UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ABRAXIS BIOSCIENCE, INC.	:	
Plaintiff,	:	Civil Action No. 07-1251 (JAP)
v.	:	**OPINION**
NAVINTA, LLC,	:	
Defendant.	:	

PISANO, District Judge.

This patent infringement action arises out of the filing of an Abbreviated New Drug Application ("ANDA") by Navinta, LLC ("Navinta"), a generic drug manufacturer, to market a generic version of an injectable form of the anesthetic Naropin. Naropin is indicated for the production of local or regional anesthesia for surgery and for acute pain management. Plaintiffs, Abraxis Bioscience, Inc. ("Abraxis") and APP Pharmaceuticals, LLC (collectively, "APP Pharma"),[1] bring this action alleging that Defendant's filing of the ANDA constituted infringement of three patents relating to the active ingredient in Naropin: United States Patent No. 4,870,086 (the "'086 patent"), entitled "Optically Pure Compound and a Process for Its Preparation," United States Patent No. 5,670,524 (the "'524 patent") entitled "Methods and

[1]Upon motion by Abraxis, APP Pharma was joined in this action by Order dated March 30, 2009.

Compositions for the Treatment of Pain Utilizing Ropivacaine," and United States Patent No. 5,834,489 (the "'429" patent), also entitled "Methods and Compositions for the Treatment of Pain Utilizing Ropivacaine." Plaintiff alleges that Navinta has infringed claims 1, 2, 3, and 6 of the '086 patent, and has infringed and will induce infringement of claims 1 and 9 of the '524 patent and claim 1 of the '489 patent.

Defendant has asserted counterclaims against APP Pharma alleging unfair competition, violations of the Sherman Act, 15 U.S.C. §§ 1 and 2, and tortious interference with prospective economic advantage. There claims were bifurcated by Order dated July 31, 2008. Defendant also counterclaimed for a declaration of noninfringement of the '086, '524 and '489 patents.[2]

The filing of the instant lawsuit triggered a 30-month stay on the Federal Drug Administration's approval of Navinta's ANDA, and the stay expires on August 5, 2009. At a hearing held on May 29, 2009, the parties requested that the Court schedule a trial date that would permit the Court to decide the issues in the case prior to the expiration of the stay. To that end, a bench trial was held from July 20, 2009 to July 28, 2009.[3]

I. Witnesses Presented at Trial

A. Plaintiff's Witnesses

Abraxis proffered the following expert and fact witnesses at trial: Dr. Jerry Atwood,

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[2]Navinta's also counterclaimed for a declaration of invalidity of the '525 and '489 patents, but these counterclaims were not asserted at trial. In the Pretrial Order, Navinta did not identify validity as an issue to be tried. During trial, Navinta did not offer any evidence of invalidity, and no Navinta expert offered any invalidity opinion.

[3]The parties submitted written opening and closing statements.

Dr. Leonard Chyall, Dr. Gordon Amidon, Dr. Jeffrey Gudin, and Deena Reyes, and presented testimony of other witnesses through deposition testimony.

B. Defendant's Witnesses

Navinta proffered the following expert and fact witnesses at trial: Dr. Robert Gawley, Dr. Raymond Squire, David Picard, Dr. Christopher Newton Jobdevairakkam, Dr. Hugo Steinfink, Dr. Pankaj Dave, and Dr. Peter Griffiths, and presented the testimony of other witnesses through deposition testimony.

C. Credibility Determinations

It is not unusual in a case such as this one that the factfinder is faced with contradicting expert opinions. Such is the case in the instant matter, particularly with respect to the expert testimony of Drs. Atwood and Gawley, each of whom testified about, among other things, the attributes and chemistry of ropivacaine compositions, and each of whom offered starkly differing opinions in this regard. As a result, the Court, as factfinder, must determine what weight and credibility to give to the testimony. *See Energy Capital Corp. v. United States*, 302 F.3d 1314, 1329 (Fed.Cir.2002) ("As for the relative weight given to the testimony of both sides' expert witnesses, we accord the trial court broad discretion in determining credibility because the court saw the witnesses and heard their testimony."); *Gyromat Corp. v. Champion Spark Plug Co.*, 735 F.2d 549, 552 (Fed. Cir.1984) ("The credibility of the witnesses and the weight to be given to their testimony and the other evidence in the record . . . is a matter for the trier of the facts.")

The Court finds that although APP Pharma's expert, Dr. Atwood, and Navinta's

expert, Dr. Gawley, are each highly qualified in their respective specialties, to the extent that Drs. Atwood and Gawley give differing opinions on an issue, the Court accorded Dr. Atwood's testimony more weight in reaching the factual determinations set forth herein. Dr. Atwood's more extensive experience in the area of supramolecular chemistry, the manner in which testified, and the reasons he gave in support of his opinion all convinced the Court, as factfinder, to accept Dr. Atwood's testimony. Additionally, Dr. Atwood's opinions are consistent with testing performed by another of Plaintiff's expert, Dr. Chyall. With respect to Dr. Gawley, certain inconsistencies in his testimony and Navinta's own experts' criticisms of certain materials relied upon by Dr. Gawley, among other things, contributed to the Court according lesser weight to Dr. Gawley's opinions.

With respect to the '524 and '489 patents, the Plaintiffs and Defendant offered the testimony of experts Dr. Gudin and Dr. Squire, respectively. Overall, the Court found their testimony to be largely consistent. However, to the extent that their testimony may have conflicted on a particular issue, the Court accorded Dr. Gudin's testimony more weight. The Court reached this conclusion based upon Dr. Gudin's background and experience, the manner in which he testified, and the reasons he gave in support of his opinions.

Upon hearing the evidence at trial and considering the testimony and documentary evidence, the Court makes the following findings of fact and conclusions of law.

II. FACTUAL BACKGROUND

A. The Parties and the Patents

1. Plaintiff Abraxis is a corporation organized and existing under the laws of the State of

Delaware, having a principal place of business in Los Angeles, California. Plaintiff APP Pharma is a limited liability company organized and existing under the laws of the State of Delaware, having a principal place of business in Chicago, Illinois. Defendant Navinta is a limited liability corporation organized and existing under the laws of the State of New Jersey, having a principal place of business in Ewing, New Jersey. The parties are drug companies involved in, among other things, the development and manufacture of pharmaceuticals.

2. On March 1, 2007, Navinta entered into a Collaboration Agreement with Sandoz AG. This agreement gives Sandoz AG and its U.S. subsidiary Sandoz, Inc. (collectively "Sandoz") exclusive rights to "sell, market and distribute" the ANDA Products. (Picard Testimony, 7/23/09 Tr. at 732:4-8, 732:19-22; PLT 134.)

3. The United States Patent & Trademark Office issued U.S. Patent No. 4,870,086, entitled “Optically Pure Compound And A Process For Its Preparation,” on September 26, 1989. The inventor of the ‘086 Patent is Rune V. Sandberg. The '086 Patent will expire on or about September 24, 2010.

4. The Patent Office issued U.S. Patent No. 5,670,524, entitled “Methods And Compositions For The Treatment Of Pain Utilizing Ropivacaine,” on September 23, 1997. The United States Patent & Trademark Office issued U.S. Patent No. 5,834,489, also entitled “Methods And Compositions For The Treatment Of Pain Utilizing Ropivacaine,” on November 10, 1998. The inventor of the ‘524 and ‘489 patents is Arne Torsten Eek. The ‘524 and ‘489 patents will expire on or about September 23, 2014.

5. The ‘524 and ‘489 patents claim inventions regarding the use of low concentrations of

ropivacaine for pain relief.

B. The ANDA

6. On or about November 13, 2006, Navinta submitted to the U.S. Food & Drug Administration ANDA 78-601, which requests approval to engage in the commercial manufacture, use and sale of a "Ropivacaine Hydrochloride Injection" product. (Pretrial Order, Stipulated Fact 4.)

7. On or about February 2, 2007, Navinta mailed to, among others, Abraxis a "Notification of Certification of Invalidity, Unenforceability, and/or Non-Infringement for U.S. Patent No. 4,870,086 Pursuant to § 505(j)(2)(B)(iv) of the Federal Food, Drug and Cosmetic Act." (Pretrial Order, Stipulated Fact 5.)

C. The Prior Art

8. In 1985, WO 085/00599 to Thuresson (hereafter "Thuresson") disclosed a ropivacaine composition that was about 90% enantiomerically pure and 80% optically pure. As a result of its impurity, the 1-propyl-2',6'-pipecoloxylidide hydrochloride compound of Thuresson was unsuitable and not in use as an anesthetic in 1985. ('086 Patent at 1:11-35, PLT 1; Atwood Testimony, 7/20/09 Tr. at 22:16-24, 24:20-21, 26:22-25.)

9. The Thuresson compound was hygroscopic, meaning it did not have a defined water content and would take on water from the atmosphere. This is not a desirable trait for a pharmaceutical compound or composition because it would require one to analyze the compound's water content on a daily or perhaps even hourly basis. It would put an undue burden on the analytical process, either in the plant or in a pharmacy. For example, if there is

a certain desired dosage and if one has a high water content, the dosage that is administered might be too low for the effective use of the pharmaceutical. (Atwood Testimony, 7/20/09 Tr. at 25:23-26:4, 29:8-17, 30:3-6.)

10. A "Navinta Process Development Report" prepared by Navinta's Research and Development Department under the supervision of its Chief Scientific Officer, Dr. Newton, states that the quantity of "optical isomer" in the compound used in Thuresson is at about 90%, which would translate to an optical purity of about 80%. The report states that the purpose of Navinta's project was to "resolve the drawbacks observed with the literature methods," including Thuresson. (Newton Testimony, 7/24/09 Tr. at 831:11-833:10; Gawley Testimony, 7/23/09 Tr. at 675:7-676:14; PLT 161-0010 & 161-0011.)

11. The Thuresson compound did not ever result in a commercial product. (Atwood Testimony, 7/20/09 Tr. at 26:18-25.)

12. The Thuresson compound was cited by the patent examiner during the prosecution of the '086 Patent. (Gawley Testimony, 7/22/09 Tr. at 595:7-8.) However, the Patent Office ultimately issued the ‘086 Patent over Thuresson. (PLT 1-0001.)

D. The Invention of the ‘086 Patent

13. The '086 Patent discusses optically-pure enantiomer compositions. Many chemical compounds can exist as mirror images of each other. Researchers refer to one "image" of a compound as the "S" enantiomer, and refer to its mirror image as the "R" enantiomer. (Atwood Testimony, 7/20/09 Tr. at 18:6-23; PLT 378-0008.)

14. "Enantiomeric purity" is a measure of how much more of one enantiomer there is than

the other enantiomer in a mixture of enantiomers. For example, a mixture of 90% S-enantiomer and 10% R-enantiomer has 90% enantiomeric purity. (Atwood Testimony, 7/20/09 Tr. at 19:23-20:1; PLT 378-0009.)

15. One enantiomer will rotate light in a clockwise direction while its mirror image will rotate light in the opposite direction. The ability of enantiomers to rotate light is called "optical activity" and is designated by the symbols (+) and (-). Thus, (-) indicates there is more (S)-enantiomer than there is R-enantiomer. (Atwood Testimony, 7/20/09 Tr. at 19:5-10; 20:2-16; 28:20-25, 68:25-69:3, 78:3-6, 231:17-20.)

16. Measured optical activity of an enantiomer inherently indicates that the enantiomer is "optically pure." A mixture having 90% enantiomeric purity contains 90% S enantiomer and 10% R enantiomer. This is equivalent to an optical purity of 80% because 20% of the mixture would consist of 10% S enantiomer and 10% R enantiomer. This 20% of the mixture would not have any optical activity, because the optical activity of the 10% R enantiomer would cancel out the 10% S enantiomer. (Atwood Testimony, 7/20/09 Tr. at 20:17-21:2; 7/21/09 Tr. at 231:17-20; PLT 378-0011, 378-0031.)

17. The (S) enantiomer of the compound (S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride is more potent and more stable than the (R) enantiomer. ('086 Patent, PLT 1 at 1:27-29.)

18. One objective of the '086 Patent was "to obtain a product consisting of the substantially pure (S)-(–)-enantiomer." ('086 Patent, PLT 1 at 1:32-35; Atwood Testimony, 7/20/09 Tr. at 27:8-10.) Another objective of the '086 Patent was to produce the compound

(S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride in a form "which is stable and which does not change by storing at ordinary room temperature and humidity." ('086 Patent, PLT 1 at 1:29-32; Atwood Testimony, 7/20/09 Tr. at 27:8-10.)

19. Example 1 in the '086 specification details how Dr. Sandberg realized high optical purity and stability. Dr. Sandberg conceived of taking the optically impure materials, heating them with water and acetone, and then taking advantage the R-enantiomer's lesser solubility than the desired S-enantiomer. Thus, Dr. Sandberg created in a solution both the R and the S-enantiomers of the desired compound and, due to the low solubility of the R-enantiomer, was able to filter out the R-enantiomer to produce an aqueous solution of the optically pure S-enantiomer. (Atwood Testimony, 7/20/09 Tr. at 33:7-19, 34:13-17; Atwood Testimony, 7/21/09 Tr. at 256:20-25; '086 Patent, PLT 1 at 2:56-3:5; PLT 378-0013, 378-0020.)

20. In Example 1 of the '086 Patent specification, a second filtration step is performed to produce the S-enantiomer with an optical purity greater than or equal to 99.5%. (Atwood Testimony, 7/20/09 Tr. at 36:10-15.)

21. Thus, the optically pure compound (S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride disclosed in the '086 patent achieved the objective of a greatly increased amount of the (S) enantiomer relative to the (R) enantiomer. (Atwood Testimony, 7/20/09 Tr. at 21:18-20.)

22. A person of skill in the art would understand that a goal of the '086 invention was a compound with a defined water content. Claim 1 of the '086 Patent, by claiming the

monohydrate form of the compound (ropivacaine hydrochloride monohydrate, or "RHM"), accomplished this objective by providing the compound in a form that was stable and not hygroscopic. RHM has exceptional stability in both solution and in the solid state. (Atwood Testimony, 7/20/09 Tr. at 34:22-25, 39:20-25.

23. RHM as a solid is so stable that, according to the '086 Patent, it has to be heated at 75°C for 16 hours under a high vacuum to remove the water. This indicates that the water is locked into the structure of the RHM composition. The locked-in nature of the water is a key to understanding the stability of RHM, both in the solid state and in solution. (Atwood Testimony, 7/20/09 Tr. at 42:15-21; PLT 1 at 1:44-51.)

24. The stable water content offered by RHM is desirable for pharmaceuticals because it allows for extended storage and accurate dispensation by weight. Studies have confirmed a shelf life of up to five years for RHM. (Atwood Testimony, 7/21/09 Tr. at 232:7-11, 232:13-233:1.)

25. The '086 inventions were significant to the fields of chemistry and medicine. The inventions represented "elegant and exceptionally well-practiced chemistry" because they addressed serious problems that had plagued chemists for a long time. The '086 Patent solved both an optical purity problem and a stability problem. (Atwood Testimony, 7/20/09 Tr. at 38:24-39:4.) Dr. Sandberg's inventions received the 1995 Gaston Labat Lecture award from the American Society of Regional Anesthesia, at which it was noted that RHM was the

"'white knight slaying the dragon' of cardiotoxicity," a reference to the use of the anesthetic bupivacaine, in the late 1970s and early 1980s, which resulted in a significant number of cases of cardiac arrest, including numerous fatalities during childbirth. (Gudin Testimony, 7/22/09 Tr. at 465:6-14; 481:13-20; Squier Testimony, 7/23/09 Tr. at 701:6-7; Atwood Testimony, 7/28/09 at Tr. 1121:11-13; PLT 37.)

E. Naropin

26. Naropin is a branded drug marketed and sold in the United States by Plaintiff APP Pharma. The U.S. Food and Drug Administration approved NDA 20-533 for Naropin on September 24, 1996. (Gudin Testimony, 7/22/09 Tr. at 464:19-22.)

27. APP Pharma sells Naropin in concentrations of 0.2%, 0.5%, 0.75% and 1.0% by weight. (Gudin Testimony, 7/22/09 Tr. at 539:24-540:1; PLT 50-0004.)

28. Naropin is substantially optically pure and has less than 0.5% of the (R)-(+) enantiomer. (Atwood Testimony, 7/20/09 Tr. at 82:2-5; PLT 369-0002.)

29. On November 21, 1996, the original assignee of the '086 Patent, Astra Lakemedel Aktiebolag ("Astra LA"), applied for an extension of the '086 Patent term pursuant to 35 U.S.C. § 156. (PLT 277.)

30. Astra LA stated in its application: "The sole active ingredient in Naropin is Ropivacaine HCl or (S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate." Astra further stated that the "active ingredient in Naropin…is claimed in the patent." Astra also presented in its application a claim chart stating that Claim 1 of the '086 Patent covers Naropin because RHM is the active ingredient. Astra AL explained that the claims covered

the drug product as an isotonic solution, not just as a bulk drug in solid form. (PLT 277-0001, 277-0002, 277-0004, 277-0006.)

31. Two different legal advisors within the Patent Office reviewed Astra's application and concluded that the '086 claims covered the Naropin solution. (PLT 4-0140, 4-0142.)

32. In several letters from FDA officials to high-ranking PTO officials, the FDA stated its conclusion that the "human drug product claimed by the patent is NAROPIN™ (ropivacaine hydrochloride monohydrate)." (PLT 4-0141, 4-0145, 4-0149.)

33. A Notice published in the Federal Register, at 62 Fed. Reg. 38565 (July 1997), states in part: "FDA recently approved for marketing the human drug product NAROPIN™ (ropivacaine hydrochloride monohydrate)." (PLT 4-0148. *See also id.* 4-0147.)

34. Based on the PTO's and FDA's independent conclusion that the Naropin solution contains RHM and is covered by the '086 Patent claims, the Patent Office extended the term of the '086 Patent by 1,400 days. (PLT 373.)

III. DISCUSSION

A. Claim Construction

The parties have requested that the Court construe the certain claim terms found in claims 1, 2, 3 and 6 of the '086 patent. Claim 1 of the '086 patent claims "(S)-(-)-1-propyl-2',6'- pipecoloxylidide hydrochloride, wherein the compound is in the form of its monohydrate." ('086 Patent at 4:10-12.) Claim 2 of the '086 Patent states: "The compound according to claim 1, wherein it is substantially optically pure." ('086 Patent 4:13-14.) Claim 3 of the '086 Patent states: "The compound according to claim 1, wherein it

contains less than 0.5% by weight of the corresponding (R)-(+)-enantiomer." ('086 Patent at 4:15-17.) Claim 6 of the '086 Patent states: "A method for inducing local anesthesia, which comprises administering to mammals including man needing local anesthesia an anesthetizing amount of the compound according to claim 1." ('086 Patent, PLT 1 at 4:35-38.)

The following terms from claim 1 are in dispute: (i) "(S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride, wherein the compound is in the form of its monohydrate;" and (ii) "(S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride." Also, the term "the compound according to claim 1," which is found in claims 2, 3 and 6 of the '086 patent, is likewise in dispute.

a. Claim Construction Principles

35. In order to prevail in a patent infringement suit, a plaintiff must establish that the patent claim "covers the alleged infringer's product or process." *Markman v. Westview Instrs., Inc.*, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). "It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (internal quotations omitted) (citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576 (Fed. Cir. 1996) ("we look to the words of the claims themselves . . . to define the scope of the patented invention"); *Markman*, 52 F.3d at 980 ("The written description part of the specification itself does not delimit the right to exclude. That is the function and purpose of claims."). Consequently, the first step in an infringement analysis involves determining the meaning and the scope of the claims of the patent. *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175

F.3d 985, 988 (Fed. Cir. 1995). Claim construction is a matter of law, *Markman v. Westview Instrs., Inc*., 52 F.3d 967, 979 (Fed. Cir. 1995) *aff'd* 517 U.S. 370 (1996), therefore, it is "[t]he duty of the trial judge . . . to determine the meaning of the claims at issue." *Exxon Chem. Patents, Inc. v. Lubrizoil Corp.*, 64 F.3d 1553, 1555 (Fed. Cir. 1995).

36. Generally, the words of a claim are given their "ordinary and customary meaning," which is defined as "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Id.* at 1312-13 (citations omitted). In this regard, the Federal Circuit has noted that

> It is the person of ordinary skill in the field of the invention through whose eyes the claims are construed. Such person is deemed to read the words used in the patent documents with an understanding of their meaning in the field, and to have knowledge of any special meaning and usage in the field. The inventor's words that are used to describe the invention--the inventor's lexicography--must be understood and interpreted by the court as they would be understood and interpreted by a person in that field of technology. Thus the court starts the decisionmaking process by reviewing the same resources as would that person, viz., the patent specification and the prosecution history.

Id. (quoting *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1477 (Fed.Cir.1998)).

37. A person of ordinary skill in the art at the time of the '086 patent would be a person with a degree in pharmaceutical chemistry, pharmacy, or medicine, or its equivalent. This person also would have at least two years experience, either in the area of pharmaceutical compounds, pharmaceutical products and/or pharmaceutical preparations, or in the area of anesthetics and/or anesthesiology. (Atwood Testimony, 7/20/09 Tr. at 43:25-44:5.)

38. In the process of determining the meaning of a claim as understood by a person skilled

in the art, a court may look to various sources from which the proper meaning may be discerned. These sources include "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Phillips,* at 1314. While a court is permitted to turn to extrinsic evidence, such evidence is generally of less significance and less value in the claim construction process. *Id.* at 1317. Extrinsic evidence would include evidence that is outside the patent and prosecution history, and may include expert testimony, dictionaries and treatises. *Id.*

39. Claims should not be construed so as to exclude preferred embodiments. *OSRAM GmbH v. U.S Int'l Trade Comm'n*, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (reversing ITC's claim construction, and stating: "[t]his conclusion is reinforced by the undisputed fact that the volume-based measure would exclude the OSRAM products that the patents were designed to cover"); *Hoechst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1581 (Fed. Cir. 1996) (a claim construction that excludes the preferred embodiment is rarely, if ever, correct).

40. Limitations should not be read into the claims based on the disclosure of a preferred embodiment. *Eolas Techs. Inc. v. Microsoft Corp.*, 399 F.3d 1325, 1336 (Fed. Cir. 2005) (refusing to limit claims to embodiments disclosed in specification because "absent a clear disclaimer in the specification, the embodiments in the specification do not limit broader claim language"). *See also Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1288 (Fed. Cir. 2009) ("When the specification describes a single embodiment to enable the invention, this court will not limit broader claim language to that single application 'unless the patentee has

demonstrated a clear intention to limit the claim scope using "words or expressions of manifest exclusion or restriction."""); *Liebel-Flarsheim Co. v. Medrad*, Inc. 358 F.3d 898, 904, 906 (Fed. Cir. 2004) (it is error to import a limitation from the specification into the claim; standing alone, an embodiment disclosed in the specification does not limit the claims); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1327 (Fed. Cir. 2002) (when specification describes only a single embodiment, claims of patent are not to be construed as restricted to that embodiment unless patentee demonstrates a clear intention to limit claim scope using words or expressions of manifest exclusion or restriction).

41. Likewise, limitations should not be read into the claims based on examples disclosed in the specification. *See, e.g., JVW Enters., Inc. v. Interact Accessories, Inc.*, 424 F.3d 1324, 1335 (Fed. Cir. 2005) (improper to import limitations into claims from examples or embodiments, even when specification describes very specific embodiment); *Dow Agrosciences LLC v. Crompton Corp.*, 381 F. Supp. 2d 826, 831 (S.D. Ind. 2005) ("particular formulations or examples appearing in the specification may not be read to limit the claim"); *Heil Co. v. Curotto Can Co.*, 2004 WL 2600134 (N.D. Cal. Nov. 1, 2004) ("it is generally improper to limit the scope of the claim to the examples set forth in the specification").

42. To disavow or disclaim claim scope, the inventor must clearly state such an intent. *Voda v. Cordis Corp.*, 536 F.3d 1311, 1320 (Fed. Cir. 2008) (while "specification may reveal an intentional disclaimer, or disavowal, of claim scope by the inventor," any such disclaimer or disavowal "must be clear"); *Conoco, Inc. v. Energy & Environmental Int'l., L.C.*, 460 F.3d 1349, 1357-58 (Fed. Cir. 2006) (while inventor may "use the specification to intentionally

disclaim or disavow the broad scope of a claim," this "intention must be clear" and "cannot draw limitations into the claim from a preferred embodiment").

b. Construction of the Disputed Terms

"(S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride, wherein the compound in the form of its monohydrate"

43. This disputed term in claim 1 of the '086 patent shall be construed consistent with Plaintiff's proposed construction to cover solutions and shall not be not limited in the manner proposed by Defendant, *i.e.*, to solid, crystalline RHM.

44. The words of claim 1 do not specify any physical state. The words of claim 1 also do not specify any characteristics of the claimed compound (e.g., melting point) that would suggest a particular physical state. (Gawley Testimony, 7/23/09 Tr. at 653:24-654:8.)

The '086 patent applicant never disclaimed or disavowed RHM in solution or in any other way indicated that the claimed monohydrate was limited to a solid. No disavowal or disclaimer exists in the claim language, in the '086 specification, or in the '086 prosecution history. (Atwood Testimony, 7/21/09 Tr. at 260:15-16.)

46. Other claims of the '086 Patent support the conclusion that claim 1 is not limited to a solid: (1) claim 4 indicates RHM can be in solution by referring to "isolating the monohydrate" after it is created in solution. ('086 Patent at 4:18-29.) References to "isolating" the monohydrate means the monohydrate already exists in solution. When one isolates a substance, the substance has to already exist, and one is just harvesting the substance by eliminating the carrier material. (Atwood Testimony, 7/20/09 Tr. at 36:20-25,

73:1-8.) (2) claim 6 indicates that RHM can be in solution by referring to administering solutions. ('086 Patent, PLT 1 at 4:35-38.) (Atwood Testimony, 7/20/09 Tr. at 73:11-19.)

47. The '086 specification supports a construction that claim 1 is not limited to solid, crystalline RHM. In several places, the '086 specification refers to RHM either being created in, or existing in, solution. (E.g., PLT 1 at 1:55-2:3 (RHM created in solution), 2:58-64 (referring to RHM created in solution being left for crystallization), 2:27-2:50 (referring to pharmaceutical preparations in solution containing the new compound as an active ingredient), 3:15-19 (describing solution of RHM), 3:30-31 (describing solution of RHM).) (Atwood Testimony, 7/20/09 Tr. at 69:17-72:20.)

48. The '086 Patent and specification refers to RHM existing in solution and existing as a solid. (Atwood Testimony, 7/21/09 Tr. at 260:15-23; Atwood Testimony, 7/28/09 Tr. at 1119:3-8.)

49. Navinta's assertions that the '086 specification teaches that Claim 1 is limited to solid, crystalline RHM is based on either disclosures relating to a preferred embodiment, or examples. Furthermore, Example 1, which Navinta purports teaches that RHM must be a solid, actually refers to RHM in solution. (Atwood Testimony, 7/20/09 Tr. at 36:2-5.)

50. Statements in the '086 specification about crystallization steps do not teach that claim 1 is limited to solid, crystalline RHM. Crystallization is not a necessary step to create RHM. It is a means of harvesting or isolating the RHM that resides in solution. (Atwood Testimony, 7/21/09 Tr. at 227:20-228:19.)

51. A well-defined water content does not dictate that RHM must be a solid. Whether in a

solid form or in solution, the well-defined water content of RHM is based on the water that is bonded tightly within the essential structures of RHM. The water content of RHM in solution is about 5.4% to 5.6%. Dr. Sandberg calculated the water content of RHM by harvesting it from solution and then applying the Karl Fischer method of measurement. This is set forth in Example 1 of the '086 Patent. (Atwood Testimony, 7/28/09 Tr. at 1116:25-1118:23.)

52. The statement in the '086 Patent specification regarding an implied water content of 5.5% refers to the theoretical calculated value for an actual mole of water per ropivacaine hydrochloride. It is a theoretical value. It is not a measured value. (Atwood Testimony, 7/21/09 Tr. at 226:22-227:7.)

53. The water content of RHM cannot be measured in solution because the RHM structural elements are surrounded by carrier water. To measure the water content, one would need to harvest the RHM structures from the solution. Even then, measuring water is difficult because extra water might be associated with the structural elements because it is coming out of water. For this reason, Dr. Sandberg quoted a range of values (5.4% to 5.6%) as the water content resulting from one example of RHM. A water content of 5.5.% for RHM is a theoretical construct, not a measured amount. (Atwood Testimony, 7/21/09 at 264:13-25.)

54. A measurement of an exact 1:1 ratio of water to ropivacaine hydrochloride would be an accident of analysis because of the difficulty of measuring the water content of RHM. Consequently, it would be more accurate to use the term "about a monohydrate" in talking about RHM. (Atwood Testimony, 7/21/09 at 265:6-13.)

55. In RHM, the ratio of waters to ropivacaine cations to chlorides is about 1:1:1. Even

though the structure is 1:1:1, each ropivacaine cation has two waters closely associated with it, and each water has two ropivacaine cations closely associated with it. (Atwood Testimony, 7/20/09 Tr. at 49:6-18.)

56. Statements in the '086 specification (or prosecution history) regarding a melting point for RHM merely identify a characteristic of RHM when it is in a solid state. They do not teach that RHM can only exist as a solid. (Atwood Testimony, 7/21/09 Tr. at 260:24-261:3.)

57. People of skill in the art would understand that RHM can exist in different physical states, including in solution, and therefore would not read claim 1 as being limited to a solid state. (Atwood Testimony, 7/20/09 Tr. at 69:14-16.)

58. RHM is a member of a class of compounds known as "amino amides." Amides are known to form monohydrates in solution, among other hydrated states. (PLT 44.)

59. When placed in a solution, RHM crystals lose the long range order associated with the crystalline solid but maintain the essential structural features and characteristics that make RHM a unique compound, including great stability, a high melting point, and water locked tightly into the structure. (Atwood Testimony, 7/20/09 Tr. at 52:10-21, 53:11-16; PLT 378-0026.)

60. When RHM is introduced to an aqueous solution, the ropivacaine, chloride and water structures do not break up or disassociate and go their own way throughout the solution, as Navinta's experts asserted during trial. Instead, water within the RHM structure stays in place locking two ropivacaine cations together. Also, due to electrostatic and hydrogen bonding, the chlorides would stay in place and hold the structure together. Accordingly, the essential

structural units of RHM would hold up in solution. (Atwood Testimony, 7/20/09 Tr. at 64:7-11; Atwood Testimony, 7/21/09 at 245:14-246:1, 263:8-11; Atwood Testimony, 7/28/09 Tr. at 1124:16-1125:4, 1138:6-1139:5, 1161:1-8; PLT 378-0027.)

61. The ropivacaine cations in RHM have a special shape. The ropivacaine cations in a structural RHM unit have a xylidine ring to the right and a piperidine ring to the left that do not interact well with water. For bulk water to penetrate the structural RHM unit, the water must fight through the hydrophobic matter and then displace the water that is already well anchored inside the structural RHM unit. (Atwood Testimony, 7/20/09 Tr. at 58:11-16, 66:5-12; PLT 378-0027.)

62. For a simple compound like sodium chloride, "dissolving" a solid will result in complete disassociation. This not the case for a complex organic compound like RHM. When RHM is "dissolved," the appearance of the solid goes away but the essential structure does not break up. When speaking about RHM, "dissolve" does not mean that the particles disassociate or break up. (Atwood Testimony, 7/21/09 Tr. at 237:14-23, 250:14-18.)

63. Certain of the structural elements of RHM subsisting in solution would contain "unit cells" that are the building blocks of a crystal lattice. The structural elements of RHM surviving in solution may combine to form additional "unit cells," which is what occurs when RHM is harvested from a solution through crystallization (or some other method). (Atwood Testimony, 7/21/09 Tr. at 243:23-244:20, 261:14-20.)

64. Navinta's U.S. Patent Application Publication No. US 2006/0276654 A1 ("the ‘654 Application") indicates that when a solution of RHM is cooled down it crystallizes quickly.

This result indicates that the essential structural units of RHM subsist in solution and that the process of crystallization quickly organizes these already-existing structural units into a crystal. (Atwood Testimony, 7/20/09 Tr. at 56:12-57:2.)

"(S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride."

65. This disputed term in claim 1 shall be construed to mean a compound with an (s)-enantiomer with an optical purity of more than 99.0%.

66. "Optical purity" is a function of how much more of one enantiomer there is than of another enantiomer. In the (S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride compound recited in claim 1 of the '086 Patent, the "(S)" denotes that the compound is the "S" enantiomer. The "(-)" denotes that the compound has some level of optical purity. (Atwood Testimony, 7/20/09 Tr. at 68:18-69:3; Atwood Testimony, 7/21/09 Tr. at 231:17-20.) *See also Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 725-26, 729 (N.D. W. Va. 2004) (where claim referred to "S(-)" enantiomer of levofloxacin but intrinsic record did not claim or identify a minimum level of optical purity, court construed claim to cover substantially optically pure levofloxacin and held that person skilled in the art would understand "S(-)" to require substantial optical purity).

67. A construction that "the compound" of claim 1 has an optical purity of more than 99.0% is consistent with other claims of the '086 Patent. For example, Claim 3 states that "the compound" contains "less than 0.5% by weight of the corresponding (R)-(+)-enantiomer." This indicates that greater than 99.5% of the (S)-(–) enantiomer is present, giving the compound an enantiomeric purity of greater than 99.5%. This translates

into an optical purity of more than 99%.

68. The ‘086 patent specification indicates that the patent achieves multiple and different objectives, one being a compound that is optically pure, another being the compound in the form of its monohydrate. ‘086 Patent, PLT 1 at col. l, lines 32-35.

69. The ‘086 applicant emphasized the optical purity of the claimed compound during the prosecution history of the ‘086 patent. The applicant pointed out to the Patent Office Examiner that WO 085/00599 to Thuresson disclosed a compound that is "neither hydrated nor optically pure," while further noting that "the claimed compound [i.e., the (S)-enantiomer] was the only compound prepared having an optical purity of over 99.0%." (PLT 4 at p. 72; Atwood Testimony, 7/20/09 Tr. at 31:22-32:3, 78:3-6.)

70. The originally filed application for the ‘086 Patent describes (S)-(-)-1-propyl-0.2',6'-pipecoloxylidide hydrochloride as having an optical purity of greater than 99%. Original claim 3 stated: "Compound according to claim 1 characterized in that it contains less than 0.5% by weight of the corresponding D-enantiomer." This also translates into an enantiomeric purity of greater than 99.5% and an optical purity of greater than 99.0%. (PLT 4-0020.)

“the compound according to claim 1”

71. Claim 2 of the ‘086 Patent states: “The compound according to claim 1, wherein it is substantially optically pure.” (‘086 Patent 4:13-14.) Claim 3 of the ‘086 Patent states: “The compound according to claim 1, wherein it contains less than 0.5% by weight of the corresponding (R)-(+)-enantiomer.” (‘086 Patent at 4:15-17.) Claim 6 of the ‘086 Patent

states: "A method for inducing local anesthesia, which comprises administering to mammals including man needing local anesthesia an anesthetizing amount of the compound according to claim 1." ('086 Patent, PLT 1 at 4:35-38.)

72. The phrase "the compound according to claim 1," as used in claims 2, 3 and 6 of the '086 patent shall be construed to refer to the optically pure compound of Claim 1: (S)-(–)-1-propyl-2',6'-pipecoloxylidide hydrochloride. This limitation does not refer to the "compound in the form of its monohydrate" as specified in Claim 1. (Atwood Testimony, 7/20/09 Tr. at 74:6-75:11, 78:12-20; Gawley Testimony, 7/23/09 Tr. at 682:5-22; PLT 378-0029.)

73. The plain language of claims 1-3 indicates that the "compound according to claim 1" is not RHM. Claim 1 is divided into two clauses. The first is "(S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride," and the second is "wherein the compound is in the form of its monohydrate." Similarly, Claims 2, and 3 are divided into two clauses, the first of which in both claims is "The compound according to claim 1." The second clause in Claim 2 reads "wherein it is substantially optically pure" and the second clause in Claim 3 reads "wherein it contains less than 0.5% by weight of the corresponding (R)-(+)-enantiomer." Thus, in each of these three claims, the first clause announces a particular compound. The second clause refers to a compound identified in the first clause, and then adds a limitation to that compound. As exemplifed by claim 1, the compound identified in the first clause is the optically pure compound of claim 1: (S)-(–)-1-propyl-2',6'-pipecoloxylidide hydrochloride.

74. Use of the phrase "the compound" in the second clause of claim 1 indicates an antecedent basis in the claim. Thus "the compound" referenced in the second clause of claim 1 can only refer to (S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride, not that compound in the form of its monohydrate. *See AmeriFab, Inc. v. Voest-Alpine Indus., Inc., 2005 WL 1827907*, at *9 (S.D. Ind. July 29, 2005) (holding that the phrase "a method of cooling the interior wall of an electric-arc furnace" provides "an antecedent basis for the claim's reference to 'the electric-arc furnace' in elements two and three" of the disputed claim); Robert C. Faber, Landis on Mechanics of Patent Claim Drafting § 10:7.4 at 10-44 (2007) ("When a previously identified element or step is repeated, it is introduced by a definite article 'the' or 'said.'").

75. When claims 2, 3 and 6 use the phrase "the compound according to claim 1," the rules of claim construction require that the term "compound" as used in those claims be given the same meaning that "compound" has in Claim 1. Because the term "the compound" in Claim 1 only refers to optically pure (S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride, this same construction must be applied to claims 2, 3 and 6. *See Rexnord Corp. v. Laitram Corp*., 274 F.3d 1336, 1342 (Fed. Cir. 2001) ("A claim term should be construed consistently with its appearance in other places in the same claim or in other claims of the same patent."); *Phonometrics, Inc. v. Northern Telecom Inc.*, 133 F.3d 1459, 1465 (Fed. Cir. 1998) ("A word or phrase used consistently throughout a claim should be interpreted consistently.").

76. The specification teaches that the '086 patent claims an invention of optically pure (S)-(–)-1-propyl-2',6'-pipecoloxylidide hydrochloride that is distinct from the invention of that compound in the form of its monohydrate. Indeed, the '086 specification teaches that the

three composition claims of the '086 Patent are directed to different objectives. Claim 1, by claiming the monohydrate form, satisfies the objective of a stable compound. Claims 1, 2, 3, and 6, by claiming optically pure (S)-(–)-1-propyl-2',6'-pipecoloxylidide hydrochloride, satisfy the other objective of obtaining a product consisting of the substantially pure (S)-(–) enantiomer.

II. DISCUSSION

B. Infringement Analysis

77. Submission of an ANDA is an act of patent infringement if the ANDA seeks approval for a drug that is claimed in a patent or the use of which is claimed in a patent. 35 U.S.C. § 271(e).

78. Determination of infringement is a "two-step process, wherein the court first construes the claims and then determines whether every claim limitation, or its equivalent, is found in the accused device." *Roche Palo Alto LLC v. Apotex, Inc.*, 531 F.3d 1372, 1377 (Fed. Cir. 2008).

79. In a Hatch-Waxman infringement case, the proper infringement inquiry focuses on the actual product that will enter the market upon FDA approval. *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997) (court "must focus on what the ANDA applicant will likely market if its application is approved"); *Ben Venue Labs. v. Novartis Pharm. Corp.*, 146 F. Supp. 2d 572, 579 (D.N.J. 2001) ("the statute requires that an infringement inquiry be focused on what is likely to be sold following FDA approval, not necessarily on the ANDA itself"). In analyzing infringement in a Hatch-Waxman case, "the Court must look to the

whole of the product, which means considering its ultimate useable state, as well as the ANDA-contemplated process and compound." *EKR Therapeutics, Inc. v. Sun Pharm. Indus., Ltd.*, 2009 WL 901761, *12 (D.N.J. Mar. 31, 2009) (determining that infringement analysis should include state of drug at point of administration).

80. A comparison between an accused product and a commercial embodiment of a patented product can be used to establish infringement where the commercial product demonstrates the presence of the relevant claim limitations. *Glaxo Group, Ltd. v. TorPharm, Inc.*, 153 F.3d 1366, 1374 (Fed. Cir. 1998).

81. Indirect infringement may be established by demonstrating either (1) inducement of infringement, or (2) contributory infringement. 35 U.S.C. § 271(b) and (c); *AquaTex Indus., Inc. v. Techniche Solutions*, 419 F.3d 1374, 1379-80 (Fed. Cir. 2005).

82. A party is liable for inducement of infringement if it is shown that: (1) another party directly infringes the claim; (2) the party intentionally encourages the acts that constitute direct infringement; and (3) the party knows or should know that its actions will cause direct infringement. 35 U.S.C. § 271(b); *DSU Med. Corp. v. JMS Co.*, Ltd., 471 F.3d 1293, 1305-06 (Fed. Cir. 2006) (en banc).

83. The trier of fact considers the totality of the circumstances in determining whether a party is liable for inducement of infringement, recognizing that inducement can be "established through circumstantial evidence." *Broadcom Corp. v. Qualcomm, Inc.*, 543 F.3d 683, 699 (Fed. Cir. Sept. 24, 2008) ("the district court did not err in instructing the jury to consider 'all of the circumstances'").

84. The encouraging actions need not be communicated to the direct infringer. *Ricoh Co., Ltd. v. Quanta Computer, Inc.*, 550 F.3d 1325, 1341-42 (Fed. Cir. 2008). *See also Dennison Mfg. Co. v. Ben Clements & Sons, Inc.*, 467 F. Supp. 391, 428 (S.D.N.Y 1979) (inducement may be found where defendant does not actually instruct ultimate users of the product in its use, if the intended use of the product is readily apparent).

85. The U.S. Supreme Court has held that "instructing how to engage in an infringing use" constitutes "active steps" to "encourage direct infringement." *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 936 (2005).

86. A defendant who is aware of a patent and supplies a product to a customer with instructions on how to use the product, which instructions when followed lead to infringement, encourages acts which constitute direct infringement. *Minn. Mining and Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1305 (Fed. Cir. 2002). *See also Biotec Biologische Naturverpackungen GmbH & Co. v. Biocorp., Inc.*, 249 F.3d 1341, 1351 (Fed. Cir. 2001) (defendant induced infringement by providing instructions to customers on how to use a product in a manner that constituted direct infringement).

87. Statements in a package insert that encourage infringing use of a drug product are alone sufficient to establish intent to encourage direct infringement. *AstraZeneca LP v. Apotex, Inc.*, 2009 WL 1456643 (D.N.J. May 22, 2009) (where patent claimed once daily dosing and accused ANDA product was indicated for twice daily dosing, court found statements in package insert suggesting "downward titration" and "taper[] to the lowest effective dose" encouraged once daily dosing and were sufficient to evidence inducement).

See also EKR Therapeutics, Inc. v. Sun Pharm. Indus., Ltd., 2009 WL 901761 (D.N.J. March 31, 2009) (granting summary judgment of infringement, and determining that the court need not engage in traditional inducement analysis, based on express instructions in drug packaging); *Alcon Labs., Inc. v. Bausch & Lomb, Inc.*, 52 U.S.P.Q.2d 1927, 1933-34 (N.D. Tex. 1999) (granting preliminary injunction against infringement of method claims in view of express indication of package insert); *Biotechnology Gen. Corp. v. Duramed Pharms., Inc.*, 325 F.3d 1356 (Fed. Cir. 2003) (reversing and remanding for factual determination of whether consumers using product in accordance with package instructions would infringe patent).

88. A party is liable for contributory infringement if the defendant: (1) sells or offers to sell a material component of a composition for use in a patented method; and (2) the component is not a staple article or commodity of commerce suitable for substantial non-infringing use. 35 U.S.C. § 271(c).

89. Navinta bears the burden of proving substantial non-infringing uses. *University of California v. Hansen*, 54 U.S.P.Q.2d 1473, 1480 (E.D. Cal. 1999) (granting plaintiff's motion for summary judgment of contributory infringement because, "Aside from defendants' statements that the slides can be used for other uses than diagnosing FIV and that 'from time to time customers mention their intent' to use the slides for another use, defendants have shown no facts indicating that anyone actually does use the slides for anything other than diagnosing FIV" (emphasis in original)); *CFMT, Inc. v. Steag Microtech, Inc.*, 14 F. Supp. 2d 572, 592 (D. Del. 1998) (denied JMOL because jury had sufficient evidence to conclude that defendant contributed to infringement where plaintiff produced no evidence regarding

substantial non-infringing use and defendant failed to offer "any evidence that customers use the Marangoni dryer in some non-infringing way").

90. In analyzing whether something is "suitable for substantial non-infringing use," the Court should consider whether the product infringes other patents in addition to the method of use patents asserted in the instant action. *See Sony Corp. of Am. v. Universal City Studios*, Inc., 464 U.S. 417 (1984) (in analyzing liability for contributory infringement, U.S. Supreme Court considered infringement of copyrights owned by non-parties to constitute an infringing use).

a. The '086 Patent

i. Navinta's ANDA Product Infringes Claim 1 of the '086 Patent

91. Claim 1 of the '086 Patent states: "(S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride, wherein the compound is in the form of its monohydrate." ('086 Patent, PLT 1 at 4:10-12.) Thus, claim 1 has two elements: (1) *(S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride*, which has an optical purity of more than 99%, and (2) is in the form of its monohydrate. As set forth below, Navinta's ANDA products have both of these elements, and, therefore, infringe claim 1.

• Navinta's ANDA Products Contain (S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride With an Optical Purity of More than 99%

92. Navinta's Package Insert states that its "Ropivacaine Hydrochloride Injection is a sterile, isotonic solution that contains the enantiomerically pure drug substance." (Newton Testimony, 7/24/09 Tr. at 829:25-830:2.) The ropivacaine base that Navinta uses to make its

ANDA Products is essentially 100% enantiomerically pure. (PLT 72-0007.) If the base is 100% enantiomerically pure, the RHM that results from the manufacturing process for the ANDA Products will be 100% enantiomerically pure. (Atwood Testimony, 7/20/09 Tr. at 109:2-7; Newton Testimony, 7/24/09 Tr. at 818:12-15.)

93. Various Certificates of Analysis submitted by Navinta to the FDA, and provided by SMS Pharmaceuticals Ltd. and Emcure Pharmaceuticals Ltd., specify a finished product specification of not less than 99.5% optical purity. These same Certificates of Analysis confirm that the enantiomeric purity of both Navinta's actual starting ropivacaine API and the final Navinta ANDA Products is essentially 100%. (PLT 72-0007; Atwood Testimony, 7/20/09 Tr. at 105:20-106:9; Gawley Testimony, 7/23/09 Tr. at 656:1-21.)

94. Other Navinta manufacturing documents confirm the essentially 100% enantiomeric and optical purity of the ANDA Products. A test on Batch VRVB 001 reported 99.94%. enantiomeric purity of 99.92%, and tests on batch number VRVC 002 reported the Navinta ANDA Products shows that the R-enantiomer was present in an amount of less than 0.08% and that the S-enantiomer was present in an amount of approximately 99.92%. (PLT 11-0448; PLT 11-0463; 3/3/09 Newton Depo. at 80:7-81:24, 96:1-16, 98:20-99:4.)

95. The essentially 100% enantiomeric purity of the Navinta ANDA Products indicates the ANDA Products are 100% optically pure. (Atwood Testimony, 7/20/09 Tr. at 151:12-15; 3/3/09 Newton Depo. at 27:23-28:21.)

96. Navinta's ANDA Products are supplied as the "pure (S)-(-) enantiomer." The Navinta ANDA Products do not contain any significant or even measurable quantity of racemate

(R)-(+) enantiomer. (Atwood Testimony, 7/20/09 Tr. at 154:22-155:5; PLT 72-0002, 72-0004 and 72-0006.) Navinta's certificates of analysis exhibit quality control and are based on an actual batch of a Navinta ANDA Product sample. Even though it is relatively easy to detect the R-(+) enantiomer, none was detected in Navinta's batch. This indicates that racemization would not occur during the shelf life of Navinta's ANDA Products. (Atwood Testimony, 7/21/09 at 267:3-268:1; PLT 72-0004.)

97. The optical purity of RHM in an aqueous solution will not change during the shelf-life of the drug, which the testing indicates is three to five years for RHM. (Atwood Testimony, 7/21/09 Tr. at 232:4-11.)

98. Statements made by Abraxis in its Patent Term Extent application regarding the possible racemization of Naropin are only a disclosure of a possibility, and it is an unlikely possibility. (Atwood Testimony, 7/21/09 Tr. at 235:1-5; PLT 277 at p.6.)

• Navinta's ANDA Products Contain the RHM Composition Claimed in Claim 1 of the '086 Patent

99. In its original November 2006 ANDA filing, Navinta's ANDA sought approval for solutions that contain enantiomerically pure "ropivacaine hydrochloride," and water for injection, in single dose containers in 0.2%, 0.5% and 1.0% concentrations. (PLT 48-0002.)

100. According to Navinta's current Package Insert Labeling, Navinta's ANDA seeks approval for sterile isotonic solutions that contain enantiomerically pure "ropivacaine hydrochloride," and water for injection. The Labeling calls the ANDA Products "Ropivacaine Hydrochloride" and "Ropivacaine Hydrochloride Injection." (PLT 156-0001.)

101. Navinta's original and current Labeling each assert that Navinta's "Ropivacaine Hydrochloride Injection" products contain ropivacaine hydrochloride, which is "chemically described as "S(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride." (PLT 48-0002; PLT 156-0001.)

102. The ingredients of the Navinta ANDA Products are non-hygroscopic ropivacaine base, hydrochloric acid, sodium hydroxide as a pH adjusting agent, sodium chloride as an isotonic agent, water for injection as a vehicle, and hydrochloric acid or sodium hydroxide as a pH adjusting agent. (PLT 39-0002, 39-0003, 39-0004; Atwood Testimony, 7/20/09 Tr. at 93:2-7; 3/3/09 Newton Depo. at 171:20-172:1, 173:20-174:3.)

103. Batch Manufacturing Records in Navinta's ANDA describe the complete procedures for manufacturing the accused ANDA Products. (PLT 60, 62, 251, 252; Newton Testimony, 7/23/09 Tr. at 778:21-23.)

104. The manufacturing process disclosed in Navinta's ANDA for the ANDA Products includes these steps:

- Create an aqueous solution out of hydrochloric acid and water;
- Add ropivacaine base and stir to create a clear solution;
- Add an excess of hydrochloric acid and stir to create a homogenous solution;
- Add sodium hydroxide to adjust pH;
- Add water for injection as a vehicle and stir;
- Add sodium chloride, stir, and adjust pH; and
- Filter the solution.

(Newton Testimony, 7/23/09 Tr. at 781:6-16.)

105. Water is a "vehicle" in Navinta's ANDA Products. A "vehicle" is a carrier. It is not an active ingredient; it does not have any chemical reactions with the pharmaceutical ingredient. It is a way of delivering the active ingredient and perhaps certain excipients into the system. (PLT 51-0003; Atwood Testimony, 7/20/09 Tr. at 93:8-20, 108:6-14; Newton Testimony, 7/24/09 Tr. at 834:6-9; Dave Testimony, 7/27/09 Tr. at 989:23-25; 3/3/09 Newton Depo. at 61:25-62:2, 159:24-160:5.)

106. The manufacturing method disclosed in Navinta's ANDA creates a Navinta ANDA product that is an aqueous solution of RHM. In the key step of 4.9.2 (some Navinta Batch Records identify this same step as 4.6.13), ropivacaine base is added to a hydrochloric acid solution and stirred until a clear solution forms. RHM is created at step 4.9.2—by this time the ropivacaine base has all been reacted to RHM. (PLT 62-0029; Atwood Testimony, 7/20/09 Tr. at 109:8-110:4; Atwood Testimony, 7/28/09 Tr. at 1127:7-1128:8; PLT 60-0030, 251-0035, 252-0036, 378-0050 to 378-0052.)

107. When ropivacaine base is added to a solution of hydrochloric acid and water, the base immediately interacts with the acid. A chemical reaction occurs in which the acid transfers a hydrogen atom to the ropivacaine base. The positively charged hydrogen, referred to as a proton, binds to the piperdine ring, resulting in a ropivacaine cation and a chloride anion. (Atwood Testimony, 7/28/09 Tr. at 1127:9-14, 1127:19-22, 1129:19-23.)

108. A consequence of the reaction between hydrochloric acid and ropivacaine base is to increase the solubility of the ropivacaine base, exposing the carbonyl oxygen and amide

proton (the parts of the ropivacaine base that interact favorably with water) to water. Once a water molecule from the surrounding solution locks into this key position, it forms a strong hydrogen bond with the ropivacaine hydrochloride, and the essential unit structure of RHM is formed. This essential unit structure is capable of binding with other nearby structures, due to favorable interactions between the structures. (Atwood Testimony, 7/28/09 Tr. 1127:23-1128:6, 1129:5-9, 1129:15-18, 1130:2-3, 9-11.)

109. Abraxis's scientific testing verified the presence of RHM in Navinta's ANDA products. Abraxis engaged Dr. Leonard J. Chyall, Ph.D., a principal at SSCI, a division of Aptuit, Inc., and others working under Dr. Chyall's direction (individually or collectively, hereafter "Aptuit"), to determine whether Navinta's ANDA Products contain RHM. (Chyall Testimony, 7/21/09 at 276:4-12.)

110. Dr. Chyall and his colleagues conducted their tests at Aptuit's laboratory in West Lafayette, Indiana. (Chyall Testimony, 7/21/09 at 274:8-20-275:17-23.)

111. X-ray powder diffraction ("XRPD") is an established, sensitive technique scientists can use to, among other things, determine the identities of molecules, their corresponding 3-dimensional structures, and the bonding that exists between molecules. An XRPD pattern is unique to the chemical being studied and serves as a "chemical fingerprint" that scientists can interpret or compare to an XRPD pattern of a reference sample. (Atwood Testimony, 7/20/09 Tr. at 123:25-124:5; Chyall Testimony, 7/21/09 at 276:15-23.)

112. Aptuit performed XRPD testing on three sets of samples: (1) Samples of the 0.2%,

0.5% and 1.0% strengths of APP Pharma's Naropin drug products; (2) Samples of the 0.2%, 0.5% and 1.0% ANDA Products that Navinta produced during discovery; and (3) Samples of 0.2%, 0.5% and 1.0% solutions generated by Aptuit by partially simulating the critical steps (i.e., step 4.9.2) of the manufacturing process Navinta has represented its collaborators will use to prepare the ANDA Products.

113. Aptuit compared the XRPD patterns for these samples to an XRPD pattern Aptuit obtained from RHM reference material that Aptuit sourced from the US Pharmacopeia (USP). Aptuit independently verified that the USP reference sample was the solid monohydrate form of ropivacaine hydrochloride by comparing the XRPD pattern of the USP sample to a computer-generated XRPD pattern based on published information regarding the structure of RHM. (PLT 123; Atwood Testimony, 7/20/09 Tr. at 123:17-21; Chyall Testimony, 7/21/09 at 277:16-278:1, 281:8-282:6, 294:23-297:18; PLT 60-0030; PLT 382-0023.)

114. Aptuit placed a portion of each sample in an open glass Petri dish and allowed each sample to naturally evaporate at ambient temperature in a fume hood. This process removed the carrier or vehicle water. Aptuit subjected the remaining solid material to XRPD testing. (Atwood Testimony, 7/20/09 at 125:7-9; Chyall Testimony, 7/21/09 at 278:12-24, 279:7-25.)

115. Aptuit found that RHM was present in each of the 0.2%, 0.5% and 1.0% samples of Naropin. (PLT 125; Atwood Testimony, 7/20/09 Tr. at 127:15-22; Chyall Testimony, 7/21/09 at 284:20-285:12, 287:10-288:3, 288:4-9.)

116. Aptuit found that RHM was present in each of the 0.2%, 0.5% and 1.0% samples generated by partially replicating Navinta's disclosed method of manufacture for the ANDA Products, thus indicating that a monohydrate of ropivacaine hydrochloride is formed in an aqueous solution during the manufacture of Navinta's ANDA Products. (PLT 127; Atwood Testimony, 7/20/09 Tr. at 131:19-132:10; Atwood Testimony, 7/28/09 Tr. at 1109:14-19; Chyall Testimony, 7/21/09 at 298:19-299:11, 300:21-301:2, 301:6-19, 301:22-302:9.)

117. Aptuit found that RHM was present in the 0.2% and 0.5% samples of the ANDA Products in an amount that was identical to the results for the corresponding Naropin samples. (PLT 125; Atwood Testimony, 7/20/09 Tr. at 128:2-21; Chyall Testimony, 7/21/09 at 288:17-289:7, 289:12-18.)

118. Aptuit found that the XRPD pattern for the 1.0% samples of the ANDA Products differed from the 1.0% Naropin sample, and the 0.2% and 0.5% samples of the ANDA Products and Naropin. However, Dr. Atwood's analysis of the relevant XRPD patterns demonstrate the presence of a significant amount of RHM in the crystalline evaporite generated from the 1.0% ANDA Product. (PLT 21; Atwood Testimony, 7/20/09 Tr. at 129:9-18; Atwood Testimony, 7/28/09 Tr. at 1106:13-20, 1107:4-8, 1108:13-16; Chyall Testimony, 7/21/09 at 289:21-291:2, 293:12-294:4.)

119. The fact that RHM crystallizes upon evaporation of the Navinta ANDA Products indicates that RHM is in the Navinta ANDA Product solutions from which the crystalline

RHM was harvested. (Atwood Testimony, 7/20/09 Tr. at 131:5-9.)

120. Navinta's Dr. Steinfink asserted that Dr. Chyall's test results for the 1.0% ANDA Product showed the existence of a polymorph form C. Dr. Steinfink based his conclusion only on a visual comparison of Dr. Chyall's test results and a graph of the polymorph form C taken from the Bergstrom article. (Steinfink Testimony, 7/24/09 Tr. at 884:5-7; PLT 125, 126.) According to Plaintiff's expert, however, superimposing the Bergstrom graph with the graph reflecting Dr. Chyall's test results shows that anhydrous form C of ropivacaine hydrochloride is not a match for Dr. Chyall's sample. (Atwood Testimony, 7/28/09 Tr. at 1144:16-1145:16; PLT 383-0001 to 383-0004.)

121. Dr. Chyall's Raman Spectroscopy analysis also confirmed the presence of RHM in the ANDA Products. Raman Spectroscopy is an analytical technique that scientists use to study organic molecules either in the solid state or in solution. It provides another form of a chemical fingerprint of a chemical composition or compound. (Atwood Testimony, 7/20/09 Tr. at 132:21-133:2.)

122. Aptuit obtained Raman spectra for the 1.0% solutions of Naropin and the Navinta ANDA Product. An overlay plot of the Raman spectra for the 1.0% solutions of Naropin and the Navinta ANDA Products shows that both samples exhibit peaks in the same location. This indicates that the solutions have the same chemical composition. The match of Raman spectra "fingerprints" of the Naropin and Navinta ANDA Product solutions indicates that the

same ropivacaine species, RHM, is present in both solutions. (PLT 128; Atwood Testimony, 7/20/09 Tr. at 133:6-18; Atwood Testimony, 7/28/09 Tr. at 1110:20-22; Chyall Testimony, 7/21/09 at 304:9-22; 5/13/09 Griffiths Depo. at 135:1-11, 136:6-10; PLT 378-0063, 380-0017.)

123. The Navinta ANDA products have a defined water content, which further confirms the presence of RHM in the ANDA products. A solid is needed in order to measure defined water content. (Atwood Testimony, 7/20/09 Tr. at 96:19-98:11.) Certificates of Analysis for the Active Pharmaceutical Ingredient in the ANDA Products specify not more than 0.5% water by KF (% water by weight), and a defined water content of 0.02-0.07% water by weight. *(See, e.g.*, PLT 72-0007; Atwood Testimony, 7/20/09 Tr. at 106:10-23.)

124. The Navinta ANDA Products have a defined water content of about 5.4% to about 5.6%. This defined water content indicates the presence of RHM. (Atwood Testimony, 7/20/09 Tr. at 153:24-25; Atwood Testimony, 7/28/09 Tr. at 1131:19-24, 1155:9-16.)

125. Additionally, Navinta has stated that its product is the same a Naropin, which contains RHM. The FDA approved the Naropin Package Insert with the chemical structure of ropivacaine hydrochloride monohydrate printed on its face. (PLT 50-0004.) The Naropin Package Insert indicates that Naropin contains "Ropivacaine HCl, which is chemically described as (S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate." (Atwood Testimony, 7/20/09 Tr. at 80:10-20; PLT 50-0004.) Navinta's ANDA states that the "Active Ingredient" or "API" for Naropin is "Ropivacaine hydrochloride monohydrate." (PLT 8-0054,

8-0066.) The Naropin Package Insert describes Naropin as a "sterile, isotonic solution that contains the enantiomerically pure drug substance, sodium chloride for isotonicity and Water for Injection." (PLT 50-0004.)

126. Naropin practices the claims of the '086 Patent. (Atwood Testimony, 7/20/09 Tr. at 79:4-7, 82:8.) Navinta's Chief Scientific Officer, Dr. Newton, testified that the ANDA Products and Naropin are "identical" and "equal" in their finished form. (Newton Testimony, 7/24/09 Tr. at 828:23-25, 829:10-15, 845:18-19.) Dr. Newton stated that the conditions of use for the ANDA Products and Naropin are the same. (Newton Testimony, 7/24/09 Tr. at 834:22-835:3.)

127. Navinta has stated in multiple ANDA submissions and in trial testimony that the active and inactive ingredients of Naropin and the ANDA Products are the same or equivalent. (PLT 39-0002 to 39-0004; Newton Testimony, 7/24/09 Tr. at 16-22; Dave Testimony, 7/27/09 Tr. at 989:12-15; Atwood Testimony, 7/20/09 Tr. at 92:12-93:1.)

128. In order to request a waiver of vivo bioavailability studies to establish the safety and efficacy of the ANDA Products, Navinta was required to assert that it has the same API as Naropin. (Amidon Testimony, 7/21/09 at 360:24-362:8.) Navinta has admitted that, after completing all of the manufacturing processes for the ANDA Products, Navinta cannot "see any difference in the product between Navinta's ANDA product and Naropin in the injection solution." (3/3/09 Newton Depo. at 64:24-65:4; Atwood Testimony, 7/20/09 Tr. at 87:4-88:3; PLT 378-0032.)

129. The Naropin Package Insert states: "Ropivacaine Hydrochloride Injection is a sterile,

isotonic solution that contains the enantiomerically pure drug substance, sodium chloride for isotonicity and Water for Injection." (PLT 50-0004.) Navinta's Proposed Package Insert states the exact same thing: "Ropivacaine Hydrochloride Injection is a sterile, isotonic solution that contains the enantiomerically pure drug substance, sodium chloride and Water for Injection." (PLT 156-0001.)

130. Navinta has admitted that the pharmacokinetics and the pharmacodynamics of the ANDA Products are the same as the pharmacokinetics and the pharmacodynamics of Naropin. (3/3/09 Newton Depo. at 44:8-17; 47:1-10.)

131. A comparison of the disclosed physical properties of the Navinta ANDA Products and Naropin, as specified in the Package Inserts for each product, shows that the API's for Naropin and the ANDA Products have identical physical properties. (PLT 48-0002; PLT 156-0001; PLT 50-0004.)

132. The US Pharmacopeia ("USP") definition Of "Ropivacaine Hydrochloride Injection." further supports the conclusion that Navinta'a ANDA product contains RHM. The United States Pharmacopeia (USP) is an official public standards–setting authority for all prescription and over–the–counter medicines manufactured or sold in the United States. The FDA is responsible for enforcing the USP standards. The USP is described by Plaintiff's expert the "bible" for pharmacists and is the single most important reference for a pharmacist making pharmaceutical products. Prescription and over–the–counter medicines available in the United States must, by federal law, meet USP's public standards. (Atwood Testimony, 7/20/09 Tr. at 10:14; Amidon Testimony, 7/21/09 Tr. at 342:12-18343:9-13, 344:2-13,

346:17-347:6.)

133. A USP "monograph" contains the official drug name, tests and analytical procedures one may use to identify the drug, and the procedures one should follow to ensure that a drug product complies with the USP monograph and related legal requirements. (Amidon Testimony, 7/21/09 Tr. at 345:3-7.) The FDA requires that the identity of a pharmaceutical product must comply with the identity of a drug product as characterized in the USP monograph for that drug product. An approved drug that is found not to be in compliance with USP standards could be deemed adulterated and subject to a recall notice by the FDA. (Amidon Testimony, 7/21/09 Tr. at 346:17-25, 347:1-6; PLT 379-0012.)

134. Navinta's current Package Insert Labeling describes the ANDA Products as "Ropivacaine Hydrochloride" and "Ropivacaine Hydrochloride Injection" products. Accordingly, the ANDA Products must meet the USP regulatory standards for "Ropivacaine Hydrochloride" and "Ropivacaine Hydrochloride Injection." (PLT 156-0001; Amidon Testimony, 7/21/09 Tr. at 349:3-6, 349:25-350:10, 351:16-19.)

135. The USP monograph for "Ropivacaine Hydrochloride Injection" states that "Ropivacaine Hydrochloride Injection is a sterile solution of Ropivacaine Hydrochloride in Water for Injection." (PLT 236-0004; Atwood Testimony, 7/20/09 Tr. at 100:5-9, 102:19-21; Amidon Testimony, 7/21/09 Tr. at 352:14-16.)

136. The USP monograph for "Ropivacaine Hydrochloride" states that "Ropivacaine Hydrochloride" is "(S)-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate." (PLT 236-0003; Atwood Testimony, 7/20/09 Tr. at 103:11-21; Atwood Testimony, 7/21/09 Tr. at

252:3-5; Amidon Testimony, 7/21/09 Tr. at 352:19-353:7; Newton Testimony, 7/24/09 Tr. at 830:3-5.)

137. By using the USP-defined terms "Ropivacaine Hydrochloride Injection" and "Ropivacaine Hydrochloride" in its Labeling to identify its products, Navinta is representing that the API in the ANDA Products is RHM. Pharmaceutical chemists, pharmacists, health professionals and the FDA would all understand that Navinta's ANDA Products are solutions containing RHM. (Amidon Testimony, 7/21/09 Tr. at 353:18-22, 354:2-5, 356:6-13, 364:9-365:4, 410:8-17; 3/3/09 Dave Depo. at 151:9-10; PLFT 48; PLT 379-0020.)

138. Given the USP definitions and standards, Navinta could not legally market its ANDA Products using its descriptions if its ANDA Products do not contain RHM. 21 U.S.C. §§ 331(a), 351(b).

139. Navinta's decision to describe its ANDA Products in its Labeling as "Ropivacaine Hydrochloride Injection," a term expressly defined in the USP, means that Navinta intends for its ANDA Products to be consistent with USP definitions. (Amidon Testimony, 7/21/09 Tr. at 354:14-23.) The existence of a USP monograph for "Ropivacaine Hydrochloride" indicates that RHM, and any contaminants or degradation products associated with RHM, have been tested for safety and efficacy. An API or procedure not covered by the USP monograph must be tested and analyzed before it can be listed in the USP as approved for use in humans. Thus, if Navinta maintained that its API is not RHM and therefore not covered by a USP monograph, Navinta would have to conduct clinical trials to establish that its ANDA Products are safe for use in humans. Navinta did not do this. Instead, Navinta requested a waiver of

bioequivalency testing in which Navinta represented to the FDA that the ANDA Products contain the same active and inactive ingredients as Naropin. (Amidon Testimony, 7/21/09 Tr. at 361:10-362:8; 400:8-16, 412:7-9; PLT 39-0004; PLT 48.)

140. Navinta's Analytical Validation Report, which is a part of Navinta's ANDA submissions, indicates Navinta's intent to comply with the USP monographs. The Report refers to the reference standard for RHM, which indicates that Navinta is using RHM in the ANDA Products. (Amidon Testimony, 7/21/09 Tr. at 356:19-357:21, 358:6-359:6; PLT 13-0042; PLT 379-0021, 379-0022.)

141. Navinta's Analytical Validation Report refers to an assay that is the same as the assay referenced in the USP monograph for "Ropivacaine Hydrochloride Injection." Navinta would use this assay to confirm that its ANDA Products use the same API described in the USP monograph, which is RHM. (Amidon Testimony, 7/21/09 Tr. at 359:8-360:7; PLT 13-0042.)

142. A Navinta response to a FDA deficiency notice indicates Navinta's intent to comply with the USP monograph. (Amidon Testimony, 7/21/09 Tr. at 360:12-19; PLT 341-0021.)

143. Navinta's assertions at trial that its ANDA Products need not satisfy the USP monographs for "Ropivacaine Hydrochloride Injection" and "Ropivacaine Hydrochloride" are not persuasive.

144. Navinta's Chief Scientific Officer testified that Navinta's request for a proposed monograph for "ropivacaine base" has nothing to do with Navinta's ANDA Products. This testimony indicates that Navinta recognizes that its API is not ropivacaine base, and that it is "Ropivacaine Hydrochloride" as defined by the USP, which is RHM. (Amidon Testimony,

7/21/09 Tr. at 365:23-367:11; 3/3/09 Newton Depo. at 192:24-193:4; PLT 379-0024.)

145. References in the USP monographs to ropivacaine hydrochloride anhydrous do not suggest or indicate that anything but RHM complies with the USP monographs for "Ropivacaine Hydrochloride Injection" or "Ropivacaine Hydrochloride." The USP provides that pharmaceutical manufacturers and pharmacists can base calculations for concentrations in the label on the anhydrous form. (Amidon Testimony, 7/21/09 Tr. at 380:3-14, 403:2-17, 404:17-24, 405:9-15, 408:10-409:17.)

146. Assertions by Navinta that its API is simply "ropivacaine" are inconsistent and confusing because there is no USP monograph for "ropivacaine." The absence of a USP monograph for "ropivacaine" precludes the use of "ropivacaine" as the API in the ANDA Products. (Amidon Testimony, 7/21/09 Tr. at 362:9-21, 363:14.)

ii. Navinta's ANDA Product Infringes Claim 2 of the '086 Patent

147. Claim 2 of the ‘086 Patent states: "The compound according to claim 1, wherein it is substantially optically pure." (‘086 Patent, PLT 1 at 4:13-14.)

148. The ‘086 specification defines "substantially optically pure" as 99.5% or greater. (‘086 Patent, PLT 1 at 1:40-42.) (Atwood Testimony, 7/20/09 Tr. at 75:23-76:23.)

149. Navinta's ANDA products are ropivacaine hydrochloride with an optical purity of nearly 100%. (Atwood Testimony, 7/20/09 Tr. at 154:22-155:12.) Accordingly, the ANDA Products literally infringe claim 2 of the ‘086 patent.

iii. Navinta’s ANDA Products Infringe Claim 3 of the '086 Patent

150. Claim 3 of the ‘086 Patent states: "The compound according to claim 1, wherein it

contains less than 0.5% by weight of the corresponding (R)-(+)-enantiomer." ('086 Patent, PLT 1 at 4:15-17.)

151. Claim 3 has two elements. The first element is the same as the first element in claim 2, and the second element is "contains less than 0.5% by weight of the corresponding (R)-(+)-enantiomer." Navinta documents indicate that the R-enantiomer was present in the ANDA Products in an amount of less than 0.08%, and the S-enantiomer was present in an amount of approximately 99.92%. (Atwood Testimony, 7/20/09 Tr. at 156:1-5.)

Accordingly, the ANDA Products literally infringe claim 3 of the '086 patent.

iii. Navinta's ANDA Products Infringe Claim 6 of the '086 Patent

152. Claim 6 of the '086 Patent states: "A method for inducing local anesthesia, which comprises administering to mammals including man needing local anesthesia an anesthetizing amount of the compound according to claim 1." ('086 Patent, PLT 1 at 4:35-38.)

153. The method recited in Claim 6 is comprised of five elements set forth below. The use of Navinta's ANDA Products by medical practitioners will satisfy each of these elements.

154. "*A method for inducing local anesthesia*" Navinta's Package Insert states: "Ropivacaine Hydrochloride Injection is indicated for the production of local or regional anesthesia for surgery." Thus, this first element is satisfied.

155. "*which comprises administering*" Practitioners will administer the ANDA Products by injecting the solutions into patients in the manner described in Navinta's proposed Package Insert, satisfying the second element.

156. "*to mammals including man needing local anesthesia*" Through its ANDA, Navinta is

seeking FDA approval to market the ANDA Products for use in inducing local anesthesia in man.

157. "*an anesthetizing amount*" The '086 Patent discloses that concentrations between 0.125% and 1.5% induce local anesthesia in man. ('086 Patent at 2:39-42, PLT 1.) The 0.5% and 1.0% concentrations of the Navinta ANDA Products are within this range.

158. "*of the compound according to claim 1*" This element is satisfied for the same reasons as in claims 2 and 3.

159. Thus, a physician using Navinta's 0.2%[4] ANDA Product would infringe claim 6 of the '086 Patent.

• Navinta will induce infringement of claim 6.

160. The method disclosed in claim 6 is something anesthesiologists do every day. (Gudin Testimony, 7/22/09 Tr. at 466:7-21.)

161. Navinta's Labeling instructs clinicians to use the ANDA Products in a manner that would practice the method of claim 6, and therefore instructs physicians to infringe claim 6. (Gudin Testimony, 7/22/09 Tr. at 468:10-12.)

162. Navinta reasonably knows or should know that practitioners will use its ANDA Products to practice the method of claim 6 of the '086 Patent. Navinta's amended Package Insert Labeling expressly suggests and encourages practitioners to administer the ANDA Products as a local anesthetic for inducing local anesthesia. Therefore, Navinta will induce

[4]Navinta subsequently withdrew the 0.2% concentration from its ANDA. However, because the submission of an ANDA can be an act of infringement, the Court rules on Plaintiff's claims with respect to the 0.2% concentration.

infringement of claim 6 of the ‘086 Patent. (Gudin Testimony, 7/22/09 Tr. at 466:7-21, 472:13-18.)

• Navinta will contribute to infringement of claim 6.

163. The Navinta ANDA Products are especially adapted for use in connection with the method of inducing local anesthesia as recited in claim 6 of the ‘086 patent.

164. No substantial noninfringing uses exist for the Navinta ANDA Products. Navinta's Labeling indicates that the ANDA Products are to be used as a local anesthetic. There are no other medical or non-medical uses of either ropivacaine or the Navinta ANDA Products. Furthermore, all concentrations of the Navinta ANDA Products infringe claims 1-3 of the same ‘086 patent.

B. The ‘524 and 429 Patents

165. A person of ordinary skill in the art of the ‘524 and ‘489 patents is an anesthesiologist or physician who has earned a Doctor of Medicine degree and has two or more years of additional experience in surgery or pain management. (Gudin Testimony, 7/22/09 Tr. at 485:13-16.)

i. The Invention of the '524 and '429 Patents

166. Claim 1 of the ‘524 Patent claims: "A method for treating a human experiencing pain, said method comprising: administering to said human a composition comprising a pharmaceutically acceptable salt of ropivacaine, wherein said ropivacaine is present in said composition at a concentration of less than 0.25% by weight." (‘524 Patent, PLT 2 at 3:20-24.)

167. Claim 9 of the '524 Patent claims: "A pharmaceutical composition for use in acute pain management with minimal motor blockade, comprising a pharmaceutically acceptable salt of ropivacaine at a concentration lower than 0.25% by weight." ('524 Patent, PLT 2 at 4:17-21.)

168. Claim 1 of the '489 Patent claims: "A method of treating a human so as to relieve pain with minimal motor blockade, said method comprising epidurally administering to said human a composition comprising a pharmaceutically acceptable salt of ropivacaine, wherein said ropivacaine is present in said composition at a concentration of less than 0.5% by weight." ('489 Patent, PLT 3 at 4:2-7.)

169. Motor blockade refers to the effect that a local anesthetic has on the nerves. No agents selectively block just the sensation of the nerve. Thus, when a local anesthetic is administered in the area of a nerve, it will fully block the nerve and take away the functions of strength, sensation and automatic function (e.g,. temperature, blood flow, sweating, etc.). (Gudin Testimony, 7/22/09 Tr. at 477:13-25.)

170. Ropivacaine proved to have less motor block than other local anesthetics. Research found that ropivacaine provided only 25% of the motor block provided by bupivacaine. In clinical terms, this translates to patients being able to move their limbs and participate in rehabilitation and, in the case of labor, maintains the mother's ability to push. (Gudin Testimony, 7/22/09 Tr. at 478:1-14, 481:24-482:2; PLT 0002 at 3:7-9.)

171. A low concentration of ropivacaine, such as 0.2% or less, still provides sensory block (i.e., pain relief) but avoids motor blockade. (Gudin Testimony, 7/22/09 Tr. at 479:12-15; PLT 0002 at 3:13-18.)

172. When ropivacaine is administered epidurally at 0.2% or below, it creates only a minimal motor block. (Squier Testimony, 7/23/09 Tr. at 712:16-19.)

173. Conversely, higher concentrations of ropivacaine, such as 0.5% or 1.0% concentrations, provide a profound motor block. Patients receiving this high of a concentration would have no motor function at all. (Gudin Testimony, 7/22/09 Tr. at 478:21-479:15.)

174. A significant breakthrough of the inventions claimed in the '524 and '489 patents is the ability of the claimed composition to provide appropriate sensory block (which relieves pain) while causing minimal motor blockade. (Gudin Testimony, 7/22/09 Tr. at 478:15-20.)

175. When AstraZeneca introduced Naropin in 1996, anesthesiologists immediately started using it for pain management, including labor and delivery. (Gudin Testimony, 7/22/09 Tr. at 473:19-474:5.) When Naropin first became available, anesthesiologists recognized it as a major breakthrough. Practitioners discussed Naropin at annual meetings. Naropin provided anesthesiologists with a local anesthetic that coupled long duration with safety and efficacy. Because Naropin proved to be safer than bupivacaine while providing less motor block, the introduction of ropivacaine as a local anesthetic represented a significant advance in the art. (Reyes Testimony, 7/22/09 Tr. at 557:21-558:1; Gudin Testimony, 7/22/09 Tr. at 465:6-14;

482:3-6; Squier Testimony, 7/23/09 Tr. at 701:8-12.)

176. APP Pharma's market research indicates that physicians use Naropin for four applications: (1) labor and delivery, typically in a 0.2% concentration or a 0.1% concentration combined with fentanyl; (2) post-operative pain management; (3) pain management needed in connection with chronic diseases; and (4) surgical anesthesia. The first three of these uses all concern acute pain management, which would involve the use of a 0.2% concentration. (Reyes Testimony, 7/22/09 Tr. at 560:9-561:1; Squier Testimony, 7/23/09 Tr. at 699:17-19.)

177. In clinical practice, ropivacaine is epidurally administered at concentrations of 0.2% or less. (Gudin Testimony, 7/22/09 Tr. at 490:7-22; PLT 85-0064, 85-0066.)

178. APP Pharma's market data indicates that the fastest growing segment of Naropin sales is for the 0.2% concentration, which physicians use for labor and delivery and post-operative pain management. (Reyes Testimony, 7/22/09 Tr. at 561:23-562:5, 574:11-15; PLT 381-0004.)

ii. Practitioners Regularly Dilute or Mix Higher Concentrations of Ropivacaine to Lower Concentrations for Pain Management

179. Physicians prescribe local anesthetics and/or mixtures of local anesthetics and other pain relief agents based on the needs of the patient—not based on the strengths that are commercially available from a supplier. Indeed, the concentration of the medication as packaged by the manufacturer has generally has little bearing on the amount of the concentration that a physician ultimately will deliver to the patient. (Gudin Testimony, 7/22/09 Tr. at 501:4-502:2, 503:18-504:8.)

180. Diluting ropivacaine is a simple and pervasive practice.

181. Physicians deliver medications for regional anesthesia or pain management for labor and delivery through an infusion that hangs at the patient's bedside. The medication comes from the manufacturer in a vial and then it is reconstituted, mixed or diluted either at the pharmacy or at bedside for administration to patients. (Gudin Testimony, 7/22/09 Tr. at 486:23-487:2.)

182. It is a common, indeed, daily practice for anesthesiologists and other practitioners to dilute Naropin to lower concentrations. The universal practice in anesthesia is to take the Naropin vial and dilute it to lower strengths for appropriate use in pain management with minimal motor block. (Gudin Testimony, 7/22/09 Tr. at 503:6-17, 503:18-504:8.)

183. Navinta's expert, Dr. Squier, testified that the pharmacy at the hospital where he practices routinely dilutes Naropin to make a 0.1% concentration, and that he routinely uses concentrations of Naropin below 0.2%. For example, Dr. Squier testified that his hospital dilutes Naropin to concentrations of 0.1% for use in femoral nerve blocks. This technique is used on approximately 600-900 patients per year in Dr. Squier's hospital. This use practices the inventions claimed in the ‘524 and ‘489 patents. (Gudin Testimony, 7/22/09 Tr. at 496:19-499:8; Squier Testimony, 7/23/09 Tr. at 710:6-16, 710:19-711:1, 719:12-24; 5/5/09 Squier Depo. at 110:6-25, 144:15-18, 158:10-15; PLT 380-0018, 380-0019, 380-0020.)

184. Dr. Admir Hadzic's leading textbook, Regional Anesthesia, describes concentrations

of commonly-used drugs in the epidural space and lists ropivacaine at concentrations of 0.1% to 0.2%. Because Naropin historically has not been commercially available at a 0.1% concentration, using such a concentration would require dilution prior to administration to patients. (Gudin Testimony, 7/22/09 Tr. at 488-490:4, 502:4-9; Squier Testimony, 7/23/09 Tr. at 721:25-722:6; PLT 85-0066, Table 79-13.)

185. The Hadzic textbook teaches that ropivacaine is a commonly used drug at concentrations of 0.1-0.2%. Furthermore, the Hadzic textbook includes an article that discusses pain management for labor pain, and references concentrations of ropivacaine of 0.125%, 0.25%, and 0.1%. (Squier Testimony, 7/23/09 Tr. at 721:12-22; Gudin Testimony, 5/22/09 Tr. at 527:5-529:7; PLT 156-0019; PLT 85-0052.)

186. The Hadzic text, in describing common epidural solutions, lists three concentrations of ropivacaine: 0.2%; 0.2% mixed with morphine; or 0.15% mixed with morphine. (Gudin Testimony, 7/22/09 Tr. at 490:17-20; PLT 85-0064, Table 79-6.)

187. Hospital pharmacies dilute or mix down a significant percentage of the 1.0% and 0.5% versions of Naropin because physicians primarily use Naropin in concentrations of 0.2% or below, particularly in the labor and delivery practice area. Indeed, APP Pharma's market research found that no physicians are using the 1.0% concentration for any purpose, meaning that all 1.0% Naropin products are being diluted to lower concentrations. (Reyes Testimony, 7/22/09 Tr. at 578:23-579:4, 579:14-23.)

iii. Pharmedium's Commercialization of the Diluting and Mixing of Naropin Confirms the High Demand in Medical Practice for Low, Customized Concentrations of Ropivacaine.

188. PharMEDium Services, LLC ("PharMEDium") is a pharmacy compounder. PharMEDium buys drugs from pharmaceutical manufacturers. PharMEDium either dilutes those drugs, premixes those drugs with other drugs, or transfers drugs to other sterile containers. PharMEDium then sells the resulting preparations to hospital pharmacies. (Gudin Testimony, 7/22/09 Tr. at 505:7-16; 508:23-509:12; PLT 78.)

189. PharMEDium is a regular purchaser of 30 mL single dose vials of 0.5% Naropin from APP Pharma. At present, PharMEDium only purchases 0.5% Naropin. (Reyes Testimony, 7/22/09 Tr. at 563:7-23, 564-3-12.)

190. During the last 12 months, APP Pharma sold about 650,000 30 mL units of 0.5% concentration Naropin to PharMEDium, for more than $7 million. This represents about 14% of APP Pharma's unit and dollar sales of the 0.5% concentration product during that period. PharMEDium's share of the Naropin market is growing. During the first half of 2008, PharMEDium accounted for 26.1% of 0.5% Naropin sales, and 13.0% of total Naropin sales. In 2007, PharMEDium accounted for 23.7% of all sales of 0.5% Naropin, and 11.5% of total Naropin sales. (Reyes Testimony, 7/22/09 Tr. at 563:20-25; PLT 210-0001, 211-0001, 219-0002, 219-0003, 381-0006.)

191. PharMEDium dilutes or mixes the 0.5% single-dose vials it buys from APP Pharma. PharMEDium characterizes its diluted concentrations of ropivacaine as "pain management admixtures." PharMEDium sales literature states that it offers "A complete line of pain

management admixture services for I.V. PCA and epidural therapies." PharMEDium sells 30 different sKUs of Naropin. Twenty-five of those 30 sKUs are at concentrations below 0.3%, including concentrations of 0.1%, 0.15%, 0.2%, 0.25%, and 0.3%. PharMEDium also offers mixtures of ropivacaine and fentanyl. (Reyes Testimony, 7/22/09 Tr. at 571:11-12, 577:17-20, 579:5-9; PLT 78-0003; PLT 78-0005; PLT 381-0007.)

192. APP Pharma's market research indicates that the majority of PharMEDium's sales are for epidural uses at concentrations of less than 0.3%. (Reyes Testimony, 7/22/09 Tr. at 571:15-16, 573:7-10.)

193. PharMEDium has a nationwide network of compounding centers that provide dilution drug mixing services to more than 1,900 hospitals in the United States. (Reyes Testimony, 7/22/09 Tr. at 564:18-21; PLT 78-0002.)

194. Navinta and Sandoz are aware of the diluting/mixing services that PharMEDium provides. For example, forecasts generated by Sandoz for the sale of ANDA Products include market data that refer to PharMEDium. (PLT 169-0002.)

iv. Practitioners Routinely Combine Ropivacaine with Other Anesthetic Agents, Which Results in Lower Concentrations of Ropivacaine Being Administered to Patients

195. Anesthesiologists and surgeons use "multimodal" or "balanced" analgesic techniques to manage postoperative pain. Multimodal analgesia involves using a combination of analgesic drugs, which may include using local anesthetics in combination with opioid anesthetics or other adjuvants. Combining certain analgesic drugs has a synergistic and additive effect and decreases the incidence of side effects. Today, multimodal therapy is a

mainstay of local anesthesiology practice. (Gudin Testimony, 7/22/09 Tr. at 488:16-490:2, 504:13-18; PLT 85-0064.)

196. Campbell *et al.* compare bupivacaine to ropivacaine for use in labor and delivery. Campbell describes preparing a ropivacaine/fentanyl mixture for use in labor pain management in which the concentration of ropivacaine is 0.08%. Dr. Campbell concluded that using this combination provided consistent effective labor analgesia without causing significant maternal or adverse fetal affects. A significant discovery by Dr. Campbell is that the low concentration of ropivacaine allowed pregnant mothers to walk around unassisted with minimal motor blockade during labor. (Gudin Testimony, 7/22/09 Tr. at 491:5-493:18; PLT 74-0001, 74-0002, 74-0006.)

197. Breuninger *et al.* describe the well-known practice of diluting or mixing 1.0% ropivacaine down to concentrations starting at 0.2% and ranging all the way down to 0.1% and 0.05%. They diluted ropivacaine by combining it with Ringer solutions, which is like a sterile water or normal saline solution. They also mixed ropivacaine with lidocaine or prilocaine for use as a local anesthetic in reducing postoperative pain. The Breuninger *et al.* examples results in a composition with less than a 0.25% concentration of ropivacaine. They found that these mixtures provide a broader anesthetic affect with only slightly less duration. (Gudin Testimony, 7/22/09 Tr. at 494:4-496:3, PLT 76-0001, 76-0002, 76-0004.)

198. Because some patients still experience motor block at a 0.2% concentration of Naropin, APP Pharma's market research indicates that physicians are increasingly using a 0.1% concentration of Naropin combined with fentanyl to get a synergistic effect on relieving

pain without associated motor block. (Reyes Testimony, 7/22/09 Tr. at 558:21-559:2.)

v. Practitioners Will Dilute the ANDA Products

199. Compounding pharmacies (including, for example, PharMEDium) will repackage Navinta's ANDA Products having a concentration of either 0.5% or 1% into lesser concentrations, including concentrations of less than 0.25%. Practitioners will use these repackaged products in the same manner and for the same purposes as they have been using repackaged Naropin, or the Naropin 0.2% product. (Gudin Testimony, 7/22/09 Tr. at 533:1-14, 534:4-7.)

200. Hospital pharmacies will dilute Navinta's 0.5% and/or 1.0% ANDA Products. This will result in compositions containing a pharmaceutically acceptable salt of ropivacaine (such as ropivacaine hydrochloride) at a concentration of less than 0.25% by weight ropivacaine hydrochloride. (Gudin Testimony, 7/22/09 Tr. at 5:33:9-14, 534:4-7; PLT 156-0001.)

201. Like Naropin, Navinta's ANDA Products will be packaged in 30 mL single-dose vials of 0.5% and 1.0% concentrations. (Gudin Testimony, 7/22/09 Tr. at 502:20-24, 517:18-21; Dave Testimony, 7/27/09 Tr. at 952:9-10; PLT 156-0020.) Single-dose vials are generally not a usable form of ropivacaine. For a physician to use Naropin, he or she needs diluted or mixed ropivacaine in a transfusion bag, or he or she must transfer the drug into a syringe at the point of administration to the patient. (Reyes Testimony, 7/22/09 Tr. at 565:3-8.)

vi. Price Considerations Will Encourage Pharmacies and Hospitals to Mix and Dilute the Anda Products to the Lower Concentrations of Ropivacaine That Physicians Desire, Instead of Purchasing 0.2% Naropin or Diluting Higher Concentrations of Naropin

202. The pharmaceutical industry is price driven. Sandoz's Director of Institutional Sales and Marketing, David Picard, testified that the "basic underpinnings of the generic business are that customers would convert from a higher-priced brand to a lower-priced generic for the identical presentations." (Picard Testimony, 7/23/09 Tr. at 770:1-3.)

203. Hospital pharmacies will take advantage of the lower price of the generic ANDA Products and supply diluted ANDA Products to physicians instead of either 0.2% Naropin or higher concentrations of Naropin diluted to lower concentrations. For example, hospitals will dilute a 0.5% or 1.0% ANDA Product down to 0.2% (or less) instead of buying 0.2% Naropin. Navinta's Dr. Squier admitted that this was likely to occur at his own hospital. (Squier Testimony, 7/23/09 Tr. at 726:3-13; Gudin Testimony, 7/22/09 Tr. at 5:33:9-14, 552:23-553:1; 5/5/09 Squier Depo. at 142:25-143:8, 145:23-146:8, 147:20-25, 154:24-155:7; PLT 380-0006.)

204. Physicians will use the diluted ANDA Products to practice the inventions claimed in the ‘524 and ‘489 patents.

205. If the ANDA Products are approved, physicians would use ANDA Products (which are a ropivacaine salt) that have been diluted to concentrations below 0.25% to treat pain with minimal motor blockade. (Gudin Testimony, 7/22/09 Tr. at 533:5-8, 533:21-25, 534:11-21, 535:8-14.)

206. If the ANDA Products are approved, physicians would use the ANDA Products (which are a ropivacaine salt) that have been diluted to concentrations below 0.5% (and often below 0.25%) and administer them epidurally to treat pain with minimal motor blockade. (Gudin

Testimony, 7/22/09 Tr. at 535:21-536:15.)

207. If Navinta markets and sells a 0.2% ANDA Product, physicians would use that ANDA Product (which contains a pharmaceutically acceptable ropivacaine salt) to treat pain, including by epidural administration. (Gudin Testimony, 7/22/09 Tr. at 536:19-538:5.)

208. Navinta's original Labeling for the ANDA Products encourages physicians to use the 0.2% ANDA Product for pain management. (Gudin Testimony, 7/22/09 Tr. at 538:8-16; PLT 48, 0008, 48-0022.)

vii. Navinta's Package Insert Labeling Encourages the Use of Diluted ANDA Products for Labor and Delivery and Pain Management

209. Drug companies use the Package Insert Labeling as a form of marketing. Drug companies write them as promotional material with the end user in mind. Drug companies consider them to be a critical marketing tool because it carries with it the weight of FDA approval. (Reyes Testimony, 7/22/09 Tr. at 562:16-22.)

210. All those who physically receive a Navinta ANDA Product will receive the Package Insert Labeling that is included with the product. (Picard Testimony, 7/23/09 Tr. at 746:22-25.)

211. Users of Navinta's ANDA Products will include physicians who will read Navinta's Package Insert Labeling with the benefit of professional training and significant experience with Naropin. Users of Naropin, a branded drug, are likely to be familiar with the Naropin Package Insert Labeling, which teaches that ropivacaine can be used for pain management at low concentrations. (Squier Testimony, 7/23/09 Tr. at 706:13-24, 708:24-25, 717:25-718:2;

PLT 50-0022.)

212. Navinta's original Labeling describes treating acute pain by a number of modalities, whether epidural, intermittent bolus, or use in the post-operative or labor setting, including local infiltration. (Gudin Testimony, 7/22/09 Tr. at 511:13-17; PLT 48 at p.8.)

213. Low concentrations of ropivacaine are well suited for pain management during labor and delivery. For labor and delivery, less motor block better enables patients to push with their pelvic floor muscles to help push the baby out. This is desirable because it hastens labor and thereby reduces the need for delivery by Caesarean sections or crude instrumental deliveries (i.e., removing the baby by grabbing its head with a forceps), and reduces the probabilities of complications arising during a prolonged delivery. (Gudin Testimony, 7/22/09 Tr. at 478:8-14, 480:5-21.)

214. Anesthesiologists understand that giving women in labor lower concentrations provides effective pain relief without blunting their ability to push their pelvic floor muscles. (Gudin Testimony, 7/22/09 Tr. at 479:21-480:3.)

215. APP Pharma's market research indicates that physicians like Naropin for use during labor and delivery because it allows women in labor to have maximum use of their motion function, which contributes to a positive outcome in delivery. (Reyes Testimony, 7/22/09 Tr. at 558:17-20.) A concentration of 0.5% ropivacaine or above would provide a profound motor block that would prevent a labor patient from using her pelvic muscles to push out her baby. Thus, such high concentrations of ropivacaine would not provide for an optimal delivery scenario. (Gudin Testimony, 7/22/09 Tr. at 520:21-521:3, 522:21-523:1.)

216. About 70 to 80 percent of women who have vaginal delivery get an epidural injection or catheter for labor pain management. (Gudin Testimony, 7/22/09 Tr. at 486:5-7.) Naropin's Package Insert conveys that only the 0.2% concentration of Naropin is approved by the FDA for use in labor pain management, and that epidural administration is the only FDA-approved means by which practitioners can administer Naropin for labor pain management. (Gudin Testimony, 7/22/09 Tr. at 488:9-12, 521:11-25; Squier Testimony, 7/23/09 Tr. at 711:19-712:19, 714:14-19; PLT 50-0022.)

217. The "Clinical Pharmacology" section of Navinta's Package Insert Labeling includes a subsection titled "Epidural Administration in Labor And Delivery." This section informs practitioners that using ropivacaine (in comparison to bupivacaine) resulted in "significantly fewer instrumental deliveries in mothers"—i.e., normal, headfirst, non-instrumental deliveries. The section also provides data supporting the statement that normal "spontaneous vertex" deliveries were more frequent with ropivacaine than bupivacaine, and that instrumental deliveries (those requiring the use of a vacuum extractor or a forceps) were less frequent with ropivacaine. (PLT 156-0005.)

218. The headline for this subsection, and the content of the subsection, all encourage an anesthesiologist or obstetrician to use the ANDA Products by epidural administration for labor and delivery. (Gudin Testimony, 7/22/09 Tr. at 518:2-519:13, 519:17-520:11; PLT 156-0005; PLT 380-0022.)

219. The "Precautions" section of Navinta's Labeling similarly includes a section titled "Labor And Delivery." (PLT 156-0011.) The "Labor And Delivery" subsection of the

"Precautions" section of Navinta's Package Insert Labeling again informs physicians that using ropivacaine over bupivacaine more often results in normal headfirst births (i.e., "spontaneous vertex delivery"). Instead of reading this as a "precaution," a physician would interpret this statement as a benefit to using ropivacaine, with the understanding that such a use would be by epidural administration at a concentration of 0.2% or below. (Gudin Testimony, 7/22/09 Tr. at 523:6-524:8; PLT 156-0011; Squier Testimony, 7/23/09 Tr. at 713:12-714:4, 716:18-21, 718:3-6.) Thus, this section further encourages physicians to use Navinta's ANDA Products for labor and delivery. (Gudin Testimony, 7/22/09 Tr. at 523:18-524:1.)

220. The "Labor And Delivery" subsection of the "Precautions" section of Navinta's Labeling advises physicians that they can more safely administer ropivacaine during labor and delivery by "Elevating the patient's legs and positioning her on her left side." This statement informs physicians how to lower a patient's blood pressure, and thereby instructs physicians how to avoid some of the common effects that they see when using local anesthetics in labor and delivery epidurals. (Gudin Testimony, 7/22/09 Tr. at 524:15-525:9; PLT 156-0011.) This section and the advice contained therein instructs physicians to use Navinta's ANDA Products in epidural administration in labor and delivery. (Gudin Testimony, 7/22/09 Tr. at 524:15-525:9.

221. Physicians would understand from Navinta's Labeling that the ANDA Products could be used for labor and delivery, and they would consult standard practice treatises and literature articles about the appropriate concentration to use in labor and delivery. They would find that the appropriate concentrations are at 0.2% or less. (Gudin Testimony, 7/22/09 Tr. at

522:10-15, 551:3-25.)

222. The encouraging nature of Navinta's Labeling with respect to use of the ANDA Products for labor and delivery is confirmed by APP Pharma market research. APP Pharma asked physicians whether they were influenced by the statements in the Naropin Package Insert that studies had found that using ropivacaine, in comparison to bupivacaine, resulted in fewer instrumental deliveries. The physicians responded to APP Pharma that this statement in the Naropin Labeling did encourage them to use Naropin. (Reyes Testimony, 7/22/09 Tr. at 562:9-13; PLT 50-0008.)

223. Navinta's Dr. Squier admitted that physicians desiring to use a 0.2% concentration of ropivacaine for labor and delivery could use the 0.5% or 1.0% ANDA Products diluted to concentrations of 0.2% or below. (Squier Testimony, 7/23/09 Tr. at 720:15-20.)

224. Navinta's Package Insert Labeling encourages physicians to consult current textbooks for local anesthetic techniques, including labor and delivery. The "Dosage and Administration" section of Navinta's Labeling states: "For other local anesthetic techniques standard current textbooks should be consulted." This statement encourages infringement by referring practitioners to textbooks that will describe pain management applications and recommended dosages for ropivacaine at low concentrations. (Squier Testimony, 7/23/09 Tr. at 721:5:8; Gudin Testimony, 5/22/09 Tr. at 527:5-529:7; PLT 156-0019; PLT 85-0052.)

225. Navinta's Labeling would encourage practitioners to consult is Regional Anesthesia by Admir Hadzic. (Squier Testimony, 7/23/09 Tr. at 721:9-11; Gudin Testimony, 7/22/09 Tr. at 488-490:4, 527:5-529:7; PLT 85.) Dr. Hadzic's text is one of the best known textbooks on

regional anesthesia. Dr. Hadzic's textbook teaches that ropivacaine can be used for labor pain management at concentrations of 0.125% to 0.25% followed by continuous infusion of 0.1% ropivacaine. (Gudin Testimony, 7/22/09 Tr. at 527:5-528:23.)

226. The encouragement to refer to current textbooks, coupled with the teachings contained in the textbooks regarding labor pain, encourages physicians to use ropivacaine in concentrations of 0.125% to 0.25% for labor and delivery. These concentrations would be practicing the '524 and '489 patents. (Gudin Testimony, 7/22/09 Tr. at 528:24-529:7.)

227. The "Dosage and Administration" section of Navinta's Labeling additionally states: "The smallest dose and concentration required to produce the desired result should be administered." (PLT 156-0018.)

228. Navinta's expert Dr. Squier stated that this section encourages practitioners to use the lowest concentration that they can to produce the desired result. This conforms to his own personal practice. (Squier Testimony, 7/23/09 Tr. at 719:25-720:14.)

229. In the case of a practitioner trying to use ropivacaine for labor and delivery, Dr. Squier stated that he or she would be able to use Navinta's ANDA Products in diluted form. (Squier Testimony, 7/23/09 Tr. at 720:15-20.)

230. The administration for labor and delivery that Navinta's Package Insert Labeling encourages practices the methods claimed in the '524 and '489 patents. (Gudin Testimony, 7/22/09 Tr. at 524:2-8.)

viii. Navinta And Sandoz Will Sell The ANDA Products To Long-Term Care Providers That Will Only Use The ANDA Products At Infringing Concentrations For Pain Management.

231. The "Precautions" section of Navinta's Labeling includes a subsection titled "Geriatric Use." In this subsection, Navinta informs practitioners that "Ropivacaine hydrochloride was found to be safe and effective in the patients in these studies." Navinta further informs practitioners that "care should be taken in dose selection, starting at the low end of the dosage range." These statements encourage practitioners to use the lowest dosage possible on elderly patients. (PLT 156-0011 to 156-0012.)

232. Using concentrations of 0.1% ropivacaine have proven to be especially effective in providing post-operative pain management for the elderly because it reduces narcotic requirements. Narcotics have adverse consequences, such as constipation, urinary retention, dizziness, hallucination, and slips and falls. (Gudin Testimony, 7/22/09 Tr. at 498:23-5.)

233. People might go to nursing homes or assisted living facilities to rehab from medical procedures, such as a joint replacement surgery. Such people might need pain relief with minimal motor blockade that low concentrations of ropivacaine can provide. (Gudin Testimony, 7/22/09 Tr. at 530:7-12.)

234. Consistent with the encouraging statements in the ANDA Products Labeling, and the desirability of using very low concentrations of ropivacaine on elderly patients, Navinta and Sandoz will sell the ANDA Products to group purchasing organizations that supply long-term care providers, such as nursing homes, home health care providers, and assisted living facilities. These GPOs, which include Armada, Managed Health Care Associates, and Innovatix, have been purchasing 0.5% and 1.0% Naropin. (3/4/09 Picard Depo. at 18:11-20:13.)

235. No one is performing surgery in long-term care settings such as nursing homes, home health care providers, and assisted living facilities. Practitioners working in these settings would have no use for 0.5% or 1.0% ropivacaine solutions for use in surgical anesthesia. Thus, practitioners in these settings will mix or dilute the ANDA Products down to concentrations below 0.5%, including below 0.25%, and epidurally administer the ANDA Products to patients to relieve pain while providing minimal motor blockade. (Gudin Testimony, 7/22/09 Tr. at 531:18-532:7, 531:15-532:7; 3/4/09 Picard Depo. at 19:13-15, 19:23-20:2, 37:13-39:2; 39:15-40:12; 5/5/09 Squier Depo. at 105:19-106:3; PLT 380-0023, 380-0024.)

ix. Navinta Intends To Sell Its ANDA Products For All Current Uses Of Naropin, Which Include Use Of Low Concentrations Of Naropin Covered By The '524 And '489 Patents

236. Navinta is pursuing an "A" rating for the ANDA Products. An "A" substitutability rating from the FDA will allow a pharmacy to substitute the ANDA Products for Naropin in response to any prescription or physician request for Naropin without any physician intervention or approval, including requests for concentrations below 0.5%. (Gudin Testimony, 7/22/09 Tr. at 515:3-6; Picard Testimony, 7/23/09 Tr. at 763:7-17; 3/4/09 Picard Depo. 22:20-25, 23:1-16, 25:11-13, 26:18-24, 27:21-28:1, 185:13-24; 10/22/08 Baeringer Depo. at 139:5-17.)

237. Sandoz's marketing strategy is to rely on a brand company to create a market and then enter the market with an A-rated generic and "slice from the pie that the brand has created." Thus, Navinta and its marketing collaborator Sandoz will market and sell the ANDA Products

to previous purchasers of Naropin. Navinta and Sandoz will also sell the ANDA Products to current users of non-ropivacaine anesthetics (e.g., bupivacaine) who have resisted buying Naropin in the past because of its cost. (Picard Testimony, 7/23/09 Tr. at 743:19-23; 9/11/08 Dave Depo. at 216:15-18; 3/4/09 Picard Depo. at 23:1-16; PLT 380-0025.)

238. Navinta and Sandoz will market and sell the ANDA Products for all the FDA-approved uses of all concentrations of Naropin, including concentrations of less than 0.5% for use in pain management. Navinta and Sandoz will not place limits or restrictions on the use of the ANDA products they sell. (3/4/09 Picard Depo. at 185-86.)

239. If Navinta's ANDA Products were sold at 0.5% and 1.0% concentrations, it would be an everyday practice for pharmacies and physicians to dilute those products to lower concentrations. (Gudin Testimony, 7/22/09 Tr. at 515:13-18.)

240. Navinta's 0.5% and 1.0% ANDA Products are fully substitutable with the 0.5% and 1.0% concentrations of Naropin. Practitioners could use the 0.5% and 1.0% ANDA Products for all of the same uses for which they have been using 0.5% and 1.0% Naropin. Practitioners could mix or dilute the ANDA Products in the same way they have been mixing or diluting Naropin. (Squier Testimony, 7/23/09 Tr. at 724:22-25; Gudin Testimony, 7/22/09 Tr. at 515:19-516:12; 5/5/09 Squier Depo. at 17:20-25, 198:1-19; PLT 380-0026, 380-0027.)

241. A 0.2% concentration made by diluting the 0.5% Navinta ANDA Product could be used for all the same purposes and in the same manner as a 0.2% concentration of Naropin. (Squier Testimony, 7/23/09 Tr. at 725:9-13.)

x. Navinta Knows or Should Know That Practitioners Will Use its ANDA Products at

Diluted Concentrations for Pain Management.

242. Navinta knew or should have known that the '524 and '489 patents cover acute pain management. First, the same December 2004 search report performed by Dr. Newton and "fully reviewed" by Dr. Pullagurla that revealed the '524 and '489 patents, also uncovered two articles that describe combining ropivacaine and other anesthetic agents:

· M.J. Sanchez del Aguila et al., "Premixed Solutions of Diamorphine in Ropivacaine for Epidural Anesthesia: A Study on the Long-term Stability," British Journal of Anesthesia, 90(2):179-182 (2003). This article discusses mixing ropivacaine with diamorphine.

· K. Öster Svedberg et al., "Compatibility of Ropivacaine with Morphine, Sulfentanil, Fentanyl or Clonidine," Journal of Clinical Pharmacy and Therapeutics, 27:39-45 (2002). This article discusses combinations of ropivacaine with other anesthetic agents such as morphine and clonidine. (Gudin Testimony, 7/22/09 Tr. at 499:25-500:19; PLT 92-0016, 92-0021.) Second, Abraxis sued Navinta for infringement of the '524 and '489 patents on or about March 15, 2007. Third, in Navinta's U.S. Patent Application No. 11/137,256, Example 8 discusses diluting 50 mL of a 1000 mL stock solution of ropivacaine to obtain a concentration of 0.2% ropivacaine. Thus, Navinta's '256 Patent Application shows Navinta's awareness of mixing and diluting practices. (PLT 91-0005 to 91-0006.)

243. Further, Sandoz documents confirm that Navinta knew that practitioners would dilute the ANDA products to infringing concentrations. Sandoz understood that the 0.2% concentration of Naropin accounted for more than 45% of the total sales revenue for Naropin,

and more than 66% of the total extended units sold of Naropin. Thus, Sandoz and Navinta operated under the belief that a large built-in market exists for low concentrations of 0.2% ropivacaine. (3/4/09 Picard Depo. at 134:12-136:9.)

244. On June 30, 2008, Navinta submitted an amendment to the FDA withdrawing from its ANDA any request for approval of a 0.2% ANDA Product. Before Navinta submitted this amendment, Sandoz's Dave Picard generated marketing forecasts of projected sales for a 0.2% ANDA Product. These same forecasts also projected sales for the 0.5% and 1.0% ANDA Products. After the amendment withdrawing the 0.2% ANDA Product, Matt Bohlman, the point person for Sandoz's dealings with Navinta, revised the Sandoz forecasts. The earler forecast reflected sales for the 0.5% and 1.0% concentrations, respectively, as 497,574 and 69,352 units. The later forcast increased these numbers to 623,228 and 219,150, respectively. These revisions to the sales forecasts are evidence of a belief and desire by Navinta and Sandoz that customers who otherwise would have purchased a 0.2% concentration ANDA Product will purchase 0.5% and 1.0% concentrations and dilute those products into lesser concentrations. (Picard Testimony, 7/23/09 Tr. at 742:7-10, 754:10-760:15; PLT 170-0001; PLT 179-0001; PLT 182-0001; PLT 183.)6. APP Pharma market research indicates that the 0.2% Naropin product accounts for 33% of all Naropin sales, and that sales of the 0.5% concentration to PharMEDium (which dilutes the 0.5% concentration to concentrations of 0.2% and below) accounts for 14% of all Naropin sales. (Reyes Testimony, 7/22/09 Tr. at

570:17-571:3.)

xi. Navinta Will Induce Infringement of Claims 1 and 9 of the '524 Patent and Claim 1 of the '489 Patent

245. Considering all of the above circumstances, the Court concludes that Navinta will induce infringement of claims 1 and 9 of the ‘524 patent, and claim 1 of the ‘489 patent.

246. Navinta's Package Insert Labeling is sufficient to establish Navinta's encouragement of direct infringement of the ‘524 and ‘489 patents: (1) Navinta's Labeling specifically encourages infringement by including multiple references to use of the ANDA Products in labor and delivery, which is an acute pain management application that is only FDA-approved at concentrations of 0.2% or below and by epidural administration; (2) Navinta's Labeling specifically encourages infringement by including statements referring practitioners to medical practice texts and references, which would instruct practitioners to use ropivacaine at concentrations of 0.2% or below for pain management; (3) Navinta's Labeling specifically encourages infringement by encouraging the use of the ANDA Products at the lowest possible concentrations for pain management uses.

247. In addition to the numerous encouraging statements including in Navinta's Package Insert Labeling, other evidence exists of Navinta's active encouragement of infringement: (1) The fact that Navinta's Labeling nowhere advises against the mixing or diluting of the ANDA Products to infringing concentrations is strong circumstantial evidence of Navinta's encouragement of infringement; (2) Navinta's collaboration with Sandoz to market and sell its ANDA Products to customers that will only use the products in infringing ways, such as

nursing homes and assisted living facilities, and those that have been purchasing 0.2% Naropin for pain management, constitutes an active step to induce infringement. See, e.g., Braintree Labs., Inc. v. Nephro-Tech, Inc., 81 F. Supp. 2d 1122, 1130-31 (D. Kan. 2000) (defendant actively induced infringement of method claim by targeting customers who would only use product for purposes covered by method claim); (3) Navinta's act of seeking an "A" substitutability rating for its ANDA Products, so they may be substituted for all prescriptions of Naropin (including those for concentrations of 0.2% or below for use in pain management) without any need for physician intervention or approval, is strong circumstantial evidence of Navinta's encouragement of infringement; (4) Navinta's and Sandoz's acts of targeting all Naropin customers with the intent that purchasers of the ANDA Products will use them for all the same purposes and uses of Naropin, including pain management uses of concentrations of 0.2% or below, and concentrations below 0.5% administered epidurally, is strong circumstantial evidence of Navinta's encouragement of infringement; (5) Sandoz sales forecasts that showed a marked increase in sales of 0.5% and 1.0% ANDA Products immediately after Navinta submitted an amendment removing a 0.2% ANDA Product from its ANDA submission, is strong circumstantial evidence of Navinta's encouragement of infringement; (6) Navinta's and Sandoz's targeting of group purchasing organizations that supply in-house hospital pharmacies where Navinta knows or should know that dilution and mixing of higher concentrations of ropivacaine is a routine practice, is strong circumstantial evidence of Navinta's encouragement of infringement; (7) Navinta's original ANDA filing seeking approval for a 0.2% Product, and Navinta's efforts through subsequent ANDA

amendments to preserve means of tapping the huge market for uses of concentrations of ropivacaine of 0.2% or below, is strong circumstantial evidence of Navinta's encouragement of infringement; (8) Navinta's offering of a significantly cheaper generic version of Naropin, which Navinta knows or should know will result in practitioners in need of concentrations of ropivacaine of 0.2% or below, or concentrations of below 0.5% to be administered epidurally, buying the ANDA Products and diluting or mixing them down to the desired concentrations, is strong circumstantial evidence of Navinta's encouragement of infringement; (9) Navinta did not obtain an opinion of counsel relating to its possible infringement of Abraxis's asserted patents. (Newton Testimony, 7/24/09 Tr. at 841:22-842:2, 856:20-857:12.) Failure to obtain such a legal opinion is strong circumstantial evidence of Navinta's encouragement of infringement. *Broadcom*, 543 F.3d at 699 ("Because opinion-of-counsel evidence, along with other factors, may reflect whether the accused infringer 'knew or should have known' that its actions would cause another to directly infringe, we hold that such evidence remains relevant to the second prong of the intent analysis").

248. Navinta has direct and specific knowledge that physicians, pharmacies, or other practitioners, by diluting or mixing down the ANDA Products to concentrations of 0.2% or below, will directly infringe claims 1 and 9 of the '524 patent.

249. Navinta has direct and specific knowledge that physicians, pharmacies, or other practitioners, by diluting or mixing down the ANDA Products to concentrations below 0.5% and by epidurally administering these reduced concentrations to relieve pain with minimal motor blockade, will directly infringe claim 1 of the '489 patent.

250. Navinta knows or should know that its acts will result in infringement. Navinta has been aware of Abraxis's '524 and '489 patents since 2004. Navinta has been aware of mixing and diluting practices relating to Naropin since 2004. Navinta is aware of PharMEDium's dilution and admixing of Naropin. Navinta is aware that most uses of Naropin have been at concentrations of less than 0.5%—below the lowest concentration of the ANDA Products. Navinta and Sandoz inquired into the potential extent of "conversion of strengths" in analyzing how much ANDA Product to manufacture.

xii. Navinta Will Contribute To The Infringement Of Claims 1 And 9 Of The '524 Patent, And Claim 1 Of The '489 Patent.

251. Navinta's ANDA Products constitute material components of the compositions for use in the methods described in Claim 1 of the '524 Patent and Claim 1 of the '489 Patent, and constitute material components of the compositions described in Claim 9 of the '524 Patent.

252. Navinta's ANDA Products are not staple articles suitable for substantial noninfringing use, and there are no substantial noninfringing uses of Navinta's ANDA Products, because, among other things, the ANDA Products infringe claims 1, 2, 3 and 6 of Abraxis's '086 Patent.

253. Consequently, by selling its 0.5% and 1.0% ANDA Products, Navinta will contributorily infringe Claims 1 and 9 of the '524 patent, and Claim 1 of the '489 Patent.

xiii. Navinta's 0.2% Anda Product Infringes Abraxis's Asserted Patents.

254. In its original ANDA filing, Navinta sought approval for a product with a 0.2% concentration. (PLT 48-0023.) Although Navinta withdrew the 0.2% product from its ANDA

in its June 30, 2008 amendment, Navinta has not taken any action to resolve claims relating to a 0.2% product from this lawsuit, and Navinta has refused to enter into a stipulation with Abraxis resolving any possible claims relating to a 0.2% product.

255. Navinta's manufacture and sale of a 0.2% ANDA Product will infringe claims 1, 2, 3, and 6 of the ‘086 Patent for all the reasons set forth above with respect to Navinta's 0.5% and 1.0% ANDA Products.

256. The use of Navinta's 0.2% ANDA Product, which expressly falls within the range of concentrations claimed in the ‘524 and ‘489 patents, will result in direct infringement of the ‘524 and ‘489 patents for all the reasons set forth above with respect to Navinta's 0.5% and 1.0% ANDA Products.

257. Navinta's manufacture and sale of a 0.2% ANDA Product will directly infringe claim 9 of the ‘524 patent, because the product constitutes a composition of a pharmaceutically acceptable ropivacaine salt, at a concentration of less than 0.25% by weight, that will be used for acute pain management with minimal motor blockade.

258. Navinta is liable for indirect infringement of claims 1 and 9 of the ‘524 patent, and claim 1 of the ‘489 patent, for all the same reasons set forth above with respect to Navinta's 0.5% and 1.0% ANDA Products. Furthermore, Navinta's original ANDA Product Package Insert Labeling explicitly includes an indication for pain management and dosage recommendations for the 0.2% product which instructs and encourages practitioners to use the 0.2% product when used in a manner consistent with the original package insert induces infringement of the ‘524 and ‘489 patents. (PLT 48-0022 at Table 7.)

IV. CONCLUSION

For the reasons above:

1. Judgment shall be entered in favor of Abraxis on Abraxis's claim for infringement of the ‘086 Patent.

2. Judgment shall be entered in favor of Abraxis on Abraxis's claim for infringement of the ‘524 Patent.

3. Judgment shall entered in favor of Abraxis on Abraxis' claim for infringement of the ‘489 Patent.

4. Navinta's counterclaims for declarations of noninfringement and invalidity are dismissed with prejudice.

5. Pursuant to 35 U.S.C. § 271(e)(4)(A), the Court shall order the effective date of any approval of any ANDA Products to be no earlier than September 23, 2014, the date of expiration for the ‘524 and ‘489 patents.

/s/ JOEL A. PISANO
United States District Judge

Dated: August 3, 2009