teach rotigotine free

base in a patch, it follows that the Cygnus Application – whether alone or in combination with Lipp or Pfister, which make no reference to rotigotine – does not render the claimed invention obvious.

Accordingly, the Court concludes that Actavis has failed to present clear and convincing evidence that claim 7 would have been obvious in light of the Cygnus Application alone and that claims 5, 14, and 15 would have been obvious in light of the Cygnus Application with Lipp or Pfister.

2. The claimed invention would not have been obvious in light of the combination of Miranda and Timmerman

Actavis next contends that claims 1, 5, 7, 14, and 15 would have been obvious in light of Miranda combined with Timmerman. Miranda describes transdermal systems based on adhesive polymer blends, including silicone or polyacrylate-based polymer adhesives. (*See* DTX-340 at 16) Miranda discloses using PVP as a solubility enhancing agent in concentrations between 1 and 20%. (*See id.* at 8) Miranda also states that the active ingredient can be present in relatively low concentrations, such as between 3 and 10%. (*See id.* at 15) Miranda discloses using solvents that are not water, including ethanol, which are removed during the laminate drying process. (*See id.* at 36-37) Miranda does not specifically name rotigotine as a suitable drug for its patches, but it does include a list of other drugs that are used to treat Parkinson's disease. (*See id.* at 25) Actavis describes Miranda as a "recipe" or "checklist" for making transdermal patches. (*See* D.I. 262 at 14)

Timmerman is a journal article that describes a study in which rats were treated transdermally on the skin of the neck with an ethanol/water/polyethylene glycol solution containing rotigotine free base. (*See* DTX-6 at 6) Timmerman was an early study that sought to

determine, among other things, "what effects different routes of administration (intraperitoneal (i.p.), oral and transdermal) have on potency and duration of action of both enantiomers" of rotigotine. (*Id.* at 1) Timmerman concluded that transdermal application of rotigotine, a potent dopamine agonist, was superior to oral administration. (*See id.* at 6)

Actavis contends that using rotigotine free base taught by Timmerman in a patch made according to the Miranda instructions would render the claimed invention obvious. Actavis contends a POSA would have known, from the teachings of Timmerman, that transdermal delivery of rotigotine was superior, motivating the POSA to make a transdermal patch. Actavis argues that a POSA would known that rotigotine hydrochloride has a poor ability to pass through the skin, thus motivating a POSA to use rotigotine free base, as taught by Timmerman. (*See* DTX-1 at col. 3 ll. 40-41) Actavis also contends that a POSA would have known that water-free patches were easier to manufacture. From this, Actavis states that a POSA would have been motivated to make a water-free rotigotine free base transdermal patch.

However, Actavis does not explain why a POSA would have been motivated to start from the patches taught by Miranda. At most, Actavis suggests that Miranda is a good starting point because its disclosure of a successful patch for transdermal delivery was not cited in the prosecution history of the '434 patent, and it teaches a patch that discloses all the limitations of the '434 patent except for rotigotine free base. (*See* D.I. 237 at 17; D.I. 262 at 14) But this justification appears to be based on hindsight, as it stems from the claims of the '434 patent and is not tied to the perspective of a POSA attempting to solve the challenges overcome by the claimed invention in the relevant time period. *See In Touch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014). Nor does Actavis' expert provide any compelling rationale for

combining the references or discuss the motivating factors Actavis now asserts. (*See* Potts Tr. at 553-57)

Moreover, the Court is not persuaded that a POSA would have reasonably expected that a combination of Miranda and Timmerman would be successful. Contrary to Actavis' characterization, the transdermal patch field was not a crowded field at the pertinent date. In 1998, at the time of the invention of the '434 patent, only eight transdermal patches were commercially available. (*See* Lane Tr. at 610) Even now, only about 20 drugs are available in patch form. (*See id.*) This is in sharp contrast to the thousands of drugs that are available in other dosage forms, such as by oral delivery. (*See id.*) Of the drugs available as patches, rotigotine is the only active ingredient that was introduced as a patch without first being available in a different type of formulation. (*See* DTX-41 at 1) Thus, even accepting Actavis' contention that prior art like Miranda provides a "recipe" or "check list" for making transdermal patches, a POSA would have confronted a significant challenge to create a patch that was successful at treating Parkinson's disease. The Court is not persuaded that the claimed invention would have been, at the time of the invention, as trivial and straightforward as simply combining rotigotine free base of Timmerman with the patch recipe of Miranda. This is especially true in light of the teachings of Chiang, which include preliminary studies demonstrating that path formulation can have a dramatic effect on observed skin flux. (*See* DTX-67 at 2)

Accordingly, the Court concludes that Actavis has failed to present clear and convincing evidence that claims 1, 5, 7, 14, and 15 would have been obvious in light of the combination of Miranda and Timmerman.

3. The claimed invention would not have been obvious in light of Yamanaka in combination with Timmerman

Finally, Actavis contends that the claimed invention would have been obvious in light of Yamanaka with Timmerman. As described above, Timmerman is a research article in which a solution of rotigotine free base in an ethanol, water, and polyethylene glycol solution was applied to the neck of rats. (*See* DTX-6 at 2) Yamanaka is a patent application that discloses transdermal patches for use with basic drugs. Yamanaka states that PVP can be used as part of the pressure-sensitive adhesive to improve cohesion and improve the hydrophilic nature of the adhesive, but it does not explicitly state that PVP acts as a solubility enhancing agent in the patches. (*See* DTX-339 at 4) Yamanaka is particularly directed to active ingredients containing an amino or amide group, like rotigotine. (*See id.*) The application does not specifically name rotigotine, although it does list eight other drugs used to treat Parkinson's disease. (*See id.* at 5)

Actavis contends that it would have been obvious to combine the patches taught by Yamanaka with rotigotine free base taught by Timmerman to achieve the claimed invention. Actavis has not carried its burden to demonstrate that it would have been obvious for a POSA to combine Yamanaka with Timmerman.

For the same reasons as above, the Court is not persuaded that a POSA would have been motivated to combine Yamanaka and Timmerman with a reasonable expectation of success. Dr. Potts did not explain why a POSA would have been motivated to combine the teachings of these references. (*See* Potts Tr. at 557-59) Actavis contends that a POSA would have been motivated to use rotigotine free base to increase skin permeation and would have wanted a formulation free of water for ease of manufacturing. But Actavis does not address why a POSA would have been motivated to start with the patches of Yamanaka specifically. Actavis' explanation for the

selection of Yamanaka is that "[i]t was prior art, and prior art not previously cited to the Patent Office." (Potts Tr. at 558) This is unpersuasive and insufficient.

At best, a POSA wanting to make a transdermal patch containing rotigotine as a free base might have been drawn to Yamanaka due to its stated preference for basic drugs containing amino groups, like rotigotine. Yamanaka, however, primarily discusses the drugs in their salt form. (*See* Potts Tr. at 591-92) Actavis does not explain why a POSA trying to make a patch containing rotigotine free base would select Yamanaka, given the prevalence in the Yamanaka of drugs in the salt form. Relatedly, Actavis does not explain how the teachings of Yamanaka would work in practice to result in a formulation with rotigotine free base present. Nor does Actavis address whether any modifications are necessary to ensure that rotigotine is present as a free base. Thus, the Court finds that Actavis has not demonstrated that a POSA would have been motivated to combine Yamanaka and Timmerman.

Moreover, the Court is not persuaded that a POSA would have reasonably expected that a combination of Yamanaka and Timmerman would be successful. As already stated, the Court is not persuaded that this is a crowded field, such that the asserted claims simply combine well-known and commonly-used components. Rather, there are relatively few drugs available as transdermal patches (*see* Lane Tr. at 610), and rotigotine is the only active ingredient to have a transdermal patch as its first dosage form (*see* DTX-41 at 1). It follows, the Court finds, that a POSA would have faced significant challenges in reaching the claimed invention.

Accordingly, the Court concludes that Actavis has failed to present clear and convincing evidence that claims 1, 5, 7, 14, and 15 would have been obvious in light of Yamanaka and Timmerman.

4. Objective indicia of non-obviousness support UCB

Additional support for the Court's conclusions with respect to the non-obviousness of the challenged claims is provided by UCB's evidence of secondary considerations of non-obviousness. Such evidence contributes to the Court's finding that Actavis has not made a clear and convincing showing of obviousness. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Lit.*, 676 F.3d 1063, 1075-77 (Fed. Cir. 2012).

"Objective indicia can be the most probative evidence of nonobviousness in the record, and enable[] the court to avert the trap of hindsight." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (internal quotation marks omitted); *see also Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012) ("These objective guideposts are powerful tools for courts faced with the difficult task of avoiding subconscious reliance on hindsight. . . . These objective criteria thus help turn back the clock and place the claims in the context that led to their invention."). "For objective evidence [of secondary considerations] to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995); *see also Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

The parties' dispute whether UCB has established the requisite nexus between the objective evidence and the claimed invention. Defendants contend that because Neupro contains water, the Neupro patch is not an embodiment of the '434 patent claims and, therefore, cannot serve as a basis for finding a nexus between that patch and the claims. (*See* Lane Tr. 726-35; DTX-690 at 18843; DTX-461 at 31; DTX-174 at 5-7) UCB counters that water in the Neupro patches is merely an impurity.

In the Court's view, UCB has shown a sufficient nexus between objective evidence relating to Neupro and the merits of the claimed invention. The invention of the '434 patent is a patch containing rotigotine free base in a matrix without a separate aqueous phase. Neupro has those characteristics. That Neupro patches may contain a small amount of water is not dispositive. *See, e.g., Cumberland Pharm., Inc. v. Mylan Institutional LLC*, 2014 WL 787812, at *7 (N.D. Ill. Feb. 26, 2014) (invention that is "free from a chelating agent" may have impurities that are chelating agents). UCB presented evidence that Neupro is formulated not to have water in the matrix and the NDA states that there is no water present in the finished product. (*See* PTX-287 at 8 (water "[r]emoved during processing, not present in finished product"); PTX-280 at 2 (same for Neupro 2012); PTX-223 at 2 (same for Neupro 2007)) In manufacturing Neupro, water is used as a solvent for sodium metabisulfite in the first step of the process, but the water is removed during subsequent processing steps. (*See* PTX-287 at 9, 31) Water is a known impurity present in PVP. (*See* PTX-180) (showing that Kollidon 90F, USP grade PVP, may contain up to 5% water) Thus, the fact that Neupro may contain small amounts of water is the result of impurities rather than a formulation having an aqueous phase. Accordingly, the Court finds sufficient connection to consider UCB's evidence.[8] *See In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) ("Evidence of secondary considerations must be reasonably commensurate with the scope of the claims.").

UCB offered evidence regarding three secondary considerations: long-felt but unmet need, unexpected results, and failure of others.

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[8]To be clear, even in the absence of any secondary considerations, the Court still concludes that Actavis has not demonstrated that a POSA would have been motivated to combine the various prior art references or would have had a reasonable expectation of success in doing so.

With respect to unmet need, UCB demonstrated that in 1998, many oral medications were available for patients with Parkinson's disease – including levodopa/carbidopa and dopamine agonists – but each suffered from significant drawbacks. (*See* Hermanowicz Tr. at 243-47) Oral medications available at the time were unable to control symptoms over 24 hours and patients were noncompliant in taking medication because of the "pill burden." (*Id.* at 248) There was a need for a formulation to treat the symptoms of Parkinson's disease that avoided the known problems of oral medications (*see id.* at 246-47), which Neupro, as a transdermal patch, satisfied. (*See id.* at 248-53; PTX-131; PTX-83; PTX-79) Neupro was the first and only transdermal patch available to treat Parkinson's disease. (*See* Hermanowicz Tr. at 244, 248; Potts Tr. at 563)

UCB also has shown that the claimed invention is somewhat unexpected. Cygnus created prototypes of systems without the separate aqueous phase but found that a "two phase" design was necessary to achieve adequate results, and that systems without the separate water phase resulted in only nominal skin flux. (DTX-67 at 2) Thus, a POSA would have been somewhat surprised that UCB achieved greater success with a "simple matrix." (*Id.*) However, the extent of a POSA's surprise would have been modest, particularly given that the Cygnus patches used rotigotine hydrochloride as the active ingredient, whereas the claimed invention uses rotigotine free base. (*See* DTX-41 at 3)

UCB has not demonstrated the secondary consideration of failure of others. The Cygnus rotigotine patch was used in proof of concept clinical trials. (*See* DTX-41 at 3; Potts Tr. at 543; Mueller Tr. at 362) In one study, the Cygnus patch was applied to healthy volunteers and produced plasma levels in a range useful for treatment. (*See* DTX-41 at 3; Peck Tr. at 518-19) In a second study, nine patients with Parkinson's disease were given the Cygnus patch, resulting in

reduction in severity of symptoms. (*See* DTX-41 at 3) The Cygnus patches were not a failure; they showed "promising results." (Peck Tr. at 521) Indeed, the Cygnus patches were the "prototype" for Neupro (DTX-419 at 5; Potts Tr. at 539-40), and the Cygnus studies were submitted to the FDA when Plaintiffs sought approval for Neupro (*see* Peck Tr. at 517; DTX-419 at 7). That the Cygnus patches were not developed commercially – because Cygnus' partner, DTI, opted to continue its development of a rotigotine transdermal delivery system with LTS (*see* DTX-41 at 3; Peck Tr. at 521) – does not establish failure of others.

In sum, the Court concludes that two secondary considerations of non-obviousness – long-felt but unmet need and unexpected results – favor UCB. Again, Actavis has failed to prove, by clear and convincing evidence, that any of the claims of the '434 patent are invalid as obvious.

III. Validity of the '414 Patent

The '414 patent claims a new polymorphic form of rotigotine, Form II. Actavis contends that the claims of the '414 patent are invalid because: (1) the invention was derived from LTS scientists not named as inventors, (2) prior art inherently discloses Form II, and (3) Form II was used in the United States before the date of the invention. As explained below, the Court concludes that Actavis has failed to meet its burden to prove invalidity by clear and convincing evidence under its derivation and inherent anticipation theories, but has met its burden to prove by clear and convincing evidence that the claims of the '414 patent are invalid because the invention was in use in this country before the patent's priority date.

A. The '414 patent was not derived from others

Actavis contends that the subject matter of the '414 patent was derived in whole from others. According to Actavis, LTS scientists recognized the existence of Form II before UCB

scientists and communicated their discovery to UCB by providing samples of Form II, on which UCB merely performed routine characterization that is disclosed in the '414 patent. Actavis has failed to meet its burden to prove that UCB derived its invention from LTS.

To prove derivation, the patent challenger must establish prior conception of the invention by another and communication of that conception to the patentee. *See Price v. Symsek*, 988 F.2d 1187, 1190 (Fed. Cir. 1993). Conception is the formation in the inventor's mind of a definite, permanent, specific, settled idea that constitutes the complete and operative invention defined by the claims at issue. *See, e.g.*, *Cumberland Pharm. Inc. v. Mylan Institutional LLC*, 846 F.3d 1213, 1218 (Fed. Cir. 2017). Conception requires the contemporaneous recognition and appreciation of the invention. *See Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1063-64 (Fed. Cir. 2005). "[A]n accidental and unappreciated duplication of an invention does not defeat the patent right of one who, though later in time, was the first to recognize that which constitutes the inventive subject matter." *Id.* at 1063 (quoting *Silvestri v. Grant*, 496 F.2d 593, 597 (CCPA 1974)).

Assessing conception involves consideration of whether an alleged original inventor appreciated what had been made. *See Dow Chem. Co. v. Astro-Valcour, Inc.*, 267 F.3d 1334, 1341 (Fed. Cir. 2001). The purported original inventor must have "understood his creation to have the features that[] comprise the inventive subject matter at bar." *Invitrogen*, 429 F.3d at 1064. That original inventor, however, need not have "recognized the invention in the same terms" as what is recited by the claims. *Silvestri*, 496 F.2d at 599. It is sufficient for the original inventor to have "recognized and appreciated as a new form, a compound corresponding to the compound defined by the [claims]." *Id.* "Thus, with regard to a claimed chemical compound, conception requires

that the inventor be able to define the compound so as to distinguish it from other materials, and to describe how to obtain it." *Invitrogen*, 429 F.3d 1052, 1063 (Fed. Cir. 2005) (internal quotation marks omitted); *see also Creative Compounds, LLC v. Starmark Labs.*, 651 F.3d 1303, 1312 (Fed. Cir. 2011) ("Conception requires (1) the idea of the structure of the chemical compound, and (2) possession of an operative method of making it."); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991).

On August 7, 2007, a precipitation event happened at the LTS manufacturing facility. (*See* FF ¶ 41) At the time of the event, LTS did not know what the precipitate was or why it had occurred, although LTS did recognize that something different had happened in the manufacturing process. (*See* Mueller Tr. at 332-34) In the immediate aftermath of the precipitation, there was close coordination and collaboration between LTS and UCB, with both companies collecting data and sharing information. (*See* FF ¶¶ 43-44) LTS performed some initial tests, such a melting point and solubility studies. (*See* DTX-8 at 8; Emgenbroich at 116-17) LTS documents indicate that, as a result of its preliminary tests, "the possibility of polymorph forms of Rotigotine came into the discussion." (DTX-408 at 4; *see also* DTX-409 at 15 ("The investigations conducted immediately in the [LTS] analytical department revealed that this phenomenon is, with great probability, the result of polymorphic behavior of the active ingredient."); DTX-145 at 2) In a phone call between Dr. Mueller of LTS and Dr. Wolff of UCB, the scientists considered rotigotine polymorphism as "one option" but "did not know at the time" if that is what had occurred. (Wolff Tr. at 78; *see also* Mueller Tr. at 355) Thereafter, LTS gave a sample of the precipitate to Dr. Wolff, who delivered the sample to UCB for further testing. (*See* Wolff Tr. at 90-91) By August 13, both companies had developed data that supported the conclusion that Form II was a

polymorph. (*See* FF ¶ 44) But LTS did not perform the testing that conclusively determined that Form II was a pure polymorph of rotigotine; instead, UCB performed those tests in September. (*See* FF ¶¶ 48-51)

The issue, then, is whether LTS sufficiently recognized and appreciated what had been made such that individuals at LTS conceived of the claimed invention ***before*** LTS communicated with UCB. Although it is true that LTS recognized that it had isolated something new and hypothesized that it could be a new polymorph of rotigotine, LTS did not have a definite and permanent idea of the invention, for reasons including that LTS did not know the relevant chemical structure. *See Burroughs Wellcome*, 40 F.3d at 1229 ("The alleged inventors in *Fiers* and *Amgen* claimed conception of their respective inventions before they knew relevant chemical structure – the nucleotide sequence – so the courts found no conception until experimentation finally revealed that structure."). At the time that LTS disclosed the precipitation issue and provided a sample to UCB, LTS at most suspected that a new form of rotigotine had appeared. The solubility tests and melting point determination it conducted support a conclusion that something different than Form I was formed, but they are indicative, not conclusive, of the existence of a new solid form and simply represented the first steps in a series of studies that were necessary to identify the chemical structure of Form II. (*See* FF ¶¶ 45-51) It was not until after UCB's involvement that anyone determined the composition of Form II. (*See* FF ¶ 46)

The facts here contrast sharply with those in *Silvestri v. Grant*, 496 F.3d at 600, a case relied on by Actavis, in which the CCPA determined that scientists at Bristol had recognized a new crystalline form of ampicillin. There, Bristol had performed infrared spectroscopy and water assays and concluded that the new form "look[ed] different crystallographically from most"

samples. *Id.* From that testing, Bristol concluded that it had a new form of ampicillin that was essentially anhydrous, and additional testing demonstrated that the anhydrous form showed increased stability. *See id.* As a result of all its testing, Bristol requested that the FDA promulgate new regulations regarding the new form of ampicillin. *See id.* Thus, Bristol recognized and appreciated that it had created a new form of ampicillin. Here, LTS only performed preliminary tests to take a melting point and try to dissolve the precipitate in various ways, then contacted UCB, which performed the additional analyses.

At best, Actavis can demonstrate that LTS and UCB had contemporaneous and collaborative conception of the new form of rotigotine.[9] The evidence shows that LTS very quickly involved UCB in the process of determining what the precipitate was and how it occurred, and UCB immediately began investigations. (*See* FF ¶ 42) Within days of the event, LTS and UCB scientists had a meeting to discuss the results of their early studies, from which both companies hypothesized that Form II was a "modification" of rotigotine, such as a polymorph. (*See, e.g.*, DTX-145 at 2, 15) Moreover, Dr. Mueller, an LTS scientist, testified that UCB, not LTS, collected the data presented at the August 13 meeting between the two companies. (*See* Mueller Tr. at 335-37) But even before that early meeting, Dr. Wolff was present at LTS nearly every day, where he was coordinating activities to study the precipitate. (*See* Wolff Tr. at 91) Thus, there is no testimony or corroborating evidence that LTS reached any conclusion regarding the identity of the precipitate before, or independent of, UCB. Therefore, LTS did not conceive of the invention and then communicate it to UCB. Instead, LTS experienced a manufacturing issue

[9]Actavis does not argue that LTS scientists are co-inventors; Actavis contends that LTS scientists are the only inventors. (*See* D.I. 237 at 6-7)

and LTS and UCB together began research to determine what the precipitate was.

Nor is the fact that LTS provided a sample of Form II to UCB dispositive. "Conception of a chemical substance includes knowledge of both the specific chemical structure of the compound and an operative method of making it." *Burroughs Wellcome Co. v. Barr Labs. Inc.*, 40 F.3d 1223, 1229 (Fed. Cir. 1994). By virtue of having some Form II material, LTS and UCB were in possession of a method for making more Form II. (*See* Myerson Tr. at 493) But at the time that LTS provided that sample, no one knew the composition of the precipitate. Thus, the fact that LTS had some operative method for making more Form II that was given to UCB does not end the inquiry of whether LTS recognized and appreciated the subject matter of the invention. As discussed above, Actavis has failed to meet its burden to demonstrate that LTS conceived of the invention before communicating with UCB.

Accordingly, the Court concludes that Actavis has failed to prove by clear and convincing evidence that UCB derived the subject matter of the '414 patent from LTS.[10]

B. Schacht Example 1 and '434 patent Example 2 do not inherently anticipate the claims of the '414 patent

Actavis contends that patches made according to Schacht Example 1 or the '434 patent's Example 2 – references that are undisputedly § 102(b) prior art to the '414 patent – inevitably contain Form II rotigotine. (*See* D.I. 237 at 3-6) Schacht Example 1 describes patches

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[10]UCB contends that Actavis' failure to identify by name an alleged prior inventor at LTS is fatal to its § 102(f) challenge. *See Research Found. of State Univ. of New York v. Mylan Pharm. Inc.*, 809 F. Supp. 2d 296, 335-36 (D. Del. 2011) ("It is also notable that Mylan has not identified anyone who is a missing inventor."); *but see In re Bendamustine*, 2016 WL 3381219, at *14 (D. Del. June 10, 2016); *Apotex Inc. v. Cephalon*, 2011 WL 6090696, at *18 (E.D. Pa. Nov. 7, 2011), *aff'd*, 500 F. App'x 959 (Fed. Cir. 2013). Given the Court's conclusion that UCB did not derive the invention from LTS, it unnecessary for the Court to reach this issue.

substantially similar to original Neupro patches, which were formulated to contain amorphous rotigotine. (*See* FF ¶ 67) According to Actavis, amorphous rotigotine crystallizes into Form II in the absence of an inhibitor or stabilizer. Although PVP may be used as such a stabilizer, Actavis argues that the amount of PVP in Schacht is insufficient to prevent Form II from crystallizing out of the patch. Actavis submits that this is evident based on the withdrawal of original Neupro from the market and its subsequent reformulation, as those events were mandated by the uncontrollable crystallization of Form II when using a formulation like that of Schacht Example 1, particularly 9:2 rotigotine:PVP.

Similarly, Actavis asserts that Example 2 of the '434 patent does not contain enough PVP to inhibit Form II crystal formation, making it inevitable that Form II crystals will form in patches made according to the example. Actavis relies on a later patent application, Wolff, as evidence that patches containing 9:2 or 9:3 rotigotine:PVP necessarily result in Form II crystals because such formulations lack sufficient crystallization inhibitors. (*See* DTX-345 at Table 3; FF ¶ 69)

While the Court agrees with Actavis that Form II crystals ***may*** form in patches made in accordance with Schacht Example 1 or Example 2 of the '434 patent, the Court is not persuaded that this is ***necessarily*** and ***inherently*** so.

"[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). Inherent anticipation requires that "the disclosure of the prior art is sufficient to show that the natural result flowing from the operation as taught in the prior art would result in the claimed product." *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005) (internal

quotation marks and alterations omitted); *see also King Pharm., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275 (Fed. Cir. 2010). "The mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient" to prove inherent anticipation. *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (emphasis added). Thus, "if the teaching of the prior art can be practiced in a way that yields a product lacking the allegedly inherent property, the prior art in question does not inherently anticipate." *In re Armodafinil Patent Litig.*, 939 F. Supp. 2d 456, 465 (D. Del. 2013); *see also Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043 (Fed. Cir. 1995) (affirming finding of no inherent anticipation where practice of prior art "could yield crystals of either polymorph").

Here, the Court finds that Actavis has not carried it burden to prove that Form II necessarily results from patches prepared using the Schacht or '434 patent examples. Actavis places great weight on the precipitation event that occurred at LTS' manufacturing facility, the subsequent discovery that Form II crystals were appearing in commercial Neupro patches, and the ultimate need to reformulate Neupro to prevent crystallization. While these events are certainly probative they are not dispositive of the inherent anticipation issue. This is because the patches and processes described by Schacht Example 1 and the '434 patent's Example 2 are not identical to the original Neupro patches and manufacturing processes. In particular, Schacht Example 1 uses different solvents, and Example 2 of the '434 patent has an increased PVP concentration. (FF ¶¶ 71, 78-79) Actavis has not demonstrated that these differences are immaterial as to whether Form II crystals appear. (*See* Myerson Tr. at 418-20) Further, Actavis did not prepare any samples according to the prior art examples to show that they necessarily result in Form II crystals.

Moreover, the prior art examples can be practiced in a way that does not yield Form II crystals. Various studies by UCB scientists demonstrated that whether Form II crystals are formed

is dependent on the amount of impurities present, particularly rotigotine hydrochloride. (*See* FF ¶¶ 64, 75) One study showed that 5% rotigotine hydrochloride prevented Form II crystal formation even at elevated temperature. (*See* DTX-384 at 3, 5) In other studies, small amounts of acid binder – which react with rotigotine free base to form a rotigotine salt (*see* DTX-384 at 17) – were shown to help inhibit growth of Form II crystals and retain rotigotine in amorphous form. (*See, e.g., id.* at 12, 14) UCB scientists hypothesized that the appearance of Form II crystals may have been caused by a decrease in the amount of rotigotine hydrochloride present as an impurity in commercial batches of rotigotine. (*See id.* at 24) (noting that rotigotine used to make patches before appearance of Form II had 170 ppm or more of chloride (corresponding to rotigotine hydrochloride), while rotigotine used during and after appearance of Form II had less than 14 ppm of chloride) From this evidence, the Court finds that rotigotine hydrochloride impurities can prevent formation of Form II rotigotine. (*See id.* at 20)

Rotigotine free base, which is used in the prior art examples, may contain rotigotine hydrochloride impurities. Commercially-available rotigotine free base is known to contain some rotigotine hydrochloride, up to even 0.3%. (*See* DTX-384 at 24; FF ¶ 74) Additionally, the examples do not require using commercially-available rotigotine free base. Instead, the examples may be practiced by independently synthesizing the rotigotine free base, which can be made by starting with the rotigotine hydrochloride salt. (*See* Rogers Tr. at 207, 213) Rotigotine free base made from the hydrochloride salt can be isolated in advance or made in situ. (*See* Rogers Tr. at 208-09; Emgenbroich Tr. at 121-22) When made from the hydrochloride salt, the corresponding rotigotine free base will likely contain hydrochloride impurities, regardless of whether the free base is isolated in advance or made in situ. (*See* Myerson Tr. at 429-31) Rotigotine free base

prepared in situ is known to contain residual rotigotine hydrochloride up to 10%.[11] (*See* Rogers Tr. at 212; Myerson Tr. at 426)

Although it may not ideal for an active pharmaceutical ingredient to contain such impurities, Schacht and the '434 patent do not require a more purified form of rotigotine free base to be used. Both references describe making rotigotine free base from the hydrochloride salt, indicating the propriety of utilizing such a synthesis despite the known, attendant impurities. (*See* DTX-1 at col. 4 ll. 38-40; DTX-336 at ¶ 73) Dr. Emgenbroich testified that during development of Neupro, "this kind of conversion step" was necessary because rotigotine free base was not otherwise available in significant quantities. (Emgenbroich Tr. at 121)

Thus, the Court is persuaded that a patch made according to Schacht Example 1 or Example 2 of the '434 patent will not necessarily and inevitably result in Form II. If the rotigotine free base starting material used to make a patch contains sufficient rotigotine hydrochloride impurities, such impurities may inhibit crystal growth. The evidence shows that even relatively small amounts of impurities can prevent crystallization – i.e., no Form II was observed in patches made from rotigotine containing 0.2% rotigotine hydrochloride. (*See* DTX-384 at 24) The prior art does not exclude such impurities, which are commonly present in rotigotine free base, even commercially-available rotigotine. Therefore, the Court finds that it would not be extraordinary for the rotigotine starting material to contain sufficient rotigotine hydrochloride to prevent Form II crystallization, making it reasonable to conclude that "under normal conditions" Form II may not

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[11]Example 2 of the '434 patent requires the rotigotine free base to be isolated in advance. (*See* FF ¶ 79) This does not change the Court's analysis with respect to this issue, as the evidence shows that even isolated rotigotine free base commonly contains rotigotine hydrochloride impurities. (*See* Myerson Tr. at 430-31)

be present in patches. *Schering*, 339 F.3d at 1378.

Accordingly, the Court concludes that Actavis has not carried it burden to show by clear and convincing evidence that Schacht Example 1 or Example 2 of the '434 patent inherently anticipate the claims of the '414 patent.

C. The invention of the '414 patent was in use before the priority date

Actavis contends that the invention of the '414 patent, Form II rotigotine, was "used by others in this country" because patches from affected production lots containing Form II were available to the public and used before the priority date of the patent, November 28, 2007. The Court agrees.

1. UCB has waived any argument that it is entitled to an earlier invention date

As an initial matter, the Court must resolve the parties' dispute as to the invention date that should be afforded to the '414 patent. Prior art, including prior use, under § 102(a) is measured in relation to "the invention thereof by the applicant for patent." *See also Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996). Generally, "the date of invention [is] presumed to be the filing date of the application until an earlier date is proved." *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 449 (Fed. Cir. 1986). When a defendant challenging a patent's validity introduces alleged prior art dated before the priority date of the patent, the patentee may present evidence of an earlier invention date. *See Mahurkar*, 79 F.3d at 1576-78. The patentee may establish an earlier priority date by producing evidence that the inventor (1) reduced the invention to practice before the date of the alleged prior art or (2) conceived the invention prior to the date of the alleged prior art and that the inventor exercised reasonable diligence in later reducing that invention to practice. *See Price v. Symsek*, 988 F.2d

1187, 1190 (Fed. Cir. 1993). "Though the patentee has the burden of production in antedating a reference, the burden of persuasion, by clear and convincing evidence, remains with the party that challenges an issued patent's validity." *Stamps.com Inc. v. Endicia, Inc.*, 437 F. App'x 897, 907-08 (Fed. Cir. 2011) (citing *Mahurkar*, 79 F.3d at 1576).

In its post-trial briefing, UCB contends for the first time that it is entitled to an invention date earlier than November 28, 2007, the priority date listed on the face of the '414 patent. In the pre-trial order, despite UCB's awareness that Actavis would present its § 102(a) invalidity defense at trial (*see* D.I. 211 Ex. 5 at 11), UCB did not contend that it would present evidence or argument regarding an earlier invention date. (*See* D.I. 211 Ex. 2 at 57) Instead, UCB's statement of facts to be litigated in the pre-trial order repeatedly frames the § 102(a) issue around the November 28, 2007 priority date:

> Neupro® patches were first sold in the United States in July 2007. The patent application issuing as the '414 patent was filed ***November 28, 2007***. . . . Actavis cannot prove by clear and convincing evidence that Neupro® patches having form 2 rotigotine were ever on sale or in public use in the United States, let alone prior to ***November 28, 2007***. . . . Actavis cannot prove by clear and convincing evidence that Neupro® patches publicly available in the United States contained form 2 before the '414 patent's priority date. . . . Actavis cannot prove by clear and convincing evidence that any conversion occurred in patches publicly available in the United States prior to ***November 28, 2007***.

(*Id.*) (emphasis added) Consistent with the pre-trial order, UCB's validity expert, Dr. Myerson, testified at trial that he used November 28, 2007 as the relevant date. (*See* Myerson Tr. at 373, 461-62) UCB made no suggestion at trial that it was arguing for an earlier invention date.

Because the pre-trial order "limits the issues for trial," *Hassan v. Stafford*, 472 F.2d 88, 95 (3d Cir. 1973), and UCB never raised an earlier invention date as an issue for trial, it is too late

now for UCB to ask the Court to find an earlier invention date. UCB has waived this issue. *See, e.g., S. W. Farber, Inc. v. Texas Instruments, Inc.*, 211 F. Supp. 686, 694 (D. Del. 1962). UCB failed to put Actavis on notice at any point before or during the trial that UCB intended to argue for an earlier invention date. Allowing UCB to press this argument now would expose Actavis to significant unfair prejudice, as Actavis had no reason to gather and present evidence or to cross-examine UCB's witnesses, including inventors of the '414 patent, on the invention date.[12]

Accordingly, the Court will use the presumptive invention date, the priority date of the application, here. *See Bausch & Lomb*, 796 F.2d at 449. Thus, the applicable date is November 28, 2007.

2. Form II rotigotine was used in the United States before November 28, 2007

Pursuant to 35 U.S.C. § 102(a), a patent may be found invalid if "the invention was known or used by others in this country" before the invention by the applicant. "If the invention was known to or used by others in this country before the date of the patentee's invention, the later inventor has not contributed to the store of knowledge, and has no entitlement to a patent." *Woodland Tr. v. Flowertree Nursery, Inc.*, 148 F.3d 1368, 1370 (Fed. Cir. 1998). "For prior art to anticipate because it has been 'used,' the use must be accessible to the public." *Minnesota Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed. Cir. 2002); *see also Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1305-06 (Fed. Cir. 2006). "The prior knowledge and use by a

[12]The Court's determination that UCB waived this issue is consistent with the Court's previous determination that Actavis failed to raise a non-infringement position in a timely manner. (*See* D.I. 229 at 25) Even though UCB had the burden to prove infringement, the Court held that Actavis' untimely raising of the issue made it appropriate to strike it. Likewise, the fact that Actavis ultimately must carry the burden on invalidity does not excuse UCB's after-trial introduction of this new theory.

single person is sufficient." *Coffin v. Ogden*, 85 U.S. 120, 124 (1873); *see also Brush v. Condit*, 132 U.S. 39, 48 (1889).

Actavis contends that Neupro patches containing Form II were used before November 28, 2007, and that this use invalidates the patent. Neupro, as originally formulated, launched in June 2007. (*See* FF ¶ 38) In June and July 2007, batches of rotigotine laminate were manufactured for distribution in the United States. (*See* Rogers Tr. at 176) Of particular relevance, laminate lot 47808 was produced during this period. (*See id.*) These laminate lots made in the summer of 2007 included rotigotine sourced from Cambrex (lots 16208651 and 16208652) having a low chloride content. (*See* DTX-384 at 24; DTX-457 at 19)

On November 7, 2007, UCB submitted a Field Alert Report to the FDA, alerting the FDA that "small crystalline structure (snowflakes)" had been observed on the active surface of Neupro patches in lot numbers 108547 and 47808502. (DTX-139 at 5) UCB informed the FDA that "testing confirmed on November 7, 2007 that the snowflakes contain crystalline structures of a polymorph variant (Form 2) of the active ingredient Rotigotine." (DTX-139 at 5) According to the Report, many of the examined patches contained snowflakes; of 29 batches of product (from each batch, 21 or 50 individual patches were observed), only one batch had no patches that contained visible snowflakes. (*See* DTX-139 at 10) For batches manufactured for distribution in the United States (*see* DTX-418 at 6), over 90% of the examined patches contained crystals by November 12, 2007. (*See* FF ¶ 55; DTX-139 at 10) As a result, UCB placed the remaining inventory of the affected lots on hold. (*See* DTX-139 at 6)

Subsequent testing of batches made for distribution in the United States similarly showed that large proportions of patches had snowflake crystals – i.e., rotigotine in Form II. For example,

stability testing that began on December 13, 2007 showed that more than half of the examined patches from laminate lot 47808 had crystals at the start of the testing and all patches showed crystals after one month. (*See* DTX-172 at 14) In March 2008, UCB told the FDA that it had placed affected lots on hold and discontinued distribution. (*See id.* at 11) UCB also proposed a recall of the affected lots because the crystals impacted drug release. (*See id.* at 9, 11) At this time, UCB reiterated that the crystals were Form II. (*See id.* at 9)

Thus, it is clear that patches intended for distribution in the United States – which were manufactured in June and July of 2007 – had the propensity to form snowflake crystals, likely due to the low chloride content of the rotigotine. A large number of patches examined in November 2007 from the affected lots did, in fact, contain snowflake crystals. UCB told the FDA on several occasions that the snowflake crystals were Form II.

The remaining question, then, is whether there is evidence that any affected patches containing Form II were in use before November 28, 2007. The Court concludes that Actavis has demonstrated that affected patches were in use before that date.

On November 30, 2007, just two days after the priority date, a female patient experienced an adverse event while being treated with Neupro. (*See* DTX-701 at 4) The Alert Report submitted by UCB states that the patient received samples of Neupro in September 2007 and "responded well" to treatment. (*Id.*) In November 2007, she purchased Neupro from a pharmacy – patches that were from lot 47808. (*See id.*) While using the lot 47808 patches, the patient began "clearly back-sliding, experiencing previous symptoms of losing mobility, shaking and freezing." (*Id.* at 5) The Report indicated that the patient was on the lot 47808 patches for "one week," before she "was reverted to the samples of the newer lot number." (*Id.*)

Although the Report does not provide the exact date that the patient began using the lot 47808 patches, the most reasonable inference to be drawn is that she used the patches before November 28, 2007. The patient used the lot 47808 patches for one week before she was given patches from a different lot number, and she reported her adverse reaction on November 30, at which time the "reporter stated that he w[ould] switch the patient back to the samples." (*Id.* at 5) There is no reason to believe that the patient was not immediately given new samples. UCB has not suggested that it would be routine not to immediately provide new patches to a patient presenting an adverse reaction to affected patches, especially because by this time, UCB and the FDA were aware of the snowflake problem in patches from lot 47808. Thus, it is reasonable to believe (as the Court finds) that the patient used the patches for the week leading up to November 30. Accordingly, the Court finds that this patient used patches from affected lot 47808 before November 28.

Further, it is reasonable to infer that the 47808 patches used by the patient contained Form II rotigotine. By November 12, 2007, the vast majority of patches tested from this lot contained visible snowflake crystals corresponding to Form II. (*See* DTX-139 at 10) Dr. Rogers testified that all patches made from laminate lot 47808 contained some amount of Form II, even if it was not yet visibly observable. (*See* FF ¶ 57) This is consistent with UCB's report to EMEA, the European version of the FDA, that "[a]ll finished product batches manufactured" from laminate batches 47806, 47807, and 47808 were affected. (DTX-649 at 2) The presence of Form II in the patient's batches would be consistent with the patient's symptoms and reported backsliding. (*See* DTX-172 at 9, 11) Thus, the Court finds that Form II rotigotine, the invention of the '414 patent, was used in this country before the priority date by at least one patient.

That the public's use of Form II was not appreciated at the time does not undermine the invalidating nature of this use. *See W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1548 (Fed. Cir. 1983) (finding that in assessing whether public use anticipates claimed invention under § 102(a), "it is [] irrelevant that those using the invention may not have appreciated the results."); *see also Baxter Int'l, Inc. v. COBE Labs., Inc.*, 88 F.3d 1054, 1057 (Fed. Cir. 1996) (affirming district court decision that under § 102(b) "a use by a single person not under the control of the inventor and in public, as that term of art is used, is a [use] sufficient" to invalidate patent).

Accordingly, the Court concludes that Actavis has proven by clear and convincing evidence that Form II rotigotine was used in the United States before the November 28, 2007 priority date of the '414 patent. Therefore, claims 1-3 of the '414 patent are invalid under § 102(a).

CONCLUSION

UCB has proven by a preponderance of the evidence that Actavis infringes claims 1, 5, 7, 14, and 15 of the '434 patent. Actavis has failed to prove by clear and convincing evidence that claim 1 of the '434 patent is invalid due to anticipation or that claims 1, 5, 7, 14, and 15 of the '434 patent are invalid due to obviousness. Actavis has also failed to prove by clear and convincing evidence that claims 1-3 of the '414 patent are invalid due to derivation or inherent anticipation. However, Actavis has proven by clear and convincing evidence that claims 1-3 of the '414 patent are invalid under § 102(a) because the claimed invention was in use in the United States before its priority date.

An appropriate Order follows.