UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

Kowa Company, Ltd., et al.,

Plaintiffs,

v.

Amneal Pharmaceuticals, LLC

Defendant.

Civil Action No. 14-CV-2758 (PAC)

Kowa Company, Ltd., et al.,

Plaintiffs,

v.

Apotex, Inc., et al.,

Defendants.

Civil Action No. 14-CV-7934 (PAC)

FINDINGS OF FACT AND CONCLUSIONS OF LAW

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TABLE OF ABBREVIATIONS

'993 Patent	U.S. Patent No. 8,557,993
ANDA	Abbreviated New Drug Application
API	Active pharmaceutical ingredient
DMF	Drug master file
EPO	European Patent Office
EP '406	European Patent Application No. EP 0 520 406A1
FDA	U.S. Food and Drug Administration
IDS	Information Disclosure Statement
KCL	Kowa Company, Ltd.
KPA	Kowa Pharmaceuticals America, Inc.
MSN	MSN Laboratories Pvt. Ltd.
NCI	Nissan Chemical Industries, Ltd.
PTO	U.S. Patent and Trademark Office
TPO	Third Party Observation
USP	U.S. Pharmacopeia
XRPD or PXRD	X-ray powder diffraction

HONORABLE PAUL A. CROTTY, United States District Judge:

This is a Hatch-Waxman patent infringement litigation initiated by Plaintiffs Kowa Company, Ltd., Kowa Pharmaceuticals America, Inc., and Nissan Chemical Industries, Ltd. (collectively, "Plaintiffs"), manufacturers of the cholesterol-lowering drug Livalo®, against defendants Amneal Pharmaceuticals, LLC ("Amneal"), and Apotex, Inc. and Apotex Corp. ("Apotex"), generic drug manufacturers (together, "Defendants").[1] Plaintiffs allege that Defendants' proposed Abbreviated New Drug Application ("ANDA") products would infringe U.S. Patent No. 8,557,993 (the "'993 patent"). Both Amneal and Apotex contend that the '993 patent is invalid as (1) anticipated based on prior art, under 35 U.S.C. § 102(b); and/or (2) obvious in view of prior art, under 35 U.S.C. § 103. Only Apotex asserts non-infringement; Amneal concedes infringement.

The Court held a ten-day bench trial from January 17 through January 30, 2017, with closing arguments on February 3, 2017. Each of the parties submitted extensive post-trial briefing on the '993 patent's validity and infringement. After considering the documentary evidence and testimony, the Court makes the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a). As set forth below, the Court determines that the '993 patent is valid; and that Apotex's proposed ANDA product would infringe the '993 patent.

[1] Plaintiffs commenced this litigation against eight generic drug manufacturer defendants. Defendants asserted defenses of invalidity and non-infringement. Four defendants settled before commencement of the ten-day bench trial. The fifth defendant settled mid-trial; and the sixth settled post-trial. Only Amneal and Apotex remain. On April 11, 2017, the Court issued its Findings of Fact and Conclusions of Law regarding the other patent at issue at trial, U.S. Patent No. 5,856,336, finding it valid. (*Kowa Co., Ltd. v. Amneal Pharm., LLC.*, No. 14-CV-2758 (PAC) (S.D.N.Y. Apr. 11, 2017)).

INTRODUCTION AND LEGAL STANDARDS

I. The Hatch-Waxman Act and ANDA Filings[2]

1. The Hatch-Waxman Act, titled the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, permits pharmaceutical companies to seek United States Food and Drug Administration (FDA) approval for a generic drug based on an already-approved branded drug by filing an ANDA. (*See* 21 U.S.C. § 355(j)(2)(A), (8)(B)). In so doing, the generic manufacturer may rely on the branded drug's safety and efficacy data submitted to the FDA. (*See id.*).

2. If the branded drug manufacturer's patent has not yet expired, the generic manufacturer must file a "Paragraph IV" certification, establishing bioequivalence of the proposed generic version with the approved branded version of the drug. (*See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV); 21 C.F.R. § 314.94(a)(9)). The certification must also state and explain either that the generic product will not infringe the branded manufacturer's patent, or that the patent is invalid. (*See* 21 U.S.C. § 355(j)(2)(B)(iv)(II)).

3. "An ANDA-IV certification itself constitutes an act of infringement, triggering the branded manufacturer's right to sue." (*Ark. Carpenters Health & Welfare Fund v. Bayer AG*, 604 F.3d 98, 101 (2d Cir. 2010), *cert. denied*, 131 S. Ct. 1606 (2011) (citing 35 U.S.C. § 271(e)(2)(A)). If litigation is initiated, the generic's entry to market is automatically stayed. (21 U.S.C. § 355(j)(5)(B)(iii)). "[T]his structure allows the parties to try the dueling issues of patent infringement and patent invalidity simultaneously." (*In re: OxyContin Antitrust Litig.*, No. 13-CV-3372 (SHS), 2015 WL 11217239, at *5 (S.D.N.Y. Apr. 8, 2015)).

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[2] For additional background on the policy goals of the Hatch-Waxman Act, see this Court's April 11, 2017 Findings of Fact and Conclusions of Law regarding the other patent at issue at trial, U.S. Patent No. 5,856,336. (*Kowa Co., Ltd. v. Amneal Pharm., LLC*, No. 14-CV-2758 (PAC) (S.D.N.Y. Apr. 11, 2017) at 9–10).

II. The Parties

4. Plaintiff Kowa Company, Ltd. ("KCL") is a Japanese corporation with its corporate headquarters and principal place of business in Aichi, Japan. (Compl. ¶ 2). Plaintiff Kowa Pharmaceuticals America, Inc. ("KPA") is a wholly-owned subsidiary of KCL organized under the laws of Delaware, with its corporate headquarters and principal place of business in Montgomery, Alabama. (*Id.*). Plaintiff Nissan Chemical Industries, Ltd. ("NCI" or "Nissan") is a Japanese corporation with its corporate headquarters and principal place of business in Tokyo, Japan. (*Id.* ¶ 3). Plaintiffs are manufacturers, researchers, developers, and marketers of the cholesterol-lowering drug Livalo®. (*Id.* ¶ 4).

5. Defendant Amneal is incorporated in Delaware, with a place of business in Bridgewater, New Jersey. (Amneal Answer ¶ 5). Amneal filed ANDA No. 20-5961 seeking FDA approval to market 1 mg, 2 mg, and 4 mg pitavastatin calcium tablets. (*Id.* ¶ 20).

6. Defendant Apotex, Inc. is organized in and exists under the laws of Canada, with a principal place of business in Toronto, Ontario. (Apotex Answer ¶ 5). Defendant Apotex Corp. is incorporated in and exists under the laws of Delaware, with a place of business in Weston, Florida. (*Id.* ¶ 6). Apotex Corp. sells and markets Apotex, Inc.'s products in the United States. (*Id.*). Apotex Corp. is Apotex Inc.'s agent for purposes of making regulatory submissions, including its ANDA No. 20-6068 filing, seeking FDA approval to market 1 mg, 2 mg, and 4 mg pitavastatin calcium tablets. (*Id.* ¶¶ 6, 20). Apotex's ANDA filing contains a Paragraph IV certification respecting the '993 patent. (*Id.* ¶ 22).

III. Livalo®

7. At trial, Dr. Craig Sponseller, KPA's Chief Medical Officer, provided an initial explanation of the history and workings of Livalo® pitavastatin. (*See generally* Tr. 67–136). A brief summary of relevant and uncontested facts is recited here.

8. Statins are medications that address and control abnormal increases in blood cholesterol by inhibiting the way in which the liver makes cholesterol. (Tr. 70:8–71:10). All statins generally work in the same way, but differ in the manner in which they bind to enzymes and dissolve in solvents; and how they are processed and metabolized by the body. (Tr. 71:5–17).

9. Patients have varying degrees of statin tolerance (or intolerance). (Tr. 71:25–74:13). Approximately 10-15% of patients with elevated cholesterol are statin intolerant, which amounts to approximately 4 to 6 million statin-intolerant patients in the United States. (Tr. 73:22–74:7).

10. Livalo® is a statin used to treat elevated cholesterol; or more specifically, as reflected on its label, hyperlipidemia or mixed dyslipidemia. (Tr. 77:5–11; PTX-1098 (Livalo® Label (Revised: November 2016)) at KN003466196). It does so by reducing low density protein cholesterol ("LDL-C"), total cholesterol, triglycerides, and apolipoprotein B; and/or increasing high density lipoprotein cholesterol ("HDL-C"). (Tr. Tr. 77:5–11; PTX-1098 (Livalo® Label) at KN003466196).

11. Approximately 75% of all metabolic drugs are metabolized through the "cytochrome P450" pathway (the "CYP450" or "CYP" pathway) in the liver. (Tr. 74:14–75:9). By contrast, Livalo® mostly avoids, and is only minimally metabolized by, the CYP450 pathway. (Tr. 75:10–76:1, 85:6–21).

12. There are currently seven available statins on the market; at the time Livalo® launched in the U.S. in mid-2010, there were six available statins with which Livalo® competed.[3] (Tr. 70:15–20).

IV. The '993 Patent

13. The '993 patent, "Crystalline Forms of Pitavastatin Calcium," is assigned to NCI. (PTX-1063). KCL is NCI's licensee for the '993 patent, and KPA holds a license from KCL for the '993 patent. (Amneal Compl. ¶ 15; Apotex Compl. ¶ 15). KPA sells the pitavastatin drug product under the trade name Livalo® in the United States; KCL manufactures the Livalo® products as sold by KPA. (Amneal Compl. ¶¶¶ 16–17; Apotex Compl. ¶¶ 16–17).

14. The '993 patent issued on October 15, 2013, from U.S. Patent Application No. 13/664,498 (the "'498 Application"), filed October 31, 2012. (PTX-1063 ('993 patent); PTX-0172 ('498 Application ('993 patent file history))). The '498 Application is a continuation of U.S. Patent Application No. 10/544,752 (the "'752 Application). (PTX-1337 *and* DTX-1359).[4]

15. The earliest priority date to which the '993 patent claims entitlement is February 12, 2003. (PTX-1063 (claiming entitlement to European Application No. 03405080)).

16. The '993 patent states:

> The present invention is directed to new crystalline forms and the amorphous form of Pitavastatin calcium, processes for the preparation thereof and pharmaceutical compositions comprising these forms . . . Pitavastatin calcium is known by the chemical name: (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt.

(*Id.* at 1:17–26).

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[3] Livalo® was approved by Japanese regulators and launched in Japan in 2003; was approved by the FDA in August 2009; and launched in the United States in June 2010. (Tr. 1534:17–20, 103:8–9; *see* PTX-0480; PTX-0482).

[4] Both Plaintiffs and Defendants submitted the '752 Application and file history. (*See* PTX-1337; DTX-1359). Due to a copying error, DTX-1359 was missing some pages; but the relevant testimony did not involve any such pages. (*See* Tr. 1661:9–21). For ease of reference, the Court cites both exhibits and Bates pages used and referenced in the corresponding trial testimony.

17. The '993 patent explains that Plaintiffs recently developed pitavastatin calcium "as a new chemically synthesized and powerful statin . . . [that] is safe and well tolerated in the treatment of patients with hypercholesterolemia;" and that the statin has "extremely low" interactions with other commonly-used drugs. (*Id.* at 1:43–50).

18. Claims 1, 22, 23, 24, and 25 of the '993 patent claim six different polymorphs of pitavastatin calcium, polymorphic forms A, B, C, D, E, and F, and the amorphous form; and a pharmaceutical composition comprising an effective amount of the form, and a pharmaceutically acceptable carrier. (*Id.* at 10:50–11:37, 13:7–41). Each claimed form includes a recitation of a characteristic X-ray powder diffraction pattern having specific characteristic peaks (claims 1 and 24) or a diffraction pattern substantially as depicted in specified Figures (claims 23 and 25). (*Id.*).

19. Crystalline polymorph A of pitavastatin calcium ("Form A" or "Polymorph Form A") is the subject of this action.[5]

20. The '993 patent specification discloses that "Form A may contain up to 15% water, preferably about 3 to 12%, more preferably 9 to 11% of water." (*Id.* at 6:13–14).

21. Claims 1 and 24 are directed to, *inter alia*, Form A exhibiting "a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at [recited peak positions and relative intensities]." The relevant parts of claims 1 and 24 are set forth below:

> 1. A crystalline polymorph A, B, C, D, E, F, or the amorphous form, of [pitavastatin calcium] salt wherein
>
> A) polymorph A exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 5.0 (s), 6.8 (s), 9.1 (s), 10.0 (w), 10.5 (m), 11.0 (m), 13.3 (vw), 13.7 (s), 14.0 (w), 14.7 (w), 15.9 (vw), 16.9 (w), 17.1

[5] The other polymorphic forms and the amorphous form of pitavastatin calcium claimed in the '993 patent are irrelevant to this action, and are not discussed further.

> (vw), 18.4 (m), 19.1 (w), 20.8 (vs), 21.1 (m), 21.6 (m), 22.9 (m), 23.7 (m), 24.2 (s), 25.2 (w), 27.1 (m), 29.6 (vw), 30.2 (w), 34.0 (w);
> . . . wherein, for each of said polymorphs, (vs) stands for very strong intensity; (s) stands for strong intensity; (m) stands for medium intensity; (w) stands for weak intensity; (vw) stands for very weak intensity.

> 24. A crystalline polymorph A of [pitavastatin calcium] salt, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 5.0 (s), 6.8 (s), 9.1 (s), 10.0 (w), 10.5 (m), 11.0 (m), 13.3 (vw), 13.7 (s), 14.0 (w), 14.7 (w), 15.9 (vw), 16.9 (w), 17.1 (vw), 18.4 (m), 19.1 (w), 20.8 (vs), 21.1 (m), 21.6 (m), 22.9 (m), 23.7 (m), 24.2 (s), 25.2 (w), 27.1 (m), 29.6 (vw), 30.2 (w), and 34.0 (w), wherein (vs) stands for very strong intensity; (s) stands for strong intensity; (m) stands for medium intensity; (w) stands for weak intensity; and (vw) stands for very weak intensity.

22. Claims 23 and 25 are directed to, *inter alia*, Form A having "an X-ray powder diffraction pattern substantially as depicted in FIG. 1" of the '993 patent. Relevant parts of claims 23 and 25, and Figure 1, are set forth and reproduced below:

> 23. A crystalline polymorph A . . . of [pitavastatin calcium] salt of claim 1, wherein polymorph A has an X-ray powder diffraction pattern substantially as depicted in FIG. 1 . . .

> 25. A crystalline polymorph A of [pitavastatin calcium] salt, having an X-ray powder diffraction substantially as depicted in FIG. 1.

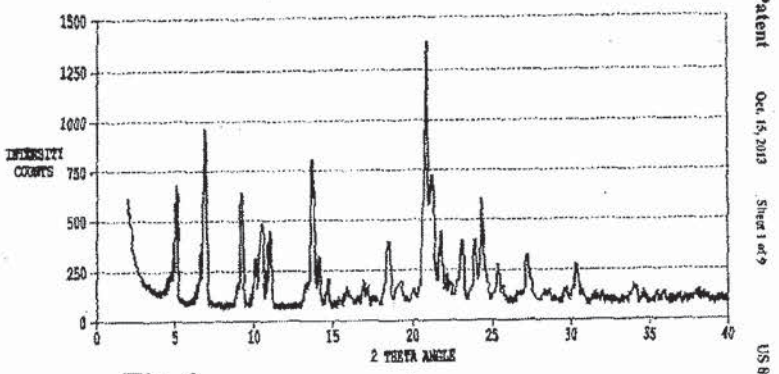


Fig. 1

23. Claim 22 states:

> 22. A pharmaceutical composition comprising an effective amount of the crystalline polymorph or amorphous form according to claim 1, and a pharmaceutically acceptable carrier.

24. The specification of the '993 patent provides:

> Powder X-ray diffraction is performed on a Philips 1710 powder X-ray diffractometer using CuK (α_1) radiation (1.54060 Å); 2θ angles are recorded with an experimental error of +/- 0.1-0.2°. A discussion of the theory of X-ray powder diffraction patterns can be found in "X-ray diffraction procedures" by H.P. Klug and L.E. Alexander, J. Wiley, New York (1974).

(*Id.* at 5:61–67 (citing PTX-1011 (Harold P. Klug & Leroy E. Alexander, *X-ray Diffraction Procedures for Polycrystalline and Amorphous Materials* (2d ed. 1974))).

25. Example 1 of the '993 patent details preparation of Form A. It instructs:

EXAMPLE 1

Preparation of Form A

> 4.15 gr of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid tert-butyl ester (Pitavastatin tert-butyl ester) was suspended in 52 ml of a mixture of methyl tert-butyl ether and methanol (10:3). To this mixture were added 2.17 ml of a 4M aqueous solution of NaOH, and the resulting yellowish solution was stirred for 2.5

> hours at 50° C. The reaction mixture was cooled to room temperature followed by the addition of 50 ml water and stirring for an additional hour. The aqueous phase was separated and once extracted with 20 ml of methyl tert-butyl ether. To this aqueous solution were added a solution of 0.58 gr CaCl2 in 80 ml of water over a period of 1 hour. The resulting suspension was stirred for about 16 hours at room temperature. The suspension was filtered and the obtained solid was dried at 40°C and 50 mbar for about 16 hours. The obtained product is crystal Form A which is characterized by an X-ray powder diffraction pattern as shown in FIG. 1. Further characterization of the obtained Form A by thermogravimetry coupled with FT-IR spectroscopy revealed a water content of about 10%. Differential scanning calorimetry revealed a melting point of 95° C.

(*Id.* at 8:32–53).

V. The Instant Dispute

26. Plaintiffs assert that Defendants' proposed ANDA products contain Form A, as claimed by the '993 patent; and would infringe claims 1, 22, 23, 24, and 25 of the '993 patent (together, the "Asserted Claims").

27. Amneal stipulates that the active pharmaceutical ingredient ("API") in its proposed ANDA product is Form A of the '993 patent, and would directly infringe the Asserted Claims. (PTX-1324 at 1). Amneal also stipulates that it will not change the polymorphic form of its ANDA product from Form A. (*Id.* at 2)

28. Apotex contends that the API in its proposed ANDA product does not meet the '993 patent claim limitations and does not infringe the '993 patent.

29. Defendants contend that the '993 patent is invalid for (1) inherent anticipation, under 35 U.S.C. § 102(b); and/or (2) obviousness, under 35 U.S.C. § 103(a).

VI. Legal Standards[6]

a. Presumption of Patent Validity

30. Patents are presumed valid, and each patent claim is "presumed valid independently of the validity of other claims." (35 U.S.C. § 282).

b. Affirmative Defense of Patent Invalidity

31. A defendant "in any action involving the validity . . . of a patent" may plead, as an affirmative defense, that the asserted patent is invalid. (35 U.S.C. § 282). Because patent validity is presumed, a defendant asserting this defense bears the burden of proving invalidity by clear and convincing evidence. (*See id.*; *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011)).

32. Patent examiners are owed deference and are "presumed to have considered" prior art references listed on the face of a patent. (*Shire, LLC v. Amneal Pharm., LLC*, 802 F.3d 1301, 1307 (Fed. Cir. 2015)). Infringement defendants thus "'have the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.'" (*Id.* (quoting *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1304 (Fed. Cir. 2008))).

33. "[T]he issue of validity does not warrant findings of whether the examiner 'really did understand what he was ruling,'" and "[i]ntrospection and speculation into the examiner's understanding of the prior art or the completeness or correctness of the examination process is

[6] The Leahy-Smith America Invents Act ("AIA"), Pub L. No. 112-29, 125 Stat. 284, was signed into law on September 16, 2011. Because the earliest priority date to which the '993 patent claims entitlement is February 12, 2003, the '993 patent is subject to pre-AIA statutes.

not part of the objective review of patentability." (*Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1329 (Fed. Cir. 2004) (quoting Trial Tr. at 790)).

i. Anticipation (35 U.S.C. § 102)

34. To be patentable, the invention must be novel; inventions lacking novelty are invalid. (35 U.S.C. § 102).

35. An invention is unpatentable as being anticipated if it "was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States." (*Id.* § 102(b)).

36. "Invalidity based on lack of novelty (often called 'anticipation') requires that the same invention, including each element and limitation of the claims, was known or used by others before it was invented by the patentee." (*Hoover Grp., Inc. v. Custom Metalcraft, Inc.*, 66 F.3d 299, 302 (Fed. Cir. 1995)).

37. Accordingly, patents are invalid as anticipated when "a single prior art reference [] expressly or inherently disclose[s] each claim limitation." (*Finisar Corp. v. DirecTV Grp., Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008)).[7] "[I]nvalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." (*Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000)).

38. "To show inherent anticipation, a defendant must demonstrate clearly and convincingly that a claim limitation not disclosed in the anticipating reference will always be present when the prior art is practiced as taught in that reference." (*In re: OxyContin*, 2015 WL 11217239, at

[7] Defendant do not assert express anticipation of the '993 patent.

*6). "[W]hen a claim limitation is not explicitly set forth in a reference, evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. It is not sufficient if a material element or limitation is 'merely probably or possibly' present in the prior art." (*In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007) (quotations and citations omitted)). "Inherency [] may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." (*Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (quotations and citations omitted) (emphasis in original)). Rather, the claimed invention must "necessarily and inevitably form[] from" the alleged anticipatory reference. (*Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1378 (Fed. Cir. 2003)).

39. Thus, "if the teachings of the prior art can be practiced in a way that yields a product lacking the allegedly inherent property, the prior art in question does not inherently anticipate." (*In re Depomed Patent Litig.*, No. 13-4507 (CCC-MF), 2016 WL 7163647, at *26 (D.N.J. Sept. 30, 2016)). Specifically, even where practice of an example taught by a prior art reference sometimes results in a patented polymorphic form, the prior art does not inherently anticipate if its teachings can also be practiced in a way that produces a different form. (*Glaxco Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047–48 (Fed. Cir. 1995) (affirming district court's rejection of anticipation defense where district court found that practice of prior art example "could yield crystals of either [the claimed or a different] polymorph")).

40. The finding of anticipation is a question of fact. (*Amkor Tech., Inc. v. Int'l Trade Comm'n*, 692 F.3d 1250, 1254 (Fed. Cir. 2012)).

ii. Obviousness (35 U.S.C. § 103)

41. An invention is invalid as obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." (35 U.S.C. § 103(a)).

42. In contrast to the anticipation inquiry, obviousness is determined by assessing "the combined teachings of the prior art, taken as a whole." (*In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995)). For purposes of obviousness, one skilled in the art is "presumed to know all of the teachings of the prior art in the field of the invention at the time of the patent's priority date." (*In re: OxyContin*, 2015 WL 11217239, at *7).

43. A party asserting obviousness "must demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." (*OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 706 (Fed. Cir. 2012) (quotations and citation omitted)).

44. "Obviousness is a question of law based on underlying factual determinations." (*Amkor*, 692 F.3d at 1254). These factual determinations include: "(1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) objective indicia of nonobviousness," that is, secondary considerations. (*Pregis Corp. v. Kappos*, 700 F.3d 1348, 1354 (Fed. Cir. 2012); *see Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966)).

45. The first three factors comprise the prima facie case. (*Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1350 (Fed. Cir. 2000)). "The Supreme Court has directed courts to reject

a 'rigid approach' with respect to the prima face case in favor of 'an expansive and flexible approach,' using common sense when assessing whether an invention would have been obvious to a person of ordinary skill in the art." (*Mitsubishi Chem. Corp. v. Barr Labs., Inc.*, 718 F. Supp. 2d 382, 425 (S.D.N.Y. 2010) (quoting *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415–16 (2007) (providing extensive analysis of obviousness inquiry)); *see OSRAM*, 701 F.3d at 707).

46. Once a patent challenger establishes a prima facie case of obviousness by clear and convincing evidence, the burden shifts to the patentee to provide rebuttal evidence of nonobviousness. (*WMS Gaming Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999). "The party asserting invalidity, however, always retains the burden of persuasion on the issue of obviousness until a final judgment is rendered." (*Mitsubishi*, 718 F. Supp. 2d at 427–28).

47. Secondary considerations of nonobviousness may include "copying, long felt but unsolved need, failure of others, commercial success, unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and skepticism of skilled artisans before the invention." (*Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 711 F.3d 1348, 1368 (Fed. Cir. 2013)).

48. These secondary considerations help courts guard against impermissible hindsight bias, "which often overlooks that the genius of invention is often a combination of known elements which in hindsight seems preordained." (*Power Integrations*, 711 F.3d at 1368 (quotations and citations omitted); *see also Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) ("In retrospect, [the inventor's] pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of invention, the

inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted.")).

c. Infringement

49. A patent is infringed when "whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States, or imports into the United States any patented invention during the term of the patent therefor." (35 U.S.C. § 271(a)).

50. Infringement is "an issue of fact, which the patentee must prove by a preponderance of the evidence." (*Siemens Med. Sols. USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc.*, 637 F.3d 1269, 1279 (Fed. Cir. 2011)). The patentee needs only prove "that it is 'more likely than not' that some quantity, however miniscule, of the [claimed form]" is present in the accused product. (*Cephalon, Inc. v. Watson Pharm., Inc.*, 769 F. Supp. 2d 761, 778 (D. Del. 2011)).

51. "To prove infringement, the patentee must show that the accused device meets each claim limitation, either literally or under the doctrine of equivalents." (*Dynacore Holdings Corp. v. U.S. Philips. Corp.*, 363 F.3d 1263, 1273 (Fed. Cir. 2004)).

52. Literal or direct infringement occurs where "every limitation set forth in a claim [is] found in an accused product, exactly." (*Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1253 (Fed. Cir. 2010) (quotations and citation omitted)).

53. Under the doctrine of equivalents, an accused product infringes where the differences between it and a patent's claimed limitations are insubstantial. (*Cadence Pharm. Inc. v. Exela PharmSci Inc.*, 780 F.3d 1364, 1372 (Fed. Cir. 2015)).

54. "The determination of infringement requires a two-step analysis: (1) a proper construction of the claim to determine its scope and meaning, and (2) a comparison of the

properly construed claim to the accused device or process." (*Conroy v. Reebok Int'l, Ltd.*, 14 F.3d 1570, 1572 (Fed. Cir. 1994)).

i. Claim Construction

55. "[T]he 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) (en banc) (quotations and citation omitted)).

56. Courts thus "look to the words of the claims themselves . . . to define the scope of the patented invention," and "generally give[] [the words] their ordinary and customary meaning." (*Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *see Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 384, 374 (1996)). This is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." (*Phillips*, 415 F.3d at 1313).

57. "[A] skilled artisan reads a claim term not only in the context of the claim at issue, but also in the context of the entire patent, including the written description and prosecution history, as well as relevant extrinsic evidence." (*Howmedica Osteonics Corp. v. Zimmer, Inc.*, 822 F.3d 1312, 1320–21 (Fed. Cir. 2016)). While the specification is "highly relevant to the claim construction analysis," there remains "a fine line between reading a claim *in light of* the written description and reading a limitation into the claim from the written description." (*Id.* at 1321 (citation omitted) (emphasis in original)). "When the claims leave little doubt as to what is intended, re-shaping the claims with material from the written description is clearly unwarranted." (*Id.* at 1322).

58. Courts must construe "only those terms . . . that are in controversy, and only to the extent necessary to resolve the controversy." (*Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed Cir. 1999)).

59. The Court held a claim construction hearing in this and related actions on October 16, 2015; the parties did not identify any claim terms of the '993 patent requiring construction. (*See* November 4, 2015 Opinion and Order at 1 n.1 ("There are no construction issues as to the '993 Patent.")).

60. Accordingly, the plain and ordinary meanings of the claim terms, as they would have had to a person of ordinary skill in the art ("POSA") as of February 12, 2003, apply to all '993 patent claim terms. (*Phillips*, 415 F.3d at 1312–13; PTX-1063).

BACKGROUND FINDINGS OF FACT[8]

VII. Crystals and Polymorphs

61. Crystals are three-dimensional solid compounds in which molecules (bonded atoms) are arranged in a regular, periodically-repeating order. (Tr. 149:14–150:15).

62. Crystal compounds can crystallize in different forms with different structures, called polymorphs. (Tr. 150:16–151:6; *see* PTX-1063 at 2:1–3 ("Polymorphism is commonly defined as the ability of any substance to have two or more different crystal structures.")).

63. The term "polymorph" includes both hydrates (crystalline forms whose structures incorporate water molecules) and solvates (crystalline forms whose structures incorporate solvent molecules). (Tr. 1708:15–18, 754:18–19).

64. Pitavastatin calcium is a hydrate. (Tr. 754:17–19, 839:12–14).

[8] The Court has made its findings or conclusions based upon its own review of the evidence and the law, even though it may utilize the parties' submissions. To the extent that any finding of fact may be considered a conclusion of law, or vice versa, each should be considered as such.

65. Different polymorphs of the same substance often exhibit different chemical, physical, and biological properties, including melting point and solubility. (PTX-1063 at 2:6–7; Tr. 628:17–25, 629:4–6, 790:14–25; 790:22–23; PTX-0358 (Stephen R. Byrn, et al., *Solid-State Chemistry of Drugs* (2d ed. 1999)) at MYLAN(Pitav)075459 ("the arrangement of molecules in a crystal determines their physical properties"), MYLAN(Pitav)075597).[9]

66. Many factors may influence and induce crystallization and solid state formation, including whether, how, or what type of polymorph will form. These include, without limitation: solvent system (pH level, temperature, type of solvent, polarity, evaporation or solvent removal conditions); mixing/stirring conditions (time, speed, type of equipment, temperature); and way in which the solvent is removed or permitted to evaporate, including drying conditions (temperature, pressure, time). (*See* Tr. 1667:9–20, 1689:2–1692:7, 1695:5–1696:11, 1699:5–18, 1699:24–1701:20; PTX-0363 (Luciana L. DeMatos et al., *Solvent Influences on Metastable Polymorph Lifetimes: Real Time Interconversions Using Energy Dispersive X-Ray Diffractometry*, 96 J. Pharm. Sci. 1069 (2007)) at KN003463611–18; PTX-0358 (Byrn 1999) at MYLAN(Pitav)075597–075757; PTX-1020 (Joel Bernstein, *Polymorphism in Molecular Crystals* (2002)) at MYLAN(Pitav)061643–70; PTX-0381 (Xue Z. Wang et al., *Advances and Future Directions in Morphology Monitoring and Control of Organic Crystals Grown from Solution*, Computer Aided Chem. Eng'g 1611 (2006)) at KN003464960–65; PTX-0359 (J. Calderon De Anda et al., *Real-time Product Morphology Monitoring in Crystallization Using Imaging Technique*, 51 Am. Inst. Chem. Eng'rs. J. 1406 (2005)) at KN003463333–41; PTX-0379 (Yoshihisa Suzuki and Kentaro Hara, *Polymorphism of Inosine. III. The Equilibrium for the*

[9] Multiple excerpts from this book were introduced at trial. (*See* DTX-1315; PTX-0358; PTX-1002). For simplicity, the Court refers only to PTX-0358.

Inosine–Dimethyl Sulfoxide–Water System, 47 Bull. Chem. Soc'y Japan 2551 (1974)) at KN003464702–03).

67. The properties of hydrate and solvate forms of a substance may differ from those of anhydrous forms of that same substance, including different density, solubility, stability, and hygroscopicity (ability to absorb or release water as a function of humidity). (PTX-0358 (Byrn 1999)).

68. Changing drying conditions can change the water content, and thus the polymorphic form, of a substance. (Tr. 838:8–15, 839:7–11, 1666:18–19, 1667:6–20, 1668:9–10; PTX-0172 at KN001334985–88).

69. Crystal structures and polymorphism are unpredictable. Those skilled in the art cannot predict whether a polymorph will form; nor can they predict the properties or structure a formed polymorph will have. This was true as of February 12, 2003, the earliest priority date of the '993 patent; and is still true today. (*See* Tr. 1683:6–1686:15).

70. For example, a 2002 reference states:

> While it may not be surprising that many pharmaceutically important materials have been found to be polymorphic, or that any particular compound may turn out to be polymorphic, every compound is essentially a new situation, and the state of our knowledge and understanding of the phenomenon of polymorphism is still such that we cannot predict with any degree of confidence if a compound will be polymorphic, prescribe how to make possible (unknown) polymorphs, or predict what their properties might be (Beyer *et al.* 2001).

(PTX-1020 (Bernstein) at MYLAN(Pitav)061822; *see also* PTX-0365 (Angelo Gavezzotti, *Are Crystal Structures Predictable?*, 27 Accts. Chem. Res. 309 (1994)) at KN003463735).

71. A 2015 reference similarly explains:

> Unfortunately, our current understanding of the mechanisms and processes involved in the nucleation and growth of crystals is still insufficient for precise control over the formation or disappearance of a polymorph (or any other crystal form).

> It should be apparent from the content of this Review that the mere existence of polymorphs and polymorphic transformations is virtually impossible to predict . . .
>
> There is no standard strategy or foolproof recipe for the search for crystal forms.

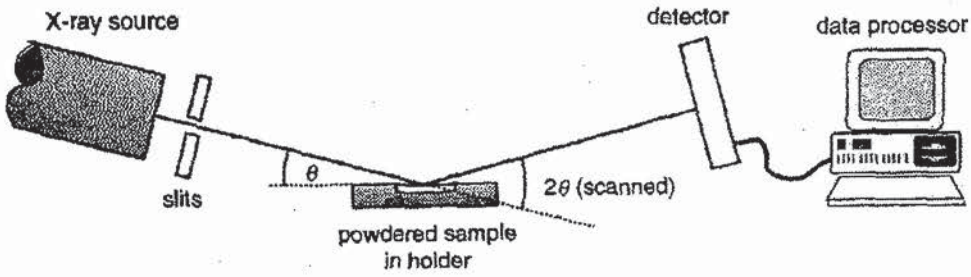
(PTX-0357 (Dejan-Krešimir Bučar et al., *Disappearing Polymorphs Revisited*, 54 Angewandte Chemie Int'l Ed. 6972 (2015)) at KN003463310, KN003463324–25).

VIII. X-Ray Powder Diffraction and Characterization

72. X-ray powder diffraction ("XRPD" or "PXRD") is a common analytic technique used to identify crystalline forms (polymorphs) and structures of a substance. (Tr. 147:21–25, 151:21–153:6, 165:9–24; *see* PTX-1074 (U.S. Pharmacopoeia 25, Ch. 941, X-Ray Diffraction (2002) ("2002 USP")) at MYLAN(Pitav)075239; PTX-1000 (Harry G. Brittain, *Methods for the Characterization of Polymorphs and Solvates*, in *Polymorphism in Pharmaceutical Solids* (Harry G. Brittan ed., 1999)) at MYLAN(Pitav)062156–57; PTX-1020 (Bernstein) at MYLAN(Pitav)061689 ("X-ray powder diffraction is probably the most definitive method for identifying polymorphs and distinguishing among them."")). This may also be referred to as a "polymorph screen." (Tr. 1682:22–23).

73. XRPD is performed by mounting a crystalline powder sample on a device and exposing it to x-rays of a certain wavelength, projected from a source at a range of angles in 2-theta ("2θ") degrees. (Tr. 153:17–154:11; *see* PTX-0358 (Byrn 1999) at MYLAN(Pitav)075513). Since crystal structures contain sets of parallel planes of atoms,[10] as x-rays strike the substance, they are diffracted by the atoms' electrons and travel in beams in different directions. (Tr. 156:22–157:15). A diffractometer measures the intensity of the x-rays that diffract across a range of angles, as shown below. (Tr. 153:17–154:11).

[10] The distance between these planes is denoted by "d" or "d-spacing." (*See* Tr. 156:22–157:15).



(PTX-0358 (Byrn 1999) at MYLAN(Pitav)075513).

74. The diffractometer creates a resultant XRPD graphical pattern, with the intensity of the diffracted x-rays on the y-axis plotted against the 2θ angle values on the x-axis, creating apparent "Bragg peaks" of various heights.[11] (Tr. 153:7–158:2). The XRPD peak pattern is uniquely characteristic of that specific solid; and is akin to a substance's fingerprint. (Tr. 160:18–161:1; 1644:16–1645:3).

75. The pattern may either be depicted graphically (known as a powder pattern or diffractogram); or as a numerical listing of characteristic peaks described by the corresponding 2θ values (or d-spacings) and relative intensities (known as a peak list). (Tr. 162:10–21; 163:20–164:14).

76. Bragg peaks are typically characterized by their position, intensity, and shape. (Tr. 158:20–160:16). Crystalline forms are characterized by sharp Bragg peaks. (Tr. 158:8–16). The dimensions of the unit cell of the crystalline polymorph structure determine peak position. (Tr. 159:1–5, 160:18–161:1, 580:10–581:2). Relative intensities of the peaks depend on positional arrangement of atoms in the unit cell and other experimental factors such as preferred orientation, instrument setup and/or abnormalities, surface roughness, granularity, beam spillover, and others. (Tr. 155:23–156:11, 159:15–160:2, 172:12–177:16, 580:10–581:2,

[11] "Bragg's law" defines powder diffraction. (Tr. 158:3–7). The Bragg equation is $n\lambda = 2d(\sin\theta)$, where n is an integer, λ is the wavelength, d is the d-spacing, and θ is the angle of incidence of x-rays relative to the crystal. (*See* Tr. 156:22–157:15 for a full explanation).

1588:13–1589:18; *see* PTX-0358 (Byrn 1999) at MYLAN(Pitav)075517; PTX-0999 (Ann W. Newman & G. Patrick Stahly, *Form Selection of Pharmaceutical Compounds*, in *Handbook of Pharmaceutical Analysis*, (L. Ohannesian & A. Streeter eds. 2002)) at PITADEF0008641). Shape of the peaks is determined by various physical aspects of the experiment, such as instrument configuration and sample size. (Tr. 160:3–16).

77. XRPD analysis and measurements, like all experimental data reporting, may be affected by variations in sample preparation, instrumental precision, accuracy, and other factors. A pattern may also contain "hidden" peaks caused by overlapping of other peaks. (Tr. 155:23–156:11, 159:6–14, 168:23–169:4, 169:22–177:15, 1588:13–1589:18).

78. A typical experimental error in measuring XRPD diffraction angles is approximately ±0.2° 2θ. (Tr. 170:20–171:2, 585:5–10).

79. Peak lists are generated by computer programs' peak-picking algorithms that identify peaks based on default and user settings. (Tr. 205:24–206:11). Accordingly, if a peak does not fall within the parameters fixed by the settings, the algorithm will not pick that peak. (Tr. 205:24–206:11, 641:25–642:9, 1592:10–16).

80. Crystal planes may sometimes arrange in a non-random order, known as "preferred orientation;" this frequently occurs in crystal substances containing needle- or plate-like crystals that lay flat or stand parallel. (Tr. 172:23–174:12, 176:22–177:1–3; *see* PTX-0358 (Byrn 1999) at MYLAN(Pitav)075517). One skilled in the art would expect pitavastatin calcium crystals to consist of needles or plates. (Tr. 1583:16–1586:2).

81. Preferred orientation may drastically affect relative intensities between two XRPD patterns of the same sample. (Tr. 172:23–175:18; PTX-0999 (Newman) at PITADEF00018641 ("The effects of preferred orientation [on peak intensities] can be profound."); *see* PTX-0358

(Byrn 1999) at MYLAN(Pitav)075517 ("[V]ariability [in relative intensities] is most often the result of preferred orientation of the crystals that comprise the powder."); PTX-1011 (Klug) at 368 ("[P]referred orientation [is] a major source of intensity errors."); Apotex-026 (2016 U.S. Pharmacopeia 39, Ch. 941 X-Ray Diffraction (2016)) at 758). Accordingly, pre-analysis "grinding" of a sample to reduce particle size is commonly performed to minimize or eliminate variation or errors from preferred orientation. (Tr. 292:8–21, 600:24–602:11; Apotex-026 (2016 USP) at 758; PTX-1011 (Klug) at 368; PTX-0999 (Newman) at PITADEF00018641).

82. Those skilled in the art routinely read an experimental XRPD diffractogram and compare it to a reference XRPD diffractogram of a particular polymorph to determine whether that polymorph is present in the sample. (Tr. 152:20–153:6, 165:14–24).

83. Those skilled in the art know that these experimental factors and errors may often cause severe variation; and that values of observed "relative intensit[ies] between the sample and the reference may vary considerably." (Tr. 170:21–22 (discussing PTX-1074 (2002 USP) at MYLAN(Pitav)075240); *see* PTX-0358 (Byrn 1999) at MYLAN(Pitav)075517; *see* Tr. 170:13–171:16, 179:17–181:5, 1647:19–22).

84. Accordingly, in light of the known experimental errors, expected relative intensity variability, and potential for algorithm-generated peak lists to "miss" peaks, not all characteristic peaks in a characteristic XRPD reference pattern need be present, nor be an exact match, in a sample XRPD for one skilled in the art to determine that the crystal form characterized by that pattern is present in the sample substance. (Tr. 169:16–170:2; Tr. 1592:12–16). For example, one of Defendants' experts, Dr. Roberts,[12] concluded that two separate XRPD patterns both

[12] Defendants offered Dr. Kevin Roberts as an expert "in the field of polymorphism, crystallization, crystal form characterization, crystallography, including PXRD analysis." (Tr. 739:11–13).

depicted Form A as defined by claims 1 and 24, despite identifying nine peaks that allegedly did not precisely match the relative intensities recited in claims 1 and 24. (*See* Tr. 776:1–777:8 (discussing DDX-346 and DDX-347), 777:3–6 ("There is some variation in relative intensities between the two data sets, but these are only what you would expect when you make experimental studies on different instruments and different example preps.")).

85. Those skilled in the art do not rely solely on peak list data; rather, they assess an XRPD pattern as a whole to determine whether it is substantially similar to the reference XRPD pattern. Experts from both sides agreed with this basic principle. (Tr. 312:2–5 (Kaduk) ("[O]ne of ordinary skill in the art at the time of the invention would assess the overall XRPD pattern and would not focus principally or exclusively on data in a peak list."), 1616:13–15 (Kaduk) ("[I]t's a mistake to look at [relative intensities in peak lists] in isolation, but you have to look at it only in the context of the complete pattern."), 647:11–13 (Sacchetti) ("We use the whole x-ray powder diffraction pattern [to identify crystalline forms]. The most common way that we do that to make it definitive is to compare the whole pattern."), 853:10–12 (Roberts) ("[Y]ou need to look at the totality of the data, the positions, and the peaks, and it would be a mistake to pick on one peak."), 1647:24–1648:5 (Apotex's withdrawn expert Dr. Craig Eckhardt deposition testimony) ("Q: To determine whether a polymorph is the same as a polymorph depicted in a diffractogram, a person of ordinary skill in the art looks at the pattern as opposed to an individual specific peak or set of peaks; isn't that right, doctor? A: If you are lucky enough to have the entire diffractogram, yes.")).

FINDINGS OF FACT AND CONCLUSIONS OF LAW: VALIDITY AND INFRINGEMENT

IX. Jurisdiction

86. This action arises under United States patent statutes, 35 U.S.C. §§ 271(e)(2), 271(b), 271(c), and 281-283. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a). Venue is proper under 28 U.S.C. §§ 1391(b)-(c) and 1400(b). Personal jurisdiction over Defendants in New York is proper pursuant to N.Y. C.P.L.R. §§ 301 and 302(a), and because Defendants are doing business in this jurisdiction. An actual controversy pursuant to 28 U.S.C. § 2201 exists concerning the infringement and validity of claims 1, 22, 23, 24 and 25 of the '993 patent.

X. Person of Ordinary Skill in the Art

87. A POSA as of February 12, 2003, the earliest priority date to which the '993 patent claims entitlement, would have either (1) a bachelor's degree in chemistry, chemical engineering, pharmacy, or related disciplines and either (a) several years of experience related to organic synthesis, API manufacturing and formulation, or evaluation of solid state forms in the pharmaceutical industry, or (b) an advanced degree in chemistry, chemical engineering, pharmacy, or related disciplines; or (2) training and experience as a chemist or similar field involved in the discovery, preparation, or characterization of crystal and polymorphic forms, and holding an advanced degree in organic chemistry, chemical engineering, or related disciplines, or equivalent work experiences such as a bachelor of science degree and several years of experience in the preparation and characterization of solid state forms. (*See* Tr. 192:23–193:9, 322:20–323:7, 787:3–15, 1628:16–25 (discussing PDEM-0138)).

88. Though the POSA definitions set forth by the experts in this action differed slightly, there is no valid suggestion that the slight differences would lead any of the experts to reach different conclusions; indeed, experts on both sides agreed that any differences in competing POSA definitions are immaterial. (Tr. 192:23–193:9, 322:20–323:7, 625:2–5, 787:16–25).

XI. Validity of the '993 Patent

89. To rebut the presumption that the '993 patent is valid, Defendants must prove invalidity by clear and convincing evidence. (*Microsoft Corp.*, 564 U.S. at 95). Defendants assert inherent anticipation and obviousness.

a. Anticipation (35 U.S.C. § 102)

90. Defendants contend that the Asserted Claims of the '993 patent are invalid as being inherently anticipated by Example 3 of European Patent Application No. EP 0 520 406A1 ("EP '406"). (DTX-0034). To prove inherency, Defendants must prove, clearly and convincingly, that Example 3 "necessarily and inevitably" produces Form A, and that Form A "will always be present when [Example 3] is practiced as taught" in EP '406. (*Schering Corp.*, 339 F.3d at 1378; *In re: OxyContin*, 2015 WL 11217239, at *6).

91. Defendants base their inherency argument on (1) Nissan's own statements, in a Third-Party Observation to the European Patent Office (EPO) during prosecution of EP 04 707 232.7 (the "'232 Application"), that EP '406 Example 3 anticipates claims of the '232 Application identical to the Asserted Claims because the resultant crystals produced by Nissan's replication of Example 3 were the crystalline polymorph A of the '232 Application, and thus Example 3 "teaches inevitably directly and unambiguously the Form A pitavastatin calcium salt of" the '232 Application;[13] (the "2006 TPO"); (2) Nissan's own scientific bases underlying these conclusions,

[13] As described in detail below, Nissan subsequently acquired the '232 Application, which is the European counterpart to the '498 Application, from which the '993 patent issued.

as expressed in the 2006 TPO and in Nissan's internal documents; and (3) Defendants' experts' confirmation of the accuracy of Nissan's experiments, conclusions, and representations. Defendants presented the expert testimony of Dr. Sessler, who opined that Nissan faithfully reproduced Example 3; and Dr. Roberts, who opined that (a) Nissan correctly interpreted its data and concluded that Form A was produced; and (b) that EP '406 inherently anticipates claims 1 and 23 through 25 of '993 patent. (*See generally* Tr. 1006:18–21, 1017:1–6, 1039:21–1040:20, 740:1–16, 743:1–23, 776:1–777:14). Defendants also contend, based on Dr. Roberts' opinion, that the U.S. Patent and Trademark Office ("PTO") Examiner, in allowing the claims of the '993 patent, overlooked or misunderstood the prior art cited by applicants during prosecution of the '993 patent. (Tr. 778:16–779:2).

92. Plaintiffs respond that Defendants have not proved that the procedure set forth in EP '406 Example 3 necessarily and inevitably results in Form A; and also emphasize the deference owed to the PTO's decision to allow the claims of the '993 patent, as EP '406 and the related 2006 TPO documents were submitted to the PTO Examiner; the Examiner signed the forms disclosing such references, thus acknowledging her review of them; and these references are listed on the face of the '993 patent. On this issue, Plaintiffs presented the expert testimony of Dr. Byrn.[14] (*See generally* Tr. 1657:12–20, 1681:18–1682:9).

93. For the reasons that follow, the Court concludes that Defendants have failed to meet their heavy burden of proving by clear and convincing evidence that practice of EP '406 Example 3 "necessarily and inevitably" results in Form A; and that EP '406 does not inherently anticipate the '993 patent.

[14] Plaintiffs described their expert Dr. Stephen R. Byrn as "an expert in synthetic and solid chemistry, drug formulation, and the manufacture and composition of pharmaceutical drug products." (Tr. 315:20–22).

i. EP '406

94. EP '406, titled "Diasteromer salt of optically active quinolinemevalonic acid," is directed to pitavasatatin calcium. (DTX-0034 at MYLAN(Pitav)014983). Nissan is listed as the applicant on EP '406, which was filed on June 24, 1992, and published on December 30, 1992. (*Id.*; *see* Tr. 740:17–741:18).

95. Example 3 discloses the only solid state form of pitavastatin calcium in EP '406 ("EP '406 Example 3" or "Example 3"). (DTX-0034 at MYLAN(Pitav)014994). Specifically, Example 3 discloses "white crystals" of pitavastatin calcium salt, as well as a method of its preparation from the pitavastatin phenethylamine salt starting material produced in Example 1 of EP '406:

> EXAMPLE 3
>
> (E)-3(R)-5(S)-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropylquinolin-3'-yl]hept-6-ene acid·1/2 calcium salt
>
> To 12.0 g of (E)-3(R)-5(S)-dihydroxy-7-[4'-(4"-flurophenyl)-2'-cyclopropylquinolin-3'-yl]hept-6-ene acid·D(+) phenethylamine salt compound ((-)| (+)||) obtained in Example 1, 24.3 ml of a 1N sodium hydroxide aqueous solution and 200 ml of water were added and stirred to dissolve the compound. To this solution, an aqueous calcium chloride solution obtained by dissolving 1.47 g of dry calcium chloride to 200 ml of water, was dropwise added. This reaction solution was stirred overnight, and the resulting white precipitate was collected by filtration to obtain 9.0 g of white crystals (melting point: 190-192° C (decomposed)).

(*Id.*).

96. EP '406 does not describe any polymorphs of pitavastatin calcium; nor does it contain any XRPD information or data. (*Id.*; *see* Tr. 830:19–831:13, 831:19–25, 1664:12–24).

ii. The '993 Patent Prosecution History

97. The '993 patent claims priority to International Patent Application No. PCT/EP2004/050066 (the "'066 PCT"). (DTX-1327; *see* PTX-1063; Tr. 221:2–14, 744:5–6).

98. The '066 PCT was originally filed by Ciba Specialty Chemicals Holding Inc. ("Ciba") on February 2, 2004; and entered the European Phase before the EPO as European Patent Application No. 04 707 232.7. (DTX-1327).

99. The '232 Application is the European counterpart to the '498 Application, from which the '993 patent issued. (DTX-1327; PTX-0172; Tr. 744:3–10). Original claims 1, 2, and 37 of the '232 Application were substantively identical to claims 1, 22, 23, 24, and 25 of the '993 patent. (*Compare* DTX-1327 at MYLAN(Pitav)059975, MYLAN(Pitav)060023 *with* PTX-1063).[15]

100. The '232 Application published on August 26, 2004. (DTX-1327).

A. EP '406 and the '232 Application

101. On December 14, 2006, N.F. Hartz ("Hartz"), of the law firm Wachterhauser & Hartz, submitted the 2006 TPO to the EPO during prosecution of the '232 Application. (DTX-1327 at MYLAN(Pitav)060024–29). The 2006 TPO argued that Example 3 of EP '406 anticipated claims 1 and 2 of the '232 Application for crystalline polymorph A of pitavastatin calcium; and that consequently, claims 1, 2 and 37 of the '232 Application lacked novelty. (*Id.* at MYLAN(Pitav)060024).[16]

102. Nissan employees Dr. Mikio Suzuki and Mr. Hiroshi Iwasaki later testified that Nissan had retained or requested Hartz to file the 2006 TPO; and evidence at trial showed that Nissan scientists conducted the replication of Example 3, the resultant data of which formed the basis of the 2006 TPO. (*See* Tr. 767:2–768:15, 1054:15–19, 1062:15–20; DTX-1332 at MYLAN(Pitav)073196).

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[15] As explained below, Nissan subsequently acquired the '232 Application from Ciba. (DTX-1327 at MYLAN(Pitav)060039).

[16] "D1" was used as a shorthand reference for EP '406 during prosecution of the '232 Application. (DTX-1327 at MYLAN(Pitav)060004).

103. The 2006 TPO stated that Example 3 of EP '406 had been "faithfully carried out." (DTX-1327 at MYLAN(Pitav)060024). The scientists chose a temperature of 15°C; and decided to wash the sample with 50 ml of water. (*Id.*). The melting point of the produced sample was measured as 96.8°C, which the 2006 TPO concluded was "practically identical to the melting point of 95°C stated in [the '232 Application], Example 1 for Form A." (*Id.* at MYLAN(Pitav)060025). The 2006 TPO also enclosed XRPD data from the obtained substance, the pattern of which the 2006 TPO concluded was "practically identical to that shown in [the '232 Application], Figure 1 for Form A." (*Id.*).

104. The 2006 TPO concluded that the produced sample was the crystalline polymorph A of pitavastatin calcium claimed in the '232 Application; and thus, "[EP '406], Example 3 teaches inevitably directly and unambiguously the Form A pitavastatin hemicalcium salt of [the '232 Application]. Therefore, original claims 1, 2 and 37 lack novelty." (*Id.*).

105. Nissan's separate internal lab report indicates (1) that the resultant substance of the replication of Example 3 referenced in the 2006 TPO was dried for 50 minutes at 40°C, until it reached a water content of 10.5%; and (2) that Nissan had previously conducted another replication of Example 3, wherein it dried the sample under reduced pressure until a water content of 5.72% was reached. (DTX-1332 at MYLAN(Pitav)073196–97; *see* Tr. 773:2–8, 775:4–12, 767:2–768:15). Nissan internally concluded that both samples, though they had different water contents, produced Form A as claimed by the '232 Application. (DTX-1332 at MYLAN(Pitav)073197).

106. Nissan subsequently acquired the '232 Application from Ciba in January 2008. (DTX-1327 at MYLAN(Pitav)060039).

107. On February 17, 2010, during prosecution of the '232 Application, the EPO accepted and adopted the 2006 TPO's showing:

> It is clear from [the] Third Party Observation . . . that the present crystalline polymorph A has been prepared by [EP '406], example 3. This crystalline polymorph A is thus known from [EP '406] and has the same melting point as for the present crystalline polymorph A. Consequently [EP '406], example 3 teaches inevitably directly and unambiguously the crystalline polymorph A pitavastatin hemicalcium salt of the present application. Therefore present claims 1, 2 and 37 lack novelty.

(*Id.* at MYLAN(Pitav)060048). The EPO thus rejected original claims 1, 2 and 37 of the '232 Application; and instructed Nissan, as the new applicant, to file new claims and an amended description taking the above into account. (*Id.* at MYLAN(Pitav)060050).

108. In its August 27, 2010 response to the EPO, Nissan changed the position it had anonymously set forth in the 2006 TPO. It instead argued that the melting points of the '232 Application Example 1 product was different from that of the EP '406 Example 3 product; and "[t]herefore, Example 3 of [EP '406] cannot directly and unambiguously disclose a crystalline polymorph A according to Example 1 of [the '232 Application]." (*Id.* at MYLAN(Pitav)060053).

109. The EPO rejected Nissan's new argument in a communication issued January 25, 2011 (the "January 2011 EPO Communication"). (*Id.* at MYLAN(Pitav)060191–96). The EPO acknowledged that Nissan was the new proprietor of the '232 Application; and that Hartz, who had filed the 2006 TPO, was now representing Nissan. (*Id.* at MYLAN(Pitav)060194). The EPO stated: "[n]o further evidence has been submitted to prove the point of view [that the melting points are different]. It is only questioned if the similarity of melting points can be seen as prove [sic] for identification of crystal forms." (*Id.*). Thus, the EPO reaffirmed its agreement with the 2006 TPO's novelty objections to the '232 Application. (*Id.*).

110. Nissan then amended claims 1 and 2 of the '232 Application to require Form A and additionally, a water content of 3-15%. (*Id.* at MYLAN(Pitav)0601206). It argued that this feature made the '232 Application novel over EP '406. (*Id.* at MYLAN(Pitav)060203–05). Upon review, the EPO agreed and permitted the amended claims of the '232 Application as novel over EP '406. (*Id.* at MYLAN(Pitav)0601286) ("It is regarded that the only novel feature for the present amended claim 1 is the water content of 3-15%.").

B. The '993 Patent's PTO Prosecution and Examination

111. The prosecution history of the '993 patent shows that the PTO considered each of EP '406, the 2006 TPO, and the January 2011 EPO Communication, during prosecution of the '993 patent, as reflected on the face of the '993 patent under "References Cited." (PTX-1063 at KN000844700–01). EP '406 was disclosed to the PTO in the priority and parent applications of the '993 patent as filed. (*Id.* at KN000844711).

112. Column 1 of the '993 patent discloses EP '406 in detail:

> A full synthetic procedure for the preparation of Pitavastatin calcium is described in EP-A-0520406. In the process described in this patent Pitavastatin calcium is obtained by precipitation from an aqueous solution as a white crystalline material with a melting point of 190-192 C.

(PTX-1063 at KN000844711 (at 1:62–67); *see* Tr. 821:16–822:3; 822:13–20; 1660:19–1661:7; Tr. 1754:4–8).

113. EP '406 and the 2006 TPO was disclosed to U.S. Patent Examiner Margaret M. Seaman ("the Examiner") on June 23, 2008 in an Information Disclosure Statement ("IDS")[17] filed in the '752 Application, the parent of the '498 Application. (DTX-1359 at MYLAN(Pitav)014575, MYLAN(Pitav)014586, MYLAN(Pitav)014583; Tr. 1662:1–20).

[17] During patent prosecution, applicants submit IDS forms to the PTO disclosing relevant background art or information and/or material references. (37 C.F.R. §§ 1.97, 1.98).

114. The same and additional information was disclosed in the '498 Application. On October 31, 2012, EP '406 was again disclosed to the Examiner in an IDS. (PTX-0172 at KN001334114–17). On April 18, 2013, the 2006 TPO and the January 2011 EPO Communication were disclosed to the Examiner in another IDS. (*Id.* at KN001334697–98, KN001334797; Tr. 1663:7–1664:3; *see* PTX-0172 at KN001334174–209 (additional documents in '993 patent file history discussing patentability of '232 Application in view of EP '406)).

115. On May 23, 2013, the Examiner signed and dated both IDS forms, confirming that she had considered the disclosed references – specifically, EP '406 (Reference AN on PTX-0172 at KN001335162); and the 2006 TPO, the January 2011 EPO Communications and related documents (References AAN-AAQ on PTX-0172 at KN001335157 and Reference AAA on PTX-0172 at KN001335158). (*See* PTX-0172 at KN001335155–64; Tr. 823:2–17, 1662:21–1664:3).

116. In a May 30, 2013 Office Action, the Examiner allowed the claims of the '498 Application that became part of the '993 patent, stating:

> The closest art [are] US Patents 5011930, 5856336 and 5872130 which disclose the compound pitavastatin sodium and how it is made. However, the hemicalcium salt or its amorphous or crystalline forms are not disclosed.

(PTX-0172 at KN001335152).

117. U.S. Patent 5,856,336 and EP '406 disclose the hemicalcium salt of pitavastatin. (DTX-0032; DTX-0034 at MYLAN(Pitav)014994; *see* Tr. 778:19–20, 780:23–781:19, 1754:4–8).

118. None of the three patents cited in the May 30, 2013 Office Action, nor EP '406, disclose the crystalline or amorphous forms of pitavastatin. (DTX-0032; DTX-0264; DTX-1334; DTX-0034).

iii. Defendants' Inherency Arguments

119. Despite the facts that the face of the '993 patent lists EP '406, the 2006 TPO, and the January 2011 EPO Communication; that these references were presented to the Examiner at least once, and some multiple, times; and that the Examiner signed and dated the IDS forms specifically listing these references, confirming that she had considered the references in allowing the claims of the '993 patent to issue, Defendants argue that EP '406 nonetheless inherently anticipates the '993 patent.

120. Defendants' inherency argument rests on two related contentions.

121. First, Defendants contend that their experts "confirmed" that EP '406 Example 3 anticipates Form A of the '993 patent, based on their opinions of Nissan's replication underlying the 2006 TPO: specifically, (1) Dr. Sessler's opinion that Nissan's test was a faithful reproduction of, and falls within the scope of, EP '406 Example 3;[18] and (2) Dr. Roberts' opinions that (a) Nissan correctly interpreted its data and concluded that Form A was produced, and (b) EP '406 inherently anticipates claims 1, 23, 24 and 25 of the '993 patent. (*See* Tr. 1006:18–21, 1017:1–6, 1039:21–1040:20, 740:1–16, 743:1–23, 776:1–777:14).

122. Second, Defendants submit, based on Dr. Roberts' opinion, that the Examiner "either overlooked" (even though the Examiner specifically cited) or "fundamentally misunderstood the state of the prior art." (Def. PFFCL ¶¶ 17, 126; *see* Tr. 778:16–779:2).

A. EP '406 Example 3

123. Dr. Sessler testified that that patents are written at an intermediate level of detail, with a POSA as the target audience; and that patent instructions may not necessarily provide every

[18] Defendants offered Dr. Jonathan Sessler as an expert in "organic and inorganic chemistry, including supermolecular chemistry, medicinal chemistry, preparative chemistry, ion exchange and salt exchange reactions and preparation, isolation and crystallization of solid forms." (Tr. 1005:18–21).

specific detail. (Tr. 1009:4–1011:9). In such instances, Dr. Sessler opined, a POSA uses his or her experience to "fill in" omitted details. (Tr. 1010:15–18). He testified that EP '406 Example 3 was written at this "POSA level" of detail. (Tr. 1018:7–1020:23).

124. After reviewing the 2006 TPO and Nissan's internal documentation of that experiment, and comparing Nissan's experiment to EP '406 Example 3, Dr. Sessler opined that Nissan's replication was a faithful reproduction of, and falls within the scope of, EP '406 Example 3. (Tr. 1017:1–6, 1022:7–1040:20; *see* DTX-0056; DTX-1327). Dr. Sessler opined that aside from scaling down Example 3 by a little over half, which he testified is not expected to change the result, Nissan did not deviate from the instructions provided in Example 3. (Tr. 1027:1–2, 1027:21–1028:3).

125. Dr. Sessler testified that Example 3 did not specify two "POSA level details" that Nissan scientists thus had to "fill in:" (1) stirring temperature and (2) washing and drying conditions, as part of the collection by filtration required by Example 3. (Tr. 1029:23–1030:3). He opined that where a patent does not specify a stirring temperature, a POSA would default to using an ambient temperature; and Nissan's choice of 15°C was within the range of ambient temperatures. (Tr. 1030:4–1032:4). Dr. Sessler also opined that washing and drying is a routine and required part of collection by filtration, as evidenced by the fact that Example 3 reports a yield; and that Nissan's choice to dry the crystals under reduced pressure for 50 minutes at 40°C was not a deviation from the parameters of Example 3. (Tr. 1032:5–1035:16; *see* DTX-0056).

126. Dr. Roberts reviewed and analyzed the XRPD, melting point, and other data submitted in the 2006 TPO and contained in Nissan's internal lab report detailing the replication underlying the submission; and opined that Nissan had correctly interpreted the results and concluded that Form A was produced. (Tr. 751:14–777:14).

127. Dr. Roberts also compared both the diffraction patterns and the peak lists of the sample produced by Nissan and of the Form A claimed by the '993 patent. (Tr. 775:22–777:8). He testified that there "*is some variation in relative intensities* between the two data sets, but these are only what you would expect when you make experimental studies on different instruments and different example preps;" and concluded that the diffraction patterns and associated peak list data matched. (Tr. 777:3–6; *see* Tr. 776:2–15–777:8). Dr. Roberts thus agreed with Nissan's analysis of the data provided in the 2006 TPO. (Tr. 776:7–11, 776:23–777:2).

128. From his review of the 2006 TPO, including its statements and data; Nissan's internal data underlying its submisson, the report of which also referred to a prior replication; and Dr. Roberts' own analysis of Nissan's data submitted to the EPO, Dr. Roberts opined that Example 3 of EP '406 inherently anticipates claims 1, 23, 24 and 25 of the '993 patent. (Tr. 740:1–16, 743:1–23).

B. The Examiner's Review

129. Dr. Roberts supports his conclusion that the Examiner misunderstood or overlooked the prior art and erroneously allowed the '993 claims with (1) his own determination that EP '406, which discloses pitvastatin calcium salt, was the closest prior art; and (2) his interpretation of the wording of the Examiner's May 30, 2013 Office Action allowing the claims. (Tr. 778:16–779:2, 779:22–780:8).

130. Dr. Roberts confirmed that the sole basis of his opinion regarding the Examiner's examination was his review of the '993 patent file history; but later admitted that he is "not experienced in file history reading." (Tr. 779:4–10, 784:8–9).

131. Dr. Roberts also supports his opinion by speculating and assuming that the Examiner reviewed the over-85 references disclosed by the applicant in a single day, based on the fact that

the Examiner signed and dated all of the IDS forms listing the prior art references on May 23, 2013; and/or speculating, based on his personal opinion, that 85 references is too many for a patent examiner to review in a single day. (Tr. 778:17–779:2, 783:13–784:14, 778:10–13 (Roberts) ("[The Examiner] had a lot of references to consider . . . [and] go through, and it does appear to me that she most definitely did not consider the prior art").

iv. Conclusion Regarding Inherent Anticipation

132. As an initial matter, Defendants present no evidence to support Dr. Roberts' speculative assumption that the Examiner reviewed all 85 references in one single day. Applicants submitted some of the prior art to the same Examiner as early as June 2008, in the '752 Application; and submitted some of the same and additional prior art on October 31, 2012 and April 18, 2013, in the '498 Application. (DTX-1359 at MYLAN(Pitav)014575, MYLAN(Pitav)014586, MYLAN(Pitav)014583; PTX-0172 at KN001334114–17, KN001334697–98, KN001334797, KN001334174–209).

133. Further, the Court does not credit Dr. Roberts' second assumption that 85 references is too many to consider in one day, for the reasons clearly illustrated by the following testimony:

THE COURT: Why is that relevant? Is 85 too much review of the data?
THE WITNESS [Dr. Roberts]: It is a very large set of documents, your Honor. In going through the prosecution history, it is quite a lot of paperwork to go through and see the detail.
THE COURT: Why do you say 85 is too much, just because it is a lot of documents?
THE WITNESS [Dr. Roberts]: I think it is quite a lot of detail of documents that need careful reading.
THE COURT: How many file histories have you read?
THE WITNESS [Dr. Roberts]: I'm not experienced in file history reading.
THE COURT: Maybe she was just reading extra particular points. You can certainly review 85 if you're looking for specific information.
THE WITNESS [Dr. Roberts]: I'm not an expert in that, I don't think.

(Tr. 783:23–784:14).

134. It is well-established that patent examiners are "presumed to have considered" the prior art references listed on the face of a patent. (*Shire*, 802 F.3d at 1307). In assessing patent validity, courts do not undertake "findings of whether the examiner 'really did understand what he was ruling.'" (*Norian Corp.*, 363 F.3d at 1329). Indeed, "[i]ntrospection and speculation into the examiner's understanding of the prior art or the completeness or correctness of the examination process is not part of the objective review of patentability." (*Id.*).

135. Dr. Roberts' opinion that Nissan correctly interpreted its testing data and concluded that Form A was produced has no relation to his conclusion that the Examiner "overlooked" the prior art. Such a conclusion is outside the scope of his expert opinion. Dr. Roberts admitted that he is "not an expert" nor "experienced in file history reading;" that he has no experience before either the PTO or the EPO; that he has never authored a patent; that he has never prepared an IDS; and that he has never spoken to a patent examiner. (Tr. 784:8–9, 13–14; *see* Tr. 819:19–820:2, 820:9–23). By contrast, the Examiner is "assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents." (*PowerOasis*, 522 F.3d at 1304 (citation omitted)).

136. The '993 file history demonstrates that the Examiner considered EP '406, the 2006 TPO, and the January 2011 EPO Communication in allowing the claims that would become the '993 patent. Neither Dr. Roberts nor the Court can speculate whether the Examiner, – who signed the IDS forms disclosing EP '406, the 2006 TPO, and the January 2011 EPO Communication, confirming that she had considered them; and who is presumed to have considered these three references, as they are cited on the face of the '993 patent – in determining that three other patents were the closest prior art instead of EP '406, "really did understand what [s]he was ruling." (*Norian Corp.*, 363 F.3d at 1329 (quotations omitted); *see*

Shire, 802 F.3d at 1307). Dr. Roberts' testimony fails to convince the Court that Defendants have met "the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job." (*Shire*, 802 F.3d at 1307).

137. After reviewing all of the evidence and testimony, and considering the deference owed to the Examiner and PTO, the Court concludes that there is insufficient evidence to clearly and convincingly find that following the parameters of EP '406 Example 3 would necessarily produce Form A of the '993 patent.

138. Though Defendants have proffered evidence demonstrating that Nissan twice produced Form A following Example 3, "[i]t is not sufficient if a material element or limitation is 'merely probably or possibly' present in the prior art." (*In re Omeprazole*, 483 F.3d at 1378; *see Cont'l Can*, 948 F.2d at 1269).

139. To meet their burden, Defendants must not only show that Example 3 "***can*** produce [Form A]; rather, they must show by clear and convincing evidence that performing Example [3] ***necessarily and inevitably*** produces [Form A] - *i.e.*, that Example [3] cannot be performed without producing [Form A]." (*In re Depomed*, 2016 WL 7163647, at *50).

140. Example 3 does not specify any drying conditions, such as time, temperature, or pressure.[19] (DTX-0034 at MYLAN(Pitav)014994; Tr. 837:4–8, 840:5–7, 1019:24–1020:5, 1042:25–1043:11, 1048:9–11, 1665:25–1666:2).

141. As Dr. Sessler explained, a POSA following Example 3 would have numerous reasonable drying conditions from which to choose and with which to "fill in" the unspecified drying conditions, with a reasonable combination of temperature, pressure, and time. (Tr. 1010:15–18, 1020:18–23, 1021:15–21, 1029:23–1032:4, 1043:12–18, 1044:6–9, 1044:16–

[19] Nor does Example 3 provide any stirring conditions, such as temperature, speed, or time (other than "overnight"). (DTX-0034; *see* Tr. 836:18–24, 1665:23–24).

1046:14, 1667:4–16). Dr. Sessler himself testified that the range of options "could be quite broad." (Dereka Decl. Exh. D at 60:23; *see id.* at 60:3–61:1; Tr. 1043:12–1044:9).[20] Dr. Sessler and Dr. Byrn both agreed that a reasonable temperature "would range from air drying to moderate temperature to a drying oven;" that a reasonable pressure "would range from a laboratory vacuum pump through an aspirator to actually no vacuum at all;" and that time is variable. (Tr. 1046:7–13; *see* Tr. 1044:22–1045:14, 1046:14–18, 1667:9–16).

142. The evidence demonstrates that different drying conditions may change the water content, and thus the polymorphic form, of a substance. (*See* Tr. 838:8–15, 839:7–11, 1666:18–19, 1667:6–20, 1668:9–10; PTX-0172 at KN001334985–88). EP '406 does not disclose that pitavastatin calcium is a hydrate, or that drying conditions affect its water content. (Tr. 840:2–4, 1666:1–1667:3).

143. Thus, a POSA following Example 3, "filling in" and choosing the drying conditions from a "broad" range of options, could produce a pitavastatin calcium product with varying water contents and possibly, varying polymorphic forms. (Dereka Decl. Exh. D at 60:3–61:1; Tr. 1043:12–1044:9, 1665:2–1667:20, 1671:23–1672:10, 1681:23–1682:1 (Byrn) ("[T]here is insufficient information in EP '406, example 3, to make a given form, make Form A or any other given form for that matter. You can get different forms from following that procedure.), 1682:2–9). Additional evidence in the record illustrates this.

144. For example, an unauthored "Experimental report" dated December 10, 2012, submitted to the PTO during prosecution of the '993 patent, concludes that subjecting crystalline pitavastain calcium to different humidity levels, thereby changing its water content, changes the

[20] Defendants' letter of February 22, 2017 argues that this exhibit (containing portions of Dr. Sessler's deposition testimony), submitted with Plaintiffs' post-trial filings, is "not part of the official trial record" and "wholly improper." The trial transcript clearly reflects that Plaintiffs played a video of the cited portions, and that the court reporter simply did not type the words recited in the video and reflected in the deposition transcript. (*See* 1044:6–9).

polymorphic form from Form A to Form E. (PTX-0172 at KN001334985–88; *see* Tr. 1668:7–1670:20). Specifically, the report states: "[i]t was confirmed that between 'crystal form A' and 'crystal form E' of pitavastatin calcium . . . reversible transformation of crystal form was made by influence of relative humidity." (PTX-0172 at KN001334985). The report observed pitavastatin calcium as Form A at humidity of 49% or lower, and as Form E at humidity of 50% or above; and noted that "[a]t the humidity of 48 to 52%, data showing coexistence of crystal form A and crystal form E may sometimes be obtained." (*Id.* at KN001334986). Dr. Byrn reviewed this report's data and opined, based on his experience, that it was reliable and "completely consistent with all the science that I know about this system and hydrates." (Tr. 1734:7–8; *see* Tr. 1733:6–7, 1733:16–19, 1734:20–25, 1736:1–7). Dr. Byrn also referenced this experimental report in his responsive expert report. (Tr. 1735:12–14).

145. Additionally, Section 3.2.S.2.6 of Nissan's Drug Master File ("DMF") No. 27761, directed to the manufacturing process of pitavastatin calcium, states that "[t]he content of water included in pitavastatin calcium impacts the stability and physical properties." (PTX-0175 at KN001336642). The DMF also states: "[e]ach method contains the same amount of crystal water and have the same crystal form, Modification A, controlled by a well-designed drying and milling step." (*Id.*). Dr. Byrn testified that he understands "Modification A" to be Form A of the '993 patent; and that this language means that Nissan controlled the water content of its pitavastatin calcium API through a careful drying process to maintain Form A. (Tr. 1764:20–1765:15).

146. Finally, an Indian patent application, titled "Novel Polymorphic Form of Pitavastatin Calcium," references the '993 patent and discloses a new crystalline Form P, the production of which is very similar to EP '406 Example 3 (the "Form P Application"). (PTX-0849; *see* Tr.

1673:1–1677:18, 1747:4 (Byrn) (Form P Application is "extremely close to [E]xample 3")). The Form P Application process uses a different relative amount of calcium chloride than that used in EP '406 Example 3, but the same starting material, solvents, and steps described. (*See* Tr. 1674:5–1677:18; *compare* PTX-0849 *with* DTX-0034; Tr. 1747:5–16 (Byrn testifying that minor differences between Example 3's statement that substance was stirred "overnight" and Form P Application's statement that substance was "stirred" did not affect his opinion that Form P Application "is essentially the same as the '406;" and noting that neither includes stirring temperature). Dr. Byrn opined that the Form P Application is reliable; and that "[t]his whole [preparation] process is within the '406 procedure, and here we are making form P, a new form." (Tr. 1677:4–6, 1745:16–1746:17).[21]

147. In other words, the record reflects that "several reasonable selections were available to one of skill in the art and that even slight differences in procedure may lead to differences in the form of [pitavastatin calcium] produced." (*In re Armodafinil Patent Litig. Inc.*, 939 F. Supp. 2d 456, 486 (D. Del. 2013)).

148. Defendants' inherency argument relies on the expert opinion of Dr. Roberts,[22] which is based on one or two experiments.[23] Dr. Roberts admitted, however, that he is not an expert in process chemistry; and was unqualified to testify as to the steps provided in Example 3:

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[21] As further evidence that Example 3 does not inherently anticipate the '993 patent, Plaintiffs introduced a second Indian patent application by the same applicant that references the '993 patent and describes a novel crystalline Form M of pitavastatin calcium. (PTX-0850). The preparation for Form M differs a bit from Example 3, but, similar to Example 3, starts with alpha-methylbenzylamine (phenethylamine); uses a sodium hydroxide solution to form pitavastatin sodium *in situ*; and adds a calcium source to perform a salt swap to obtain a different, pitavastatin calcium novel Form M. (*Compare id.* at 8–10 *with* DTX-0034, DTX-0056 at MYLAN(Pitav)073196; *see* Tr. 1677:19-1681:17).

[22] Dr. Sessler did not opine on inherency.

[23] As explained *infra*, Dr. Roberts relied on both (1) Nissan's replication of Example 3 as set forth in the 2006 TPO, and (2) Nissan's internal data underlying that submission, which also referred to a prior replication. (*See* Tr. 743:15–20).

Q [Mr. Bauer]: So the 12 grams of the phenylethylamine salt is then 24.3 milliliters of a normal sodium hydroxy solution and 200 milliliters of water were added to that phenethylamine salt, correct?
A [Dr. Roberts]: Are you asking me to comment on the process of chemistry when I don't have expert knowledge in that area? I can repeat to you what is written, but if you want me to make a conclusion of that, I cannot do that. I do not have expert knowledge in synthetic process of chemistry. And I haven't been asked to give an opinion on that, neither have I offered any.
Q: Dr. Roberts, you just spent three hours saying that a certain process inherently anticipates claim 1 of the '993 patent and you're relying on example three. Let's try this again. Example one, there is 24.3 milliliters of one normal sodium hydroxy equate solution [] added to the phenylethylamine salt, correct? That's the description, do you agree with me?
A: Would you like to read that out?
Q: Right.
...
[RECESS]
...
Q: As we were saying, Dr. Roberts, this example describes taking a phenylethylamine salt and putting it in a solution of one normal sodium hydroxide solution and 200 milliliters of water, is that correct?
A: That's what I read.
Q: Right. And the phenylethylamine salt actually goes into the solution and water, right?
A: I'm sorry. Can you say that again?
Q: The phenylethylamine salt is soluble in water?
A: I don't know that directly.
Q: OK. When you react the phenylethylamine salt with sodium hydroxide, pitavastatin sodium forms in situ, correct?
A: I can't comment on that. I don't have the knowledge to know. I don't know. I have already made clear that in my presentation, that I'm not offering an opinion, nor have I been asked to provide an opinion on the process chemistry, and this is the process chemistry. I don't have the knowledge base to do that.

(Tr. 832:14–833:9, 834:13–835:5).

149. Dr. Roberts' concession discredits his inherency opinion: a conclusion that Form A of the '993 patent "necessarily and inevitably forms from" a POSA's practice of Example 3 would seem to require some knowledge of process chemistry. (*Schering Corp.*, 339 F.3d at 1378).

150. Dr. Roberts also noted that Nissan's lab report indicates that Nissan previously followed Example 3 and obtained a sample of what it internally concluded was Form A, with 5.72% water content. (DTX-1332 at MYLAN(Pitav)073197). From this and the 10.5% water content of the

sample produced by Nissan's second replication, and the fact that Nissan concluded both were Form A, Dr. Roberts opined that Example 3 can produce Form A having a range of water contents from 5.72% to 10.5%. (Tr. 774:24–775:12).

151. The variables chosen and employed by Nissan's scientists and in the two replications represent just two limited sets of testing parameters; and the testing results represent just two sets of data points produced by those decisions of how to fill in Example 3's unspecified details. (*See* Tr. 1048:12–19 (Dr. Sessler confirming that the experiment underlying the 2006 TPO "represents a single set of parameters resulting in a single piece of data")).

152. Defendants have not clearly and convincingly shown that this limited testing and selection of variables, where a POSA could have selected alternative reasonable conditions while remaining within the parameters of Example 3 and possibly obtained a different polymorphic form, "realized the full scope of reasonable experimental possibilities." (*In re Armodafinil*, 939 F. Supp. 2d at 486). The Court thus cannot conclude that Form A "will always be present when [Example 3] is practiced as taught" in EP '406. (*In re: OxyContin*, 2015 WL 11217239, at *6).

153. Thus, Defendants have not shown inherent anticipation, because the evidence does not clearly and convincingly show that practice of Example 3 "necessarily and inevitably" produces Form A; nor that Example 3 cannot "be practiced in a way that yields a product lacking the allegedly inherent property [of Form A]." (*In re Depomed*, 2016 WL 7163647, at *26 (citation and quotation omitted) (finding no inherent anticipation where defendants' two replications of prior art produced claimed polymorph, one of which was a mixture of claimed polymorph and another polymorph; and plaintiff's replication produced different polymorph); *see Glaxco*, 52 F.3d at 1047 (finding no inherent anticipation where experiments showed that prior art example could yield crystals of either claimed polymorph or different polymorph); *In re Armodafinil*, 939

F. Supp. 2d at 486 (finding no inherent anticipation where one of defendants' experiments produced mixture of claimed polymorph and another form; and even if claim terms allowed for presence of two forms, defendants' use of "limited testing and selection of variables" failed to satisfy burden)).

154. This appears to be a close question; and "[i]f the burden of persuasion were different, the outcome might well be different." (*Warner Chilcott Co., LLC v. Teva Pharm. USA, Inc.*, 89 F. Supp. 3d 641, 659 (D.N.J. 2015), *aff'd*, 642 Fed. App'x 996 (Fed. Cir. 2016)). But there is a "clear and convincing" standard Defendants must overcome. (*Microsoft Corp.*, 564 U.S. at 95).

155. The Court concludes that Defendants have not met their burden; and have not proved invalidity of the '993 patent by inherent anticipation. (*In re Armodafinil*, 939 F. Supp. 2d at 470).

b. Obviousness (35 U.S.C. § 103)

156. Defendants also contend that the '993 patent is invalid as obvious in view of the prior art as of February 2003.

157. In considering obviousness, the Court must examine assess four factors: "(1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) objective indicia of nonobviousness." (*Pregis Corp.*, 700 F.3d at 1354).

158. To establish a prima facie case of obviousness, Defendants must demonstrate "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." (*Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quotations and citation omitted)).

159. Defendants assert that a POSA in 2003 would have been motivated by regulatory and commercial reasons to perform "routine" polymorph screens on the pitavastatin calcium disclosed in EP '406; and would have had a reasonable expectation that such a "routine" screen would produce Form A as claimed by the '993 patent. On this issue, Defendants rely on Dr. Roberts' testimony. (*See generally* Tr. 786:4–18, 810:9–811:16, 875:21–876:6).

160. Plaintiffs argue that Defendants' obviousness analysis is improperly driven by hindsight; assert that polymorph screens are not "routine;" and argue that the fundamental unpredictability of polymorphism would not have allowed a POSA to reasonably expect pitavastatin to be polymorphic, much less have a reasonable expectation of obtaining Form A or any specific polymorphs. Here, Plaintiffs rely on testimony of their expert Dr. Byrn. (*See generally* Tr. 1657:22–1658:9).

161. Plaintiffs also presented evidence of objective indicia of nonobviousness through the testimony of Dr. Miller,[24] Dr. Gotto,[25] and Dr. Bell;[26] and testimony by Mr. Mullikin[27] and Dr. Sponseller. (*See generally* Tr. 1447:10–1448:11 (Miller opining on Livalo®'s advantages and satisfaction of long-felt unmet needs), 1473:4–1476:24 (Gotto testimony regarding same), 1526:4–7 (Bell opining that Livalo® is a commercial success and that there is a nexus), 72:9–76:21 (Sponseller testimony regarding Livalo® history, development, and advantages), 1509:16–1519:22 (Mullikin testimony regarding Livalo® sales and marketing)).

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[24] Plaintiffs offered Dr. Michael Miller as an expert in "cardiovascular disease, lipidology, lipoprotein metabolism, preventive cardiology and cardiovascular epidemiology." (Tr. 1416:10–12).

[25] Plaintiffs offered Dr. Antonio Marion Gotto, Jr. as an expert in "lipidology, structure and metabolism of the plasma lipids and lipid proteins, lipid therapies and preventive cardiology." (Tr. 1466:19–21).

[26] Plaintiffs offered Dr. Gregory Bell as an expert in "the economics of the pharmaceutical industry." (Tr. 1525:22–23).

[27] Mr. Lou Mullikin is the Chief Commercial Officer at Kowa Pharmaceuticals America, which is "the U.S. promotional arm for [its] parent company KCL, Kowa Company Limited." (Tr. 1507:1–3).

162. To counter Plaintiffs' secondary considerations argument, Defendants presented the testimony of its experts Dr. Zusman[28] and Dr. Hay.[29] (*See generally* Tr. 1269:6–1270:2, 1272:10–16, 1275:8–15, 1275:24–1276:17 (Zusman opining that there was no long-felt unmet need for Livalo,® and even if there were, Livalo® did not satisfy such need; Livalo® saw no unexpected results and had no industry praise or skepticism; and that there is no nexus), 1346:3–9, 1350:23–1351:9 (Hay opining that Livalo® is not a commercial success and that there is no nexus)).

163. For the reasons that follow, the Court finds that Defendants have failed to prove by clear and convincing evidence that the '993 patent is obvious.

164. Further, the Court finds that even if Defendants had proved a prima facie case of obviousness, Plaintiffs' evidence of indicia of nonobviousness would rebut such a case.

i. Level of Ordinary Skill in the Art

165. As noted in *supra* Part X, the parties proposed substantially similar POSA definitions. There is no evidence that any differences between the various definitions would lead any of the experts to reach different conclusions; experts for both sides agreed that any competing POSA definitions are immaterial. (Tr. 192:23–193:9, 625:2–5, 787:16–25).

ii. Scope and Content of the Prior Art and Differences Between Claimed Subject Matter and the Prior Art

166. Those skilled in the art in 2003 knew that physical properties of drug substances depend on and are affected by their solid state structure. (*See, e.g.*, DTX-1314 (Michael J.

[28] Defendants offered Dr. Randall Zusman as an expert in "the field of clinical cardiology, including the treatment of patients with high cholesterol, high blood pressure, coronary artery disease, and the like." (Tr. 1227:22–25).
[29] Defendants offered Dr. Joel Hay as an expert in "pharmaceutical economics and outcomes research." (Tr. 1340:9–10). The direct and re-direct examination of Dr. Hay was conducted by former defendant Lupin, which settled post-trial.

Jozwiakowski, *Alteration of the Solid State of the Drug Substance: Polymorphs, Solvates, and Amorphous Forms*, in *Water-Insoluble Drug Formation* (2000) (Rong Liu ed.)) at MYLAN(Pitav)015499; PTX-0358 (Byrn 1999) at MYLAN(Pitav)075457–59, 68–69; *see* Tr. 790:12–792:9).

167. Polymorphism was known in the art; and statins were known to exhibit polymorphism. (*See, e.g.*, PTX-1020 (Bernstein); PTX-1000 (Brittain); DTX-1319 (Terence L. Threlfall, *Analysis of Organic Polymorphs A Review*, 120 The Analyst 10 (1995)); *see* Tr. 788:13–15, 789:14–22, 792:16–19, 795:15–16).

168. The unpredictable natures of crystal structures, crystallization, and polymorphism were known and discussed in publications at the time. (*See, e.g.*, PTX-1020 (Bernstein); PTX-0365 (Gavezzotti); *see* Tr. 1683:6–1685:3).

169. By February 2003, there were both regulatory and business motivations in the pharmaceutical industry to identify and characterize polymorphic forms of potential new drug compounds, typically by performing polymorph screens (in-house or outsourced to contract labs). (*See, e.g.*, Tr. 786:11–18, 791:22–793:11, 1756:21–1758:8, 1758:19–1759:12; DTX-1318 (Stephen Byrn et al., *Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations*, 13 Pharm. Research 7 (1995)) at MYLAN(Pitav)015333; PTX-1000 (Brittain) at MYLAN(Pitav)062153; PTX-0358 (Byrn 1999) at MYLAN(Pitav)075468–69; Tr. 1060:7–1061:3 (deposition testimony of Nissan scientists confirming that performed polymorph screen on pitavastatin calcium because Nissan thought Japanese regulators might require such data)).

170. Pitavastatin was a known statin as of February 2003; and statins were known to be useful in treating hyperlipidemia, among other conditions. (PTX-1064 at KN000844711; DTX-0034 at MYLAN(Pitav)014985).

171. Prior art as of February 2003 included EP '406, Example 3 of which, in June 1992, disclosed "white crystals" of pitavastatin calcium salt with a specific melting point. (DTX-0034 at MYLAN(Pitav)014994).

172. Prior art also included disclosure of several crystalline forms of other statins; some methods of preparing some of those statins; and at least one claim of a pharmaceutical composition containing the crystalline form of one statin. (DTX-1308 (International Publication No. WO 00/42024 (disclosing rosuvastatin and a process for making its crystalline form, and claiming a pharmaceutical composition containing crystalline form)); DTX-1309 (International Publication No. WO 03/013512 A2 (teaching crystalline forms of fluvastatin sodium hydrates)); DTX-1310 (International Publication No. WO 97/03958 (teaching crystalline forms of atorvastatin hemicalcium salt)); DTX-1311 (International Publication No. WO 02/051804 A1 (teaching crystalline forms of atorvastatin calcium and processes for their preparation))).

173. The Asserted Claims of the '993 patent claim the specific polymorph Form A of pitavastatin calcium; and a pharmaceutical composition comprising an effective amount of Form A, and a pharmaceutically acceptable carrier. (PTX-1063).

iii. Whether Obtaining Form A Would Have Been Obvious to a POSA in 2003

174. Dr. Roberts testified that by 2003, a POSA would know that the majority of compounds exhibit polymorphism; and would be motivated by both regulatory and commercial reasons to identify and characterize polymorphs of drugs. (Tr. 790:1–11, 792:22–794:10; *see* DTX-1319 (Threlfall) at MYLAN(Pitav)015545545; DTX-1318 (Byrn 1995) at MYLAN(Pitav)015333; PTX-1000 (Brittain) at MYLAN(Pitav)062153; PTX-0358 (Byrn 1999) at MYLAN(Pitav)075468–69; *see also* Tr. 1756:14–1758:8 (Dr. Byrn agreeing that a POSA may

have been motivated to identify new polymorphs of a drug using polymorph screens, but testifying that such motivation would vary depending on the stage of drug development)).

175. Dr. Roberts opined that by 2003, polymorph screens were "routine laboratory work to screen materials and then see what you get." (Tr. 795:22–23). He testified that a 1995 writing by Dr. Byrn exemplified the "routine" nature of such screening, and provided a "roadmap" for POSAs. (Tr. 794:15–797:9; DTX-1318 (Byrn 1995). Dr. Roberts cited two confidential internal polymorph screens of pitavastatin calcium, conducted in 2002 by a contract lab, and issued to Ciba, as purportedly reflective of a "typical" screening process. (Tr. 798:12–810:8; DTX-0351).

176. Thus, Dr. Roberts opined that a POSA would have been motivated to perform a straightforward, "routine" polymorph screen on the crystalline pitavastatin calcium disclosed in EP '406; and would have reasonably expected to obtain Form A from such a screen. (Tr. 810:11–24). Indeed, Dr. Roberts testified that a POSA would have a reasonable expectation of success of obtaining all polymorphic forms by performing a "properly conducted screen." (Tr. 875:21–876:6). He also opined that the properties of the resultant Form A would exhibit the characteristic XRPD data and pattern recited for Form A in the claims of the '993 patent. (Tr. 810:25–811:2).

177. Further, Dr. Roberts cited a prior art reference that discloses a pharmaceutical composition comprising pitavastatin calcium and a pharmaceutically acceptable carrier, as described in claim 22 of the '993 patent, to conclude that all of the Asserted Claims are obvious. (Tr. 811:3–816:25; DTX-1335 (WO 97/23200)).[30]

[30] Dr. Roberts also cited Nissan's International Publication No. WO 2005/063711 A1 ("WO '711), published in December 2003, which "describes a method for [] producing a drug substance called crystalline pitavastatin calcium, and later on it describes that this is controlled to be form A" of the '232 Application (and the '993 patent). (Tr. 817:17–19; DTX-0360). Dr. Roberts opined that this "near-simultaneous invention of form A further supports the obviousness of [the] '993 patent." (Tr. 9–10). But WO '711 has a priority date of December 26, 2003; and is thus

178. For the reasons that follow, the Court concludes that Defendants have failed to clearly and convincingly show that a POSA in 2003 would have had a reasonable expectation of success of obtaining the claimed Form A from a polymorph screen of the pitavastatin calcium disclosed in EP '406. Defendants' obviousness argument is driven by impermissible hindsight. (*KSR*, 550 U.S. at 421).

179. Even assuming that a POSA would have been motivated to identify and characterize new polymorphs of pitavastatin calcium, a POSA would have had to use trial and error experimentation, using a large number of variables and conditions, to do so. (*See* Tr. 1682:22–25 (Byrn) (opining that polymorph screening "would involve thousands, even many thousands of experiments"), 795:22–23 (Roberts) (opining that that a polymorph screen is "routine laboratory work to screen materials and then see what you get.")).

180. As Plaintiffs demonstrated in testimony the Court finds credible, and as courts have repeatedly concluded, crystallization and polymorphism are unpredictable. (*See* Tr. 1682:16–1686:15; PTX-1020 (Bernstein); PTX-0357 (Bučar); PTX-0365 (Gavezzotti); *In re Armodafinil*, 939 F. Supp. 2d at 491 (concluding that "polymorphism is inherently unpredictable" and noting that in 2002, "the unpredictable nature of polymorphism was discussed in publications"); *Id.* at 497 ("[T]rial and error crystallization experimentation is necessary because polymorphs are unpredictable."); *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1349 (Fed. Cir. 2005) ("The causal mechanism of polymorphic creation and transformation is not clear. Modern science does not yet understand the full complexity of the atomic interactions at play in the phenomenon of polymorphism, and specifically in the disappearance of some polymorphs.")).

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not prior art to the '993 patent. (DTX-0360; PTX-1063). Further, the cited example provides a multitude of specific crystallization conditions, suggesting an extensive amount of work. (DTX-0360 at 13–14).

181. As described herein, a POSA would know that numerous variables affect crystallization and solid state formation and would have a large variety of conditions from which to select and employ in a polymorph screen. (*See supra* Part VII). These conditions include, without limitation: starting materials, subsequent reactants, temperature of the solution, mixing and stirring conditions of the solution, cooling rate of the solution, filtration conditions, and drying conditions. (*See supra* Part VII; Tr. 1667:9–20, 1689:2–1692:7, 1695:5–1696:11, 1699:5–1701:20; PTX-0363 (DeMatos); PTX-0358 (Byrn 1999); PTX-1020 (Bernstein); PTX-0381 (Wang); PTX-0359 (De Anda); PTX-0379 (Suzuki and Hara); Tr. 874:21–875:11 (Roberts) (agreeing that polymorph screens involve numerous different parameters)).

182. Even if a POSA would have looked to solvent systems used in other prior art statins for guidance, a POSA would know that physical properties of crystalline substances differ depending on molecular arrangement; and that pitavastatin calcium has a different structure than other statins. (*See* Tr. 628:17–25, 629:4–6, 790:12–25, 1693:14–17, 1694:5–17, 1696:12–1698:21; PTX-0358 (Byrn 1999)). In Dr. Byrn's words, which the Court credits, "different compounds have different solubility and solvents, and that's not predictable. So even knowing that solvents work for atorvastatin or any other molecule doesn't tell you about [what works to identify polymorphs of] pitavastatin." (Tr. 1695:23–1696:1). Further, the solvent system is "just one of many options a person has in trying to figure out . . . or understand polymorph formation." (Tr. 1696:9–11 (Byrn)).

183. The 1995 Byrn writing, which Dr. Roberts cites as a "roadmap" which provides a POSA a reasonable expectation of success of producing Form A, notes the "wide and largely unpredictable variety of solid state properties" of drug substances, but attempts to provides some guidance:

> [T]he applicant may be unsure about how to scientifically approach the gathering of information and perhaps what kind of information is needed. This review is intended to provide a strategic approach to remove much of this uncertainty by presenting concepts and ideas in the form of flow charts rather than a set of guidelines or regulations. This is especially important because each individual compound has its own peculiarities which require flexibility in approach.
> ...
> The first step in the polymorphs decision tree is to crystallize the substance from a number of different solvents in order to attempt to answer the questions: Are polymorphs possible? Solvents should include those used in the final crystallization steps and those used during formulation and processing and may also include water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures if appropriate.

(DTX-1318 (Byrn 1995) at MYLAN(Pitav)015333–34).

184. These instructions are general and overarching; and recite only some examples of solvents from which a POSA could choose. Other literature provides additional solvents and combinations thereof to employ in screening. (*See* PTX-0358 (Byrn 1999); PTX-1000 (Brittain); DTX-1314 (Jozwiakowski)). Further, the 1995 Byrn writing additionally instructs a POSA to vary temperature, concentration, agitation and pH level of the solvent. (DTX-1318 (Byrn 1995)).

185. A POSA performing a polymorph screen on the prior art pitavastatin calcium disclosed in EP '406 would vary numerous crystallization conditions and would not have been able to predict the results of the experiments, including whether a substance would be polymorphic; what forms the possible crystal structures would have; how many polymorphic forms it would have; and/or what properties any polymorphs would have. (*See* Tr. 1682:16–1683:5; *In re Depomed*, 2016 WL 7163647, at *52–53 (crediting expert testimony demonstrating that solution crystallization involves "a large variety of conditions that could be appropriate for a particular polymorph screen," which "produces a huge number of possible choices that must be made during the course of a polymorph screen;" and agreeing that a POSA would not have been able

to predict "the structure, properties, or relative stability of any of the [polymorphic] forms" where defendants made nearly identical arguments as those presented here (including contending that "a routine polymorph screen, like the one described in the Byrn article,[31] would have revealed" the claimed polymorph))).

186. The unpredictable possible results a POSA could obtain from performing a polymorph screen of pitavastatin calcium are a far cry from evidence of a "finite number of identified, predictable solutions" that the Federal Circuit has declared "might support an inference of obviousness." (*Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) (citation omitted). Indeed, as the Federal Circuit has recognized, "[t]o the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." (*Id.* at 1358).

187. Thus, a POSA would not have had a reasonable expectation of success of obtaining the claimed Form A from a polymorph screen of the pitavastatin calcium disclosed in EP '406. (*See* Tr. 1658:6–9, 1683:1–5; *In re Armodafinil*, 939 F. Supp. 2d at 495–98 (concluding that even where, in 2002, "it was widely recognized that most drug compounds exist in multiple polymorphic forms and that there is an importance in examining polymorphism," a POSA would not have expected to obtain a specific polymorph "using well known and merely routine techniques, such as . . . polymorph screening;" and finding no reasonable expectation of success where a POSA "would have expected to resort to trial and error experimentation, using a large number of conditions, to try and make the [claimed] form"); *In re Depomed*, 2016 WL 7163647, at *53 (finding that Defendants failed to show obviousness of specific polymorph where

[31] This is the same Byrn article as relied upon by Defendants here.

Plaintiffs demonstrated that "polymorph screening consists of an unpredictable application of [individual] routine techniques" and that results "would have been impossible to predict"); *Merck & Cie v. Watson Labs, Inc.*, 125 F. Supp. 3d 503, 514 (D. Del. 2015) (even where a POSA would be motivated to discover new crystalline polymorphs of a substance, where the process required trial and error, there was no reasonable expectation of success of finding specific crystals), *rev'd on other grounds*, 822 F.3d 1346 (Fed. Cir. 2016)).

188. Moreover, "a new crystalline form of a compound would not have been obvious absent evidence that the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure of form." *Bristol-Myers Co. v. U.S. Intern. Trade Com'n*, No. 89-1530, 1989 WL 147230, at *4 (Fed. Cir. Dec. 8, 1989) (quotations and citation omitted)). "[G]eneral motivation to discover an undefined solution that could take many possible forms" is insufficient to establish obviousness where the prior art does not suggest the unknown claimed form. (*In re Armodafinil*, 939 F. Supp. 2d at 500; *see Innogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373 (Fed. Cir. 2008) ("[K]knowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references to reach the particular claimed method.")).

189. Although polymorphism was known in the art, neither EP '406 nor any other of the prior art references cited by Defendants disclose or suggest that pitavastatin calcium is polymorphic. (*See* Tr. 830:19–831:13, 1664:12–24). Indeed, EP '406 did not disclose "white crystals" of pitavastatin calcium salt until five years after the first disclosure of a pitavastatin calcium compound; the '993 patent disclosing polymorphic forms A, B, C, D, E, and F and the amorphous form was not filed until eleven years after that; and seven and eight years later, two

foreign applications disclosed novel forms M and P. (*See* DTX-0034; PTX-1063; PTX-0849; PTX-0850; Tr. 1686:19–1687:10).

190. A POSA could not have predicted whether pitavastatin is polymorphic; nor could a POSA predict, have a reasonable expectation of obtaining, or even have awareness of any specific forms, including Form A.

191. That a POSA may have been generally motivated to screen pitavastatin to determine whether it is polymorphic and to identify possible crystal polymorphs is not equivalent to obviousness where nothing in the prior art was directed to, nor suggested, the "particular structure" of unknown Form A, nor the method of its obtainment. (*In re Armodafinil*, 939 F. Supp. 2d at 500; *see id.* at 501 ("'Obvious to try' is not equivalent to obviousness in every case, particularly where, as here, the prior art provided at most general motivation to conduct trial and error experimentation in a decidedly unpredictable field."); *see also In re Kubin*, 561 F.3d 1351,1359–60 (Fed. Cir. 2009)).

192. Rather, the Supreme Court "in *KSR* did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try,' without considering the nature of the science or technology." (*Abbott Labs v. Sandoz, Inc.*, 544 F.3d at 1341, 1352 (Fed. Cir. 2008)).

193. Defendants have failed to prove a prima facie case of obviousness by clear and convincing evidence.

iv. Objective Indicia of Nonobviousness (Secondary Considerations)

194. Moreover, even if Defendants had established a prima facie case of obviousness, Plaintiffs have presented sufficient objective evidence of nonobviousness to overcome that case and to prove that the Asserted Claims were not obvious in 2003.

195. "Secondary indicators of nonobviousness must always when present be considered, and can serve as an important check against hindsight bias." (*Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (quotations and citation omitted); *see Graham*, 383 U.S. at 17; *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1129 (Fed. Cir. 2000)).

196. The parties presented extensive testimony and evidence of numerous objective indicia at trial and in post-trial briefing. Specifically, for Plaintiffs, Dr. Miller and Dr. Gotto testified regarding the advantages Livalo® provides for certain patient subpopulations (including those with statin intolerance, diabetic and prediabetic patients, patients requiring protease inhibitors to treat HIV and hepatitis C, and polypharmacy patients); and Livalo®'s satisfaction of long-felt needs, unexpected results, and industry praise. Dr. Bell testified regarding the commercial success of Livalo.® Mr. Sponseller testified regarding how Livalo® works and how it is marketed; and Mr. Mullikin testified regarding the history, sales, and promotion of Livalo.®

197. For Defendants, Dr. Zusman testified that Livalo® did not meet any long-felt need nor provide any unexpected results; and there was no widespread industry praise of Livalo.® For several reasons, the Court does not credit Dr. Zusman's testimony.[32] Dr. Zusman's primary focus is on hypertension, not lipids; and is not a member of his hospital's lipid specialty services. (Tr. 1277:6–25). He has not authored nor co-authored any publication relating to lipid

[32] While industry praise is not specifically discussed herein, the Court notes that Dr. Zusman's opinion concluding that no such praise exists was based on "googl[ing] pitavastatin just to see what came up about it;" that Dr. Zusman "imagine[d] that [he] spent a couple of hours" doing so but "didn't keep track;" and only read some of the resultant literature citations, "if [he] thought it might be something that would help [him] in forming [his] opinion." (Dereka Decl. Exh. A at 102:8–9, 104:11–12, 16–17; *see* Tr. 1293:2–19). Defendants' February 22, 2017 letter objects to this exhibit (containing portions of Dr. Zusman's deposition testimony); but the trial transcript clearly reflects that Plaintiffs played a video of the cited portions, and that the court reporter simply did not type the words recited in the video and reflected in the deposition transcript. (*See* Tr. 1293:6–10).

metabolism. (Tr. 1278:1–3). While Dr. Zusman's pre-deposition CV listed 83 publications, many related to statins, when pressed, he clarified that he was only a "clinical site investigator" for the trials in many of the publications, and did not author or co-author those publications; his updated CV provided before trial added "asterisks" to reflect this. (Tr. 1280:6–1284:11; PTX-1150 at 15; DTX-1486A at 15–24). This updated CV contains no publications about statins or cholesterol authored by Dr. Zusman. (Tr. 1284:12–16; DTX-1486A). Dr. Zusman has minimal experience with Livalo® and has prescribed it for fewer than ten patients. (Tr. 1328:22–1329:1).

198. For Defendants, Dr. Hay testified that Livalo® is not a commercial success. But that is quite inaccurate. (*See* ¶ 198 *et seq.*). Moreover, commercial success requires no minimum dollar thresholds, nor does it have any market share maximums. Finally, as described below, many of Dr. Hay's opinions are based on conclusions or documents the Court finds untenable. (*See* ¶¶ 209–12).

199. The Court finds ample evidence of secondary considerations that weigh in favor of nonobviousness, including, without limitation: commercial success, unexpected results, and satisfaction of long-felt need.[33]

A. Commercial Success

200. Commercial success of an invention is "a key secondary consideration that must be considered in an obviousness inquiry," and is "significant evidence that the invention would not have been obvious and it should be given great weight." (*Mitsubishi*, 718 F. Supp. 2d at 435–36).

[33] The Court has reviewed and considered Defendants' arguments regarding these and other secondary considerations; and rejects them as insufficient.

201. Evidence of commercial success "is only significant if there is a nexus between the claimed invention and the commercial success," (*GraftTech Int'l Holdings, Inc. v. Laird Techs. Inc.*, 652 Fed. App'x 973, 978 (Fed. Cir. 2016) (quotation and citation omitted)). The patentee must show that "the commercial success of a product *results from* the claimed invention." (*Id.* (emphasis in original) (quoting *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997)).

202. "When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." (*J.T. Eaton*, 106 F.3d at 1571 (citation omitted); *see Crocs, Inc. v. Int'l Trade Comm'n.*, 598 F.3d 1294, 1310–11 (Fed. Cir. 2010)). This nexus is presumed only if the marketed product is "coextensive with" and "embodies the claimed features." (*Brown & Williamson*, 229 F.3d at 1130).

203. "[I]f the patented invention is only a component of a commercially successful machine or process – the patentee must show prima facie a legally sufficient relationship between that which is patented and that which is sold." (*Demaco Corp. v. F. Von. Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988); *see GraftTech*, 652 Fed. App'x at 979).

204. Once the patentee shows nexus, the burden shifts to the challenger to present evidence demonstrating that other extraneous factors are responsible for such success. (*Demaco*, 851 F.2d at 1393; *Crocs*, 598 F.3d at 1311).

205. On the issue of commercial success, Plaintiffs presented the expert testimony of Dr. Bell, who opined: "Livalo is a commercial success from the perspective of nonobviousness

regarding the patents in suit, i.e., and [] there is a nexus between that success and the invention[] in the ['993 patent]." (Tr. 1526:4–7; *see generally* Tr. 1524–54).

206. Dr. Bell reviewed marketing research and information, financial information (including information from KPA's audited financial statements obtained during a conversation with Mr. Mullikin), and other relevant documents; analyzed market opportunity, the cost of bringing a new pharmaceutical to market, and barriers to success (including well-established branded statins, availability of generics, and managed care formularies); and the advantages of Livalo® in various patient subpopulations.[34] (Tr. 1519:8–16, 1527:20–24; 1536:3–1541:10).

207. Based on financial information collected from KPA, including a conversation with Mr. Mullikin, and other available information, Dr. Bell conducted a profitability analysis of Livalo® in the U.S. from its launch in 2010 through the end of 2015. (PTX-0484; *see* PDEM-0118; PDEM-0119). He evaluated product sales (accounting for gross-to-net ("GTN") reductions); net sales (accounting for manufacturing costs); gross profit (accounting for marketing, collaboration, and medical and regulatory expenses); and net income. (PTX-0484; *see* PDEM-0118; PDEM-0119). The evidence demonstrates, *inter alia*, that:

- Livalo®'s U.S. gross product sales increased every year, reaching $235 million in 2015 and totaling $859 million from launch in 2010 through 2015;
- Livalo®'s U.S. net sales increased almost every year, reaching $150 million in 2015 and totaling $600 million from launch in 2010 through 2015;
- Livalo® has generated over 4.4 million prescriptions through 2015;
- Livalo®'s net income contribution to KPA was negative in its first two years, which Dr. Bell testified is "not unusual for the launch of a new pharmaceutical product"

[34] *See* ¶ 220 *et seq.*, *infra*, for detail and testimony regarding patient subpopulations.

(Tr. 1529:9–10); then steadily increased, reaching profits of about $75 million in 2015.

(Tr. 1528:14–1532:6, 1577:20–1578:11; PTX-0484; PTX-0482 (Annual Dollar and Rx Sales for Livalo® and competing statins and generics) at 1; *see* PDEM-0118; PDEM-0119).

208. Dr. Bell also testified that Livalo®'s gross sales in Japan from its launch there in 2003 through 2012 totaled approximately $3.3 billion. (Tr. 1535:7–25; *see* PTX-0484; PTX-0480; PTX-0965). Specifically, Japanese sales in 2004, the first full year after launch, were $27 million; and were over $600 million in 2012. (PTX-0480; PTX-0965 at KN003464334).

209. Further, Mr. Mullikin, KPA's Chief Commercial Officer, testified that Livalo®'s 2016 U.S. sales totaled $279 million, $2 million more than he had forecast. (Tr. 1514:16–22).

210. Dr. Bell testified that notwithstanding substantial market barriers – including cheaper generics and other well-established name-brand statins – Livalo® has achieved commercial success in part from doctors prescribing Livalo® because, *inter alia*, it may be more appropriate for specific patient subpopulations described by Dr. Miller and Dr. Gotto. (Tr. 1541:2–10; *see* Tr. 1427:23–1429:16 (Miller), 1473:4–11 (Gotto), 1538:22–1541:10).

211. Dr. Hay, who testified for Defendants, claimed that Livalo® is not a commercial success because it did not meet Kowa's internal revenue forecasts and/or because its market share of all statins is small. (Tr. 1346:17–1350:9, 1356:3–1358:6, 1362:11–23). The Court is not persuaded. As Dr. Bell credibly explained:

> [J]ust because a product doesn't meet forecast[s] doesn't mean it isn't a commercial success as a secondary indicator of nonobviousness. It may well not be as successful as the company had hoped; it may well not be as successful as other products in the marketplace; but that doesn't mean there wasn't a market opportunity such that if it were obvious somebody else would have picked up that opportunity earlier. And here we're talking about a market opportunity that led to, you know, net sales in the U.S. alone of $600 million and profits of 200, plus, you know, over $3 billion of sales in Japan, etc. So, it's not just forecasts, and it's

> not just share. Livalo is a very small share of the statin marketplace, but the statin marketplace is a huge market.

(Tr. 1548:22–1549:10). The absolute dollars and produced volumes are really quite substantial.

212. Further, the document from which Dr. Hay collected financial data used to evaluate Livalo®'s U.S. net income and conclude no commercial success appears unreliable. (DTX-1002 (Kowa document); *see* Tr. 1356:3–1358:12). This internal Kowa document is an over-200 page printout of an Excel spreadsheet, titled "Livalo – Gross and Net Sales Forecast thru 2020;" and lists annual gross sales, gross to net percentages, net sales, and "[s]ales [r]ep headcount." (DTX-1002 at KN002715912). From this data, Dr. Hay created a chart, "Kowa Actual and Forecasted Livalo Net Income," showing that Livalo® has not yet received a positive income; has incurred a net loss of $125 million through 2012; and is forecasted to remain a net loss until at least 2020. (DDX-855; *see* Tr. 1356:25–1358:6). Dr. Hay also used discrepancies between this document and the numbers used by Dr. Bell, reported to him by Mr. Mullikin, to challenge the accuracy of Dr. Bell's profitability analysis.[35] (*See* Tr. 1360:9–1362:10).

213. But the document itself demonstrates its own dubiousness, as Dr. Bell credibly demonstrated. (*See* 1550:1–1551:23). The gross sales line provides precise amounts to the single dollar not only though 2012, when the document was created, but all the way through 2020. (DTX-1002 at KN002712912). Further, the gross to net calculation provides the same precise 30.00% ratio every year through 2020. (*Id.*). Such precision raises doubt as to the document's accuracy. Indeed, after initially reviewing this document, Dr. Bell drew the "painfully obvious" conclusion that "these are not actual sales numbers," which was one of the

[35] Dr. Hay also criticized Dr. Bell's analysis for purportedly ignoring Kowa's specific research and development costs. (Tr. 1361:9–1362:10). Dr. Bell used a "standard cost" of $800 million to bring products to the market, an estimated amount based on a survey of major U.S. pharmaceutical companies. (Tr. 1569:3–11).

reasons why Dr. Bell initiated a conversation with Mr. Mullikin to obtain the requisite financial information for his profitability analysis. (Tr. 1551:20–23).

214. Nor is the Court persuaded by Dr. Hay's arguments that some development and co-promotion partners' abandonment of pitavastatin demonstrates that Livalo® is not a commercial success. (Tr. 1346:10–16; *see* Tr. 1344:19–1345:17 (Eli Lilly's decision to terminate its co-promotion marketing partnership with Kowa after two years); 1342:25–1343:23 (Sankyo's decision to return U.S. licensing rights to Kowa in 2005); 1343:24–1344:18 (Novartis' decision to stop development of extended release version of pitavastatin for European market in 2005); DTX-0895; PTX-0286 at KN0026655372). The purported losses associated with these decisions that Dr. Hay described were primarily based on speculation;[36] and Dr. Hay admitted he had never seen any Eli Lilly financials, press releases, or SEC filings reflecting Eli Lilly's purported loss. (*See* Tr. 1344:2–18, 1345:13–17, 1388:14–1389:1, 1391:14–1393:2).

215. The Court credits the testimony of Dr. Bell and Mr. Mullikin and concludes that Livalo® is a commercial success.

216. Regarding nexus, Dr. Bell explained that his conclusion stems from three factors: (1) the FDA's approval of Livalo® and his understanding that Form A, as covered by the '993 patent, provides the stability allowing for such approval; (2) the advantages Livalo® provides for certain patient subpopulations; and (3) the fact that Kowa markets and promotes Livalo® based on its

[36] For example, Dr. Hay assigned Novartis' reported losses of $332 million on development of an extended release version of NK-104 meant for the European market to Kowa; and speculated, without evidence, that Novartis had suffered additional, earlier losses. (*See* Tr. 1344:2–18). But as Dr. Bell noted, part of that amount could represent the licensing rights Novartis paid to Kowa to access the product; and moreover, "Novartis was working on an extended release version of pitavastatin. That is most certainly not the product that is approved and marketed in the U.S." (Tr. 1544:12–14; *see* Tr. 1544:12–22).

product advantages that come from its patented features. (Tr. 1541:11–1547:10; PTX-0190; PTX-0192; PTX-0201; PTX-0961).

217. Regarding the second of these factors (patient subpopulations), Dr. Bell discussed the evidence demonstrating that because of the way it is metabolized, (primarily through a non-CYP450 metabolic pathway), including its reduced risk of drug-drug interactions, Livalo® provides advantages for, *inter alia*, patients with statin intolerance; diabetics and prediabetic patients; patients needing protease inhibitors to treat HIV and hepatitis C; and polypharmacy patients. (Tr. 1542:11–1544:18).

218. Regarding the third of these factors (marketing based on the patented features), Dr. Bell discussed Livalo®'s marketing messages, to both patients and physicians, which focus on Livalo®'s use of the non-CYP450 metabolic pathway. (Tr. 1544:19–1547:10). Additionally, Mr. Mullikin testified that the promotional efforts of Livalo® are principally direct-to-consumer, and use targeted education and the benefits described on the label. (Tr. 1518:11–20). Similarly, Dr. Sponseller described Kowa's marketing efforts "to portray the metabolism of Livalo" and explain the benefits of "taking a road less traveled:" namely, fewer drug-drug interactions as compared to other statins. (Tr. 75:11–76:21).

219. The Court credits the testimony of Dr. Bell, Dr. Kaduk, Dr. Miller and Dr. Gotto; and the testimony of Mr. Mullikin and Dr. Sponseller. Plaintiffs have established the nexus between the commercial success of Livalo® and the claimed invention of the Asserted Claims.

220. Plaintiffs have shown that Livalo® has significant sales and embodies, and is coextensive with, the claimed invention of the '993 patent. Livalo® contains pitavastatin calcium as its API. (Tr. 1599:1–11; PTX-0121; DTX-0032 at MYLAN(Pitav)009130). Specifically, Livalo® contains polymorph A, which has been demonstrated to be a stable polymorphic form.

(PTX-0154; PTX-0691; Tr. 224:20–25, 370:4–7, 375:4–376:16). Dr. Kaduk credibly opined that the API in Livalo® is the stable Form A of the '993 patent; and that Livalo® is a commercial embodiment of claims 1, 23, 24, and 25 of the '993 patent.[37] (*See generally* Tr. 1598:6–1608:21; PTX-0121; PTX-0112; PTX-0123; PTX-0175; PTX-1063). Plaintiffs are thus are entitled to a presumption of nexus between the commercial success of Livalo® and the invention of the '993 patent. (*Crocs*, 598 F.3d at 1310–11). Defendants have not met their burden of demonstrating that extraneous factors are responsible for Livalo®'s commercial success to rebut that presumption. (*Demaco*, 851 F.2d at 1393 (specifying that challenger must adduce evidence of other factors; "argument and conjecture are insufficient" (quotations and citation omitted))).

221. Even without a presumption of nexus between commercial success and the patented invention, Plaintiffs have demonstrated a legally and factually sufficient connection between the commercial success of Livalo® and features enabled by the patented invention, including Livalo®'s tolerability and reduced drug-drug interactions. (*Demaco*, 851 F.2d at 1392). The unique attributes of Livalo® and the advantages it provides for certain patient subpopulations stem from the patented features and drive its sales. (Tr. 72:9–75:18, 85:3–21, 1427:23–1429:16, 1447:10–24, 1540:6–1541:10, 1542:11–1547:10).

222. This factor weighs in favor of nonobviousness.

B. Unexpected Results

223. "Evidence of some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected tends to indicate nonobviousness." (*Trustees of Columbia Univ. in City of N.Y. v. Illumina, Inc.*, 620 Fed. App'x 916, 931 (Fed. Cir.

[37] Dr. James Kaduk, Plaintiff's expert, opined on infringement and provided testimony about, *inter alia*, crystals, polymorphs, and Form A; XRPD analysis; the plain and ordinary meaning of the Asserted Claims; and Livalo® API as a commercial embodiment of the Asserted Claims.

2015) (quotations and citation omitted)). "Nonobviousness may be established when an invention 'yield[ed] more than predictable results.'" (*Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017) (quoting *Crocs*, 598 F.3d at 1309)).

224. Evidence of unexpected benefits or results of a claimed invention discovered after the patent's filing or issue date may be considered in assessing obviousness. (*Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (Fed. Cir. 2011); *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014)).

225. When "used as evidence of nonobviousness," the unexpected results "must be shown to be unexpected compared with the closest prior art." (*Millennium*, 862 F.3d at 1368 (quotations and citation omitted)).

226. The evidence and testimony presented at trial demonstrated numerous unexpected results of pitavastatin Livalo® as compared to name-brand and generic statins, including, *inter alia*, superior tolerability and reduced drug-drug interactions.

227. Dr. Gotto, who has been involved in statin research and development since the late 1970s, started researching pitavastatin (then known as NK104) in 2000, through a Kowa-financed research grant to his lab. (Tr. 1462:2–13, 1471:1–1472:13). Among other things, his research showed "that pitavastatin was very effective in inhibiting HMG-CoA reductase. It was more active than most of the other statins." (Tr. 1472:5–7). Pitavastatin is the only statin containing a cyclopropyl group structure, which Dr. Gotto testified "may contribute to its potency." (Tr. 1476:8–12; PTX-1200 (KPA Press Release, *FDA Approves LIVALO® for Primary Hypercholesterolemia and Combined Dyslipidemia* (Aug. 3. 2009)) at KN003463954 (describing Livalo®'s "unique cyclopropyl group" that "contributes to a more effective inhibition of the HMG-CoA reductase enzyme to inhibit cholesterol production")).

228. Pitavastatin is only minimally metabolized by the CYP450 metabolic pathway. (Tr. 1428:6–7, 1476:12–15; PTX-1158 (Vivencio Barrios et al, *Searching the place of pitavastatin in the current treatment of patients with dyslipidemia*, Expert Rev. Cardiovasc. Ther. 11(12), 1597–1612 (2013)) at KN001878886).

229. Due to this unique chemical formula, Livalo® has shown surprising results, including great advantages for polypharmacy patients taking numerous other drugs for different conditions. (*See, e.g.*, Tr. 72:9–73:24, 75:11–22, 91:2–108:16, 1428:6–19, 1476:12–15).

230. As Livalo®'s principal route of metabolism is via glucoronidation, it provides greatly reduced potential for interactions with other drugs a patient may be taking that use the CYP pathway. (Tr. 1476:12–15; PTX-1158 (Barrios) at KN001878887, KN001878896; DTX-1590 (Antonio M Gotto Jr and Jennifer Moon, *Pitavasatatin for the treatment of primary hyperlipidemia and mixed dyslipidemia*, Expert Rev. Cardiovasc. Ther. 8(8), 1079–1090 (2010)) at KN001590858–59). Interactions of statins metabolized by the CYP pathway with certain inhibitors, including protease inhibitors, can result in elevated plasma concentrations of the statin or myotoxicity. (DTX-1590 (Gotto) at KN001590861). Thus, Livalo® offers a distinct advantage over other statins primarily metabolized by the CYP pathway, including atorvastatin (Lipitor®), lovastatin (Mevacor®), and simvastatin (Zocor®). (Tr. 1476:12–17; PTX-1158 (Barrios) at KN001878887, KN001878896; DTX-1590 (Gotto) at KN001590858–59).

231. Livalo® has shown no drug-drug interactions when co-prescribed with the blood thinner Coumadin (warfarin); and Dr. Gotto opined that pitavastatin was the first statin to do so. (Tr. 1494:11–14; *see* Tr. 1436:15–1438:1; PTX-0186 (Yoichiro Inagaki et al., *Drug-Drug Interaction Study to Assess the Effects of Multiple-Dose Pitavastatin on Steady-State Warfarin in Healthy Adult Volunteers*, J. Clin. Pharmacol. (2011)) at KN001396269, KN001396273–75; PTX-0196

(Christine Y. Yu et al., *Effect of pitavasatin vs. rosuvastatin on international normalized ratio in healthy volunteers on steady-state warfarin*, Current Medical Research & Opinion 28(2) (2012)) at KN001497220). Drug-drug interactions in such cases may cause increased intensity of warfarin anticoagulation, which results in increased bleeding complications. (PTX-0196 (Yu) at KN001497214). A head-to-head comparison of warfarin co-administered with Crestor® (rosuvastatin) versus Livalo® showed significantly increased International Normalized Ratio (INR), resulting in increased bleeding complications, in patients taking receiving Crestor® 40 mg; but no change in INR in patients receiving Livalo® 4mg added to warfarin at steady state. (*Id.* at KN001497214, KN001497220). The study added that "[c]ases of excessive warfarin anticoagulation have been reported for lovastatin, pravastatin, and fluvastatin;" and that simvastatin "has been shown to increase INR in patients on stable warfarin therapy." (*Id.* at KN001497220; *see* DTX-1590 (Gotto) at KN001590858–59, 861, 867).

232. Livalo® has also demonstrated advantages over other statins for diabetic or pre-diabetic patients. For example, one study found that rosuvastatin was associated with increased blood glucose levels and risk of new onset diabetes. (Tr. 1442:20–1443:21; PTX-0114 (Yasuyuki Kawai et al., *Place of pitavasatatin in the statin armamentarium: promising evidence for a role in diabetes mellitus*, Drug Design, Development and Therapy 2011:5 (2011)) at 8 (describing JUPITER Trial)). By contrast, Pitavastatin does not interfere with glucose metabolism in diabetic or non-diabetic patients. (Tr. 1428:8–9; PTX-1158 (Barrios) at KN001878886). Indeed, studies have shown that Livalo® improves the abnormal lipid and lipoprotein profile associated with certain diabetes; and studies have also shown that such improved profiles may reduce the likelihood of developing diabetes. (PTX-0114 (Kawai) at 8; PTX-0152 (Luis Masana, *Pitavastatin in cardiometabolic disease: therapeutic profile* (Cardiovascular Diabetology

12(Suppl 1):52 (2013)) at KN000993113 ("These data suggest that whereas some statins are associated with adverse effects on glycemic control, pitavastatin has a neutral and possibly beneficial effect that is likely to be especially useful in people with, or at risk of developing [type 2 diabetes]."), KN000993110–14; PTX-0990 (Divyesh Thakker et al., *Statin use and the risk of developing diabetes: a network meta-analysis*, Pharmacoepidemiology and Drug Safety (2016)) at 14). In a head-to-head study of Livalo® 4 mg compared to atorvastatin 20 or 40 mg, Livalo® had no significant effect on blood glucose levels, while atorvastatin was associated with a 7.2-7.3% increase. (Tr. 1440:12–1442:13; PTX-0185 (J. Gumprecht et al., *Comparative long-term efficacy and tolerability of pitavastatin 4 mg and atorvastatin 20-40 mg in patients with type 2 diabetes mellitus and combined (mixed) dyslipidaemia*, Diabetes, Obesity and Metabolism 13 (2011)) at KN0001393392).

233. Further, Livalo® has proved tolerable for patients who experience muscle pain symptoms while taking other statins. (Tr. 82:19–83:15, 1434:19–23; PTX-0185 (Gumprecht) at KN001393393). Dr. Miller, an active physician who treats many statin-intolerant patients, has had much success prescribing Livalo® for his patients instead of, for example, rosuvastatin or atorvastatin. (Tr. 1420:6–1422:9; *see also* Tr. 1300:23–25 (Dr. Zusman conceding that PTX-1239 indicates that Livalo® would be "a good candidate" for patient who had been resistant to two other statins); PTX-1239 (Bobbi Hollaway et al., *Tolerability and Efficacy of Pitavastatin Among Hyperlipidemic Patients Intolerant to at Least Two Other Statins* (Annual Scientific Session & Expo Poster Abstract) (Mar. 11, 2013)).

234. Livalo® has also shown surprising advantages for patients with HIV or hepatitis C, as it has not demonstrated significant interactions with anti-viral protease inhibitors, in contrast to many other statins. (Tr. 108:17–111:14, 1429:12–16 (Miller) ("[P]erhaps the biggest surprise . . .

is that the effect on exposures of pitavasatatin and protease inhibitors was minimal. And this again reflects a unique aspect that we don't see in some of the other statins."), Tr. 1494:7–10 (Gotto opining that pitavsatatin was the first or only statin to avoid interactions with HIV protease inhibitors), 1327:22–1328:21 (Zusman conceding that Livalo® 's minimal interactions with drugs used to treat HIV were "part of the reason that Livalo was chosen" for three trials by the NIH, the NHLBI, and the NIAID); *see* PTX-0356 (NIH News, *NIH Launches Largest Clinical Trial Focused on HIV-Related Cardiovascular Disease*, (Apr. 15, 2015)) at KN003462528 (explaining that pitavastatin was selected for clinical trial to assess potential of statins to reduce risk for major adverse cardiovascular events in patients with HIV because "unlike most other statins, only minimal interactions occur between pitavastatin and drugs for treating HIV")).

235. Indeed, a 2012 FDA Safety Announcement concluded that pitavastatin has no dose limitations when co-administered with protease inhibitors, in contrast to most other statins. (PTX-0190 (FDA, *FDA Drug Safety Communication: Interactions between certain HIV or hepatitis C drugs and cholesterol-lowering statin drugs can increase the risk of muscle injury* (Mar. 1 2012)) at KN001402835; *see also* PTX-0194 (Craig A. Sponseller et al., *After 52 Weeks, Pitavastatin is Superior to Pravasatatin for LDL-C Lowering in Patients with HIV* (March 2014)) (finding that pitavastatin demonstrated superior LDL-C reduction, and significantly greater reduction in apolipoprotein B, non-HDL-C, and total cholesterol compared to pravastatin)). Moreover, the FDA recently approved changes to Livalo®'s label highlighting the positive results in treating patients with HIV. (Tr. 104:17–105:14; PTX-1098 (Livalo® Label) at KN003466200).

236. Regarding all of the above results and advantages of Livalo®, the Court credits the testimony provided by Dr. Gotto, Dr. Miller, and Dr. Sponseller.

237. These unexpected results weigh in favor of nonobviousness.

C. Long-Felt Need of Patient Subpopulations

238. "Evidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer the need would not have persisted had the solution been obvious." (*Apple Inc. v. Samsung Elec. Co., Ltd.*, 839 F.3d 1034, 1056 (Fed. Cir. 2016). "[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem." (*Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993)).

239. There existed a need for additional methods of treatment for hypercholesterol patients before the first statin entered the market in 1987, as all alternative therapies had significant problems. (Tr. 1429:19–1430:12; 1284:19–24).

240. Dr. Miller and Dr. Gotto opined that while there existed other commercially available statins at the time of Livalo®'s launch, medical needs of certain patient subpopulations with high risk cardiovascular disease remained unmet. (*See* Tr. 1432:25–1433:13, 1447:10–1448:11, 1473:4–1475:20). Dr. Sponseller testified on the same topic. (*See* Tr. 72:9–74:13). Even Dr. Zusman conceded that one primary reason why there is an "ongoing need" for additional agents to treat hypercholesterolemia is because some patients are intolerant of available drugs; and that "different drugs may work differently in different patients." (Tr. 1284:21–1285:13).

241. The Court credits the testimony of Dr. Miller, Dr. Gotto, and Dr. Sponseller.

242. Numerous patient subpopulations could not tolerate, or experienced adverse drug interactions or other events with, other available statin alternatives; and thus had a long-felt but

unmet need for a different effective treatment. (*See* Tr. 1429:19–1433:13, 1447:11–1448:5, 1473:4–1475:20). As described above, these include, without limitation: the statin-intolerant; the diabetic or pre-diabetic; those with HIV; and polypharmacy patients. (*See infra*).

243. By contrast, as explained in detail above, pitavastatin Livalo® has shown great success in these and other patient subpopulations. Livalo® continues to be prescribed by physicians, and chosen for various clinical trials due to its unique features and advantages.

244. Plaintiffs have shown long-felt need for the claimed invention.

245. This factor, too, weighs in favor of nonobviousness.

v. Conclusion Regarding Obviousness

246. The Court finds that Defendants have not proven by clear and convincing evidence that claimed Form A of pitavastatin calcium would have been obvious to one skilled in the art as of February 2003. The Court further finds that even if Defendants had shown a prima facie case of obviousness, Plaintiffs have shown objective indicia of nonobviousness to rebut that case.

247. The '993 patent is not invalid as obvious in view of the prior art.

c. Conclusion Regarding Validity

248. In addition to the findings and conclusions above, the Court notes that six of the eight original defendants in this litigation involving the '993 patent have settled, indicative of industry acquiescence which "constitutes a strong showing of [the '993 patent's] validity." (*Moore Bus. Forms, Inc. v. Wallace Computer Servs., Inc.*, No. S88-359, 1989 WL 222974, at *17 (N.D. Ind. Dec. 14, 1989)).

249. Defendants have not met their burden of proving invalidity, either by inherent anticipation or by obviousness, by clear and convincing evidence. (*Microsoft Corp.*, 564 U.S. at 95).

250. The '993 patent is valid.

XII. Infringement of the '993 Patent

251. The Court proceeds to the two-step infringement analysis regarding Apotex's proposed ANDA product.[38]

252. To prove infringement, Plaintiffs must prove by a preponderance of the evidence that Apotex's proposed ANDA product meets the limitations of the Asserted Claims. (*Dynacore*, 363 F.3d at 1273). Plaintiffs need only prove "that it is 'more likely than not' that some quantity, however miniscule," of Form A is present in Apotex's proposed ANDA product. (*Cephalon*, 769 F. Supp. 2d at 778).

253. Plaintiffs presented the testimony of Dr. Kaduk, their expert, who concluded that the API in Apotex's ANDA product was the claimed Form A, and that Apotex's ANDA product infringes claims 1, 23, 24, and 25 of the '993 patent; and of Dr. Byrn, who opined that that Apotex's ANDA product infringes claim 22 of the '993 patent.

254. In asserting non-infringement, Apotex presented the testimony of Dr. Sacchetti, its expert. He opined that Apotex's API has a different structure than the claimed Form A, and does not meet the limitations of the Asserted Claims.

255. For the reasons that follow, the Court concludes that Plaintiffs have met their burden of demonstrating, by a preponderance of the evidence, that Apotex's proposed ANDA product infringes the Asserted Claims of the '993 patent.

[38] Amneal does not contest infringement of the '993 patent. (PTX-1324 at 1).

a. Step One: Construing the Asserted Claims

256. The first step of the infringement analysis is to construe the Asserted Claims. (*Conroy*, 14 F.3d at 1572). No construction issues as to the '993 patent were raised by the parties at the November 4, 2015 *Markman* hearing. (*See* Nov. 4, 2015 Opinion and Order at 1 n.1).

257. Thus, the plain and ordinary meanings of the claim terms, as they would have to a POSA, as defined at *supra* Part X, as of February 12, 2003, apply to all '993 patent claim terms. (*Phillips*, 415 F.3d at 1312–13). The parties disagree on the plain and ordinary meanings of claims 1, 23, 24 and 25.

i. Claims 1 and 24: "exhibits a characteristic x-ray diffraction pattern with characteristic peaks expressed in 2θ at . . ."

258. Defendants argue that the plain and ordinary meaning of claims 1 and 24 requires a match of all twenty-six recited peak positions and twenty-six recited relative intensities, within expected experimental error. In other words, Defendants view each and every 2θ angle value and relative intensity level (*i.e.*, very strong, strong, medium, weak, or very weak) as a separate claim limitation. (*See* Tr. 586:1–587:8, 647:14–648:5 (Sacchetti)).

259. Plaintiffs disagree, and argue that such treatment is inconsistent with the plain and ordinary meanings for a POSA. (*See* Tr. 1579:24–1580:15 (Kaduk)).

260. A POSA would understand the plain and ordinary meaning of claims 1 and 24 to include expected experimental error and variation involved with XRPD analysis. (*See* Tr. 155:23–156:11, 159:6–160:16, 168:22–177:16, 179:17–181:5, 312:2–5, 585:5–10, 647:11–13, 776:16–777:8 (Dr. Roberts concluding that XRPD data "meets the limitations of claims 1 and 24," despite "variation in relative intensities," including nine peaks that did not precisely match the relative intensities recited in claims 1 and 24, because such variation was to be expected in

"experimental studies on different instruments and different example preps"), 853:10–12, 1588:13–1589:18, 1616:3–15, 1647:19–22). "[A] person of ordinary skill's understanding of the term XRPD would include the expected error associated with the measurement being used." (*Eisai Co., Ltd. v. Glenmark Pharm., Ltd.*, No. 13-1279 (LPS), 2015 WL 1228958, at *8 (D. Del. Mar. 17, 2015); *see Takeda Pharm. Co. v. Handa Pharm., LLC*, No. C-11-00840 (JCS), 2012 WL 1243109, at *12 (N.D. Cal. Apr. 11, 2012) ("[A] person skilled in the art would not have required any discussion of the experimental error associated with XRPD diffraction, either in the specification or in the claims, to understand that the references to 'characteristic peaks at interplanar spacings (d)' allowed for such experimental error.")).

261. In *Eisai Co.*, the court construed a similar claim term, reading: "characterized by characteristic lines at [with] interplanar spacings (d values) of 10.5 Å . . . [as] determined by means of an X-ray powder pattern."[39] (*Eisai Co.*, 2015 WL 1228958, at *7 (alternations in original)). The *Eisai* court concluded:

> [T]he plain and ordinary meaning of 'characterized by' does not require all of the recited d-values to be present in every experimental run (i.e., an exact one-to-one match). Rather, as the broad claim language (drafted by the applicants and approved by the PTO) sets out, the claim limitation is satisfied as long as the crystal form can be 'characterized by' – that is ***identified by*** – reference to ***the characteristic lines*** set forth in the claim.

(*Id.* at *8 (emphasis in original)).

262. Relatedly, a court construed the term "characterized by the following major peaks in its X-ray diffractogram," including a corresponding peak list, to mean "identifiable by reference to an X-ray diffractogram that includes the major peaks below." (*Astrazeneca AB v. Dr. Reddy's Labs.*, No. 11-2317 (JAP), 2013 WL 1847639, at *9 (D.N.J. May 1, 2013)). In so doing, the *Dr.*

[39] D-spacings and 2θ angles are interchangeable terms. (Tr. 164:8–14).

Reddy's court rejected defendants' proposed construction of "having all of the referenced major peaks in its X-ray diffractogram," as it "would require an exact match;" was "too rigid;" and would fail to account for fact that "the positions of the peaks may differ somewhat because of slight experimental errors." (*Id.* at *8–9).

263. Another court, however, construed the same term to mean "having each of the referenced major peaks in its X-ray powder diffractogram within normal experimental error." (*Astrazeneca AB v. Andrx Labs, LLC*, No. 14-8030 (MLC), 2017 WL 111928, at *47 (D.N.J. Jan. 11, 2017)). But the *Andrx* court cautioned that "construing the claims to require an exact match is too rigid," and emphasized that its construction, which accounted for normal experimental error and varying relative intensities, was "not inconsistent" with the construction accepted by the *Dr. Reddy's* court. (*Id.* at *48). The *Andrx* court explained that it rejected the same construction accepted by the *Dr. Reddy*'s court because "it focuses on the question of infringement . . . and how the POSA would compare a diffractogram for a tested compound to a reference diffractogram to determine whether there is a match for purposes of infringement." (*Id.*).

264. The language of claims 1 and 24 of the '993 patent, claiming a characteristic pattern with characteristic peaks, is more analogous to the claim terms in *Eisai* than those in *Dr. Reddy's* or *Andrx*. The Court agrees with the reasoning and constructions set forth in *Eisai* and *Dr. Reddy's*: the plain and ordinary meaning of claims 1 and 24 does not require an exact match of every single recited peak position and relative intensity.

265. A POSA would understand the limitations of claims 1 and 24 to be satisfied if Form A can be identified in the substance in question by reference to the characteristic pattern with characteristic peaks and intensities set forth in claims 1 and 24 of the '993 patent.

ii. Claims 23 and 25: "having an x-ray powder diffraction pattern substantially as depicted in Fig. 1 . . ."

266. Defendants similarly contend that the plain and ordinary meaning of claims 23 and 25 requires a match of all peak positions and relative intensities of Figure 1, and consideration of peak shapes, within expected experimental error. (*See* Tr. 586:1–587:8, 647:14–648:5 (Sacchetti)).

267. Courts have understood the "ordinary and customary definition . . . [of] 'substantially'" to indicate some expected variability as "a non-specific term of approximation that avoids a numerical boundary." (*Shire LLC v. Amneal Pharm., LLC*, No. 11-3781 (SRC), 2013 WL 4045622, at *7 (D.N.J. Aug. 8, 2013); *see Liquid Dynamics Corp. v. Vaughan Co.*, 355 F.3d 1361, 1368 (Fed Cir. 2004) ("The term 'substantial' is a meaningful modifier implying 'approximately,' rather than 'perfect.'")).

268. Thus, where the claim term "X-ray powder diffraction pattern substantially as shown in FIG. 77" did not include any numerical limits, unlike other claims in the patent that set "precise numerical boundar[ies] around a specific XRPD pattern," the *Shire* court construed the term to mean "X-ray powder diffraction pattern approximately as shown in FIG. 77." (*Shire*, 2013 WL 4045622, at *6–7).

269. Similarly, the *Dr. Reddy's* court rejected defendants' proposed construction of the term "represented by FIG. 1" to mean "having an X-ray diffractogram the same as FIG. 1," as it would require a "perfectly identical" diffractogram and would disregard variances due to normal experimental error. (*Dr. Reddy's*, 2013 WL 1847639, at *9 (instead construing claim to mean "represented by Figure 1")). The *Andrx* court construed the same claim to mean "having an X-ray powder diffractogram that is the same as Figure 1 of the [patent] within normal experimental

error;" but clarified that such construction was consistent with that in *Dr. Reddy's* and "do[es] not require an exact match witb the X-ray powder diffractogram of Figure 1 to identify the claimed compound" and "does not require perfect identity." (*Andrx*, 2017 WL 111928, at *48–49).

270. As with claims 1 and 24, a POSA would understand the plain and ordinary meaning of claims 23 and 25 to include known experimental error and variation. (*See* Tr. 155:23–156:11, 159:6–160:16, 168:22–177:16, 179:17–181:5, 312:2–5, 585:5–10, 647:11–13, 776:1–12 (Dr. Roberts finding an "excellent match between the diffraction patterns" of Figure 1 of the '993 patent and Nissan's second replication of Example 3 of EP '406, and concluding that the latter was "substantially as depicted in [F]igure [1] of the '993 patent" despite identifying nine characteristic peak relative intensity differences), 853:10–12, 1588:13–1589:18, 1616:3–15, 1647:19–22; *see Eisai*, 2015 WL 1228958, at *8).

271. One skilled in the art at the time would understand the plain and ordinary meaning of claims 23 and 25 to require an approximate, not exactly identical, match of the characteristic pattern as depicted in Figure 1, viewing the patterns in totality and taking into account experimental errors and variation associated with XRPD analysis.

272. A POSA would understand the limitations of claims 23 and 25 to be satisfied if the XRPD pattern of the substance in question is substantially, or approximately, as depicted in Figure 1 of the '993 patent.

b. Step Two: Comparison of Asserted Claims to Apotex's Proposed ANDA Product

273. In the second step of the infringement analysis, the Court compares the construed Asserted Claims of the '993 patent to Apotex's proposed ANDA product. (*Conroy*, 14 F.3d at 1572).

274. The Court finds that Plaintiffs have shown by a preponderance of the evidence that Apotex's proposed ANDA product meet all of the limitations of claims 1, 22, 23, 24, and 25 of the '993 patent.

i. Apotex's Proposed ANDA Product

275. Apotex submitted ANDA No. 20-6068 to the FDA on August 3, 2013, seeking approval to market 1 mg, 2 mg, and 4 mg generic pitavastatin calcium tablets. (PTX-0045 (Section 2.3); PTX-0049 (Section 3.2.S.1); PTX-0059 (Section 3.2.S.3.1); PTX-0098 (Section 3.2.S.3.1 (MSN DMF 23488)); *see generally* Tr. 197:19–203:6, 363:17–364:3).

276. The ANDA states that the active ingredient in its proposed product is pitavastatin calcium. (PTX-0045 at APOPIT000397, APOPIT000364 (chemical name and molecular structure)). The "General Properties" section states: "Pitavastatin Calcium exhibits polymorphism. Pitavastatin Calcium consistently manufactured by the DMF holder is crystalline polymorph" (PTX-0049 at APOPIT003218); and refers the reader to DMF No. 023488, held by MSN Laboratories Pvt. Ltd. ("MSN"), "for information on the drug substance general properties." (*Id.* at APOPIT003220; *see* PTX-0098 (MSN's DMF No. 023488)).

277. The API used in Apotex's ANDA product is the pitavastatin calcium manufactured by MSN. (PTX-0049 at APOPIT003220; Tr. 362:20–365:17).

278. MSN's DMF No. 023488 contains XRPD patterns and corresponding peak lists for a reference batch of its pitavastatin calcium (PTC/A287/3/33), which "represents the bulk API product that MSN makes," and "is the one to which all other batches are compared" (the "Reference Batch"). (Tr. 595:22–596:10; PTX-0098 at APOPIT68149–53). The DMF also includes XRPD patterns and corresponding peak lists for three commercial scale process validation batches (PC0010509, PC0020609, and PC0030609) (the "Three MSN Batches") that

MSN represented to the FDA as representative batches containing the same polymorphic form. (PTX-0098 at APOPIT68154–59; Tr. 202:2–203:5).

279. The ANDA also contains an XRPD pattern (but no corresponding peak list) and analysis reports for a batch of the pitavastatin calcium API tested by Apotex (KG5040) (the "Apotex Sample Batch"). (PTX-0065; PTX-0064; *see* Tr. 209:18–210:2). The analysis summary states that regarding polymorphic identification, the Apotex Sample Batch's X-ray diffraction "[c]orresponds to standard." (PTX-0064 at APOPIT003577; *see* Tr. 210:3–23).

280. Both Apotex's and MSN's XRPD sample preparation procedures called for grinding of the sample before performing the XRPD testing. (Tr. 293:23–296:7; Apotex-071 at APOPIT3305; Apotex-145 at APOPIT11253).

281. MSN represented to the FDA that its pitavastatin calcium remained stable during the drug product manufacturing process. (Tr. 373:21–376:16 (discussing PTX-0103 at APOPIT069355 and PTX-0100 at APOPIT069324–27)). Thus, the polymorphic form manufactured by MSN is the form of the API in Apotex's proposed ANDA product. (*See id.*; Tr. 587:9–11).

282. The XRPD diffragtogram patterns and associated peak list data of the Reference Batch, the Three MSN Batches, and the Apotex Sample Batch are representative of the polymorphic form of the API in Apotex's proposed ANDA product. (Tr. 202:2–203:5, 587:9–588:6).

283. In its 2010 DMF submission, MSN characterized the pitavastatin calcium it "consistently produces" as the "prior art crystalline form-A" disclosed in PCT/EP2004/050066:

> Pitavastatin Calcium exhibits polymorphism. Based on X-Ray diffraction studies it is concluded that the manufacturing process followed by MSN Laboratories Limited for Pitavastatin Calcium consistently produces prior art crystalline form-A.
> ...

> PXRD pattern of Pitavastatin Calcium produced by MSN Laboratories Limited is compared against the disclosed pattern of crystalline form-A of Pitavastatin Calcium in literature PCT[/]EP2004/050066 / WO2004/072040.

(PTX-0069 at APOPIT011204). In reaching this conclusion, MSN relied on the XRPD diffractograms of the same Reference Batch and Three MSN Batches that, according to Apotex's ANDA, represent the API used in Apotex's proposed product. (PTX-0069 at APOPIT011204–05, APOPIT011216–23; Tr. 221:2–223:3).

284. The '066 PCT is the application to which the '993 patent claims priority and of which it is a continuation. (*See* PTX-1063). The recited characteristic peaks describing what MSN refers to as "prior art crystalline form-A" as disclosed by the '066 PCT are identical to those recited characteristic peaks that describe and claim Form A in the '993 patent. (Tr. 221:21–222:1; *compare* DTX-1327 *with* PTX-1063). Claims 1 and 2 of the '066 PCT are identical to claims 24 and 25 of the '993 patent, aside from two misspellings; and claim 38 of the '066 PCT is functionally identical to claim 22 of the '993 patent. (Tr. 222:2–14; *compare* DTX-1327 *with* PTX-1063).

285. Thus, MSN identified the API in Apotex's proposed ANDA product as the "crystalline form-A" disclosed by the application that matured into the '993 patent.

286. Despite there being no change to the diffractograms, peak lists, or batches upon which MSN relied in its original characterization of the pitavastatin calcium it produces, MSN subsequently changed its designation, declaring: "the earlier designated crystalline form-A has been renamed as crystalline form-E." (PTX-0098 at APOPIT068149). MSN's explanation for doing so was claimed to be based on an unspecified "innovator/applicant['s] . . . response against one of the third party observations" in prosecution of another patent, "assert[ing] that the compound obtained by reworking the procedure" of the prior art example "provides crystalline

form-E of Pitavastatin calcium. Hence the prior reported polymorph is crystalline form-E." (*Id.*; *see* Tr. 219:10–220:18, 1618:23–1619:8).

ii. Dr. Kaduk's Analysis and Conclusions

287. Plaintiffs' infringement case-in-chief relies primarily on the testimony and conclusions of Dr. Kaduk, their expert.

288. Dr. Kaduk first looked at Apotex's ANDA and confirmed that the API is pitavastatin calcium. (Tr. 198:1–13). He then reviewed the parts of the ANDA that describe the general properties of pitavastatin calcium, including its polymorphism; identify MSN as the manufacturer and the DMF holder; and refer the reader to MSN's DMF for information about the pitavastatin calcium's general properties. (Tr. 198:19–200:9).

289. Dr. Kaduk then reviewed the DMF's explanation that MSN originally characterized the pitavastatin calcium it consistently produces as prior art crystalline form A, but that MSN subsequently changed this characterization to prior art crystalline form E. (Tr. 200:13–201:20).

290. Next, Dr. Kaduk analyzed the XRPD patterns and associated peak lists of the Three MSN Batches and the Apotex Sample Batch (together, the "Apotex Diffractograms"), and compared them to the characteristic peak list and figures of the '993 patent. His process was essentially as follows:

- extracting the diffractogram images from the hard copy PDF document and saving each pattern as one file;
- using UN-SCAN-IT 6.0, a graph digitizing software, to digitize the images and convert them to tabular data, including by setting digitization parameters and removing extraneous data points where necessary;[40]

[40] UN-SCAN-IT is recognized in the art as for digitizing XRPD patterns for analysis. (*See* PTX-1033 (R. Alan May and Keith J. Stevnson, *UN-SCAN-IT: Graph Digitizing Software*, 130 J. Am. Chem. Soc. 7516 (2008)); PTX-1006

- overlaying the resultant digitized version of the pattern against the original source material for manual quality control;
- importing the saved digitized data from UN-SCAN-IT into Jade 9.6, a program designed to comparatively analyze XRPD data;
- using the overlay function in Jade 9.6 to compare XRPD plots;
- scaling the diffraction patterns to account for differences in intensity counts and shifting the pattern by no more than 0.2 degrees 2θ to account for instrumental variance and expected variability; and
- vertically spacing, or offsetting, the plots by 10% for better visual comparison.

(*See* Tr. 181:12–190:23).

291. In this manner, Dr. Kaduk created digitized versions of the diffractograms of the Three MSN Batches. (PTX-1278; PTX-1279; PTX-1280; *see* Tr. 204:3–208:17). After comparing the three to each other he concluded that they represented the same form, as MSN had represented to the FDA: though the three patterns "exhibit[ed] some differences[,] . . . [t]he general pattern is the same." (Tr. 208:9–17; PTX-1276 (three digitized patterns on one graph, vertically separated by 10% to avoid complete overlap)).

292. He did the same for the Apotex Sample Batch. (PTX-1275; *see* Tr. 211:2–212:3).

293. Dr. Kaduk then compared the digitized diffractograms of the Three MSN Batches to Figure 1 of the '993 patent, referenced in claims 23 and 25 of the '993 patent. He did this by creating another comparative overlay, reproduced below, with the Three MSN Batches' patterns

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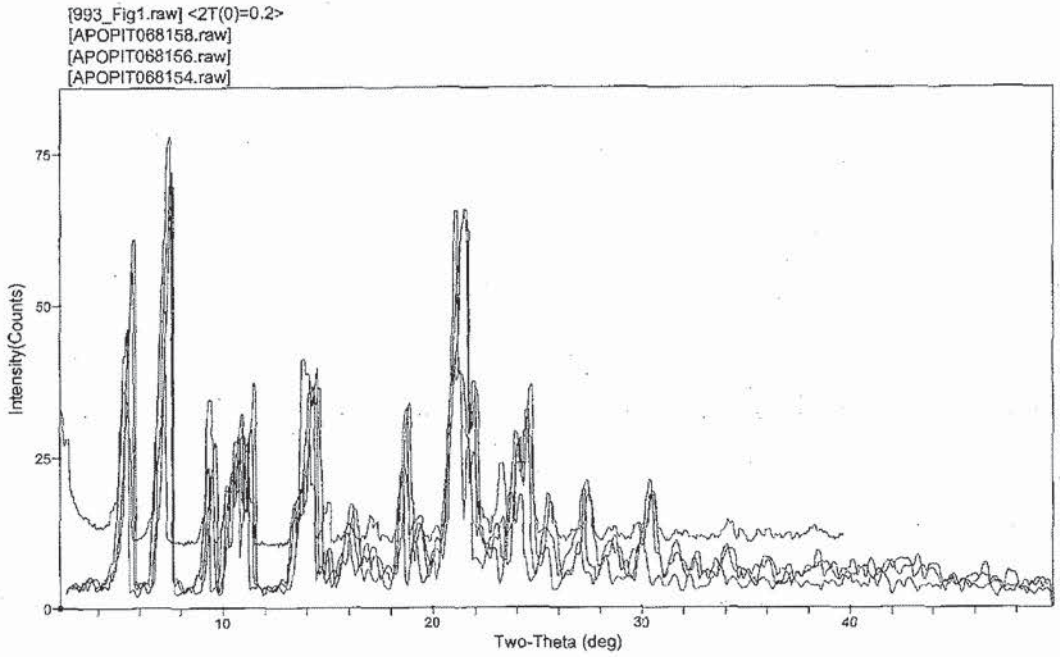
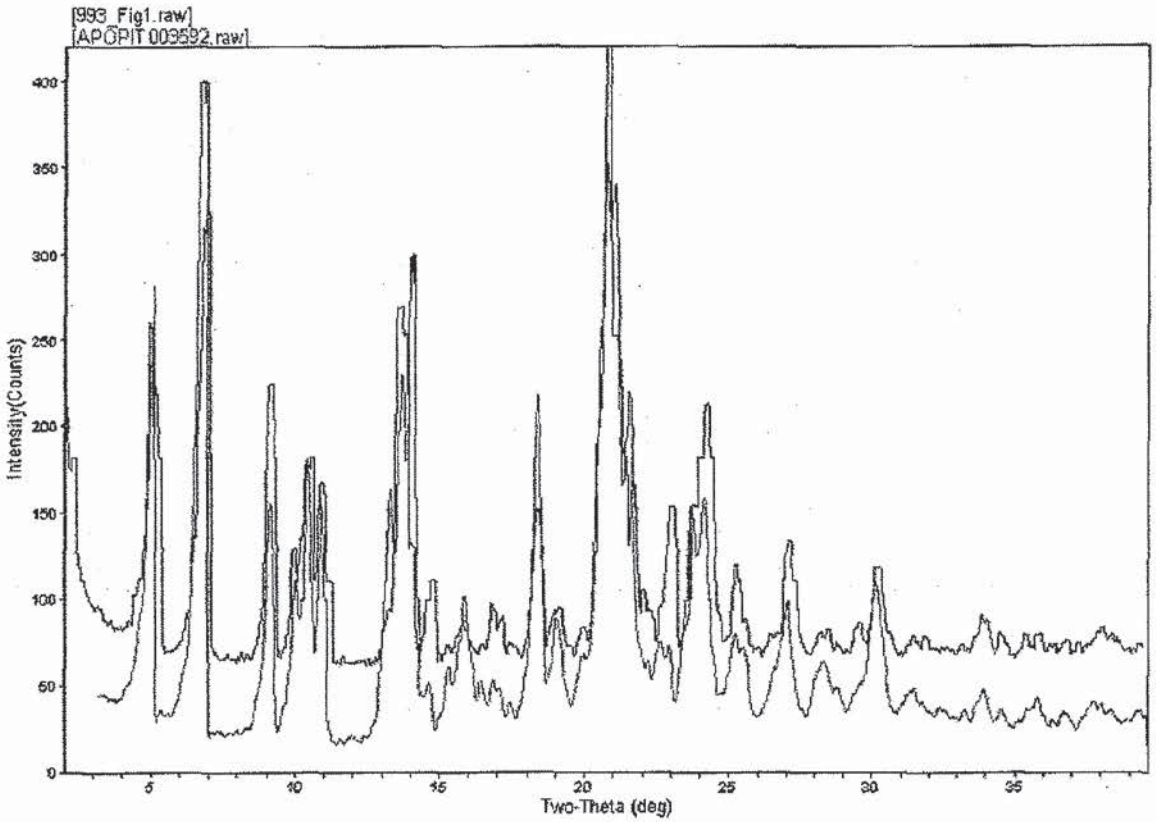
(Dimitra Skorda and Christos G. Kontoyannis, *Identification and Quantitative Determination of Atorvastatin Calcium Polymorph in Tablets Using FT-Raman Spectroscopy*, 74 Talanta 1066, 1067 (2008)) at KN003465580; Tr. 331:15–19 (Byrn) ("I think I bought my first copy of UN-SCAN-IT in the 1990s. So I knew that was a reliable program."), 1644:8–14 (Apotex withdrawn expert Eckhart deposition testimony) (testifying that he considers UN-SCAN-IT reliable)).

at the same scale at the bottom and Figure 1 vertically offset by 10% to avoid overlap. (PTX-1277; *see* Tr. 208:18–209:3).



(PTX-1277).

294. He compared the Apotex Sample Batch to Figure 1 of the '993 patent in the same manner. (PTX-1274; *see* Tr. 212:4–9, 214:1–5). This comparative overlay is reproduced below:



(PTX-1274).

295. Dr. Kaduk also compared the computer-generated associated peak lists and tabular data extracted from the diffractogram patterns to the characteristic peaks and relative intensities recited in claims 1 and 24 of the '993 patent. (Tr. 213:11–25).

296. From this analysis, Dr. Kaduk concluded that the Apotex Diffractograms all depict crystalline Form A of the '993 patent. (Tr. 208:4–209:3; 212:4–12).

297. Based on this analysis and conclusions; his review of the relevant claims, figures and tables in the '066 PCT and conclusion that they were the same as those in the '993 patent; and his review of the relevant diffraction data in the earlier-dated MSN DMF and the subsequent MSN DMF included in Apotex's ANDA and conclusion that they were the same, Dr. Kaduk testified that he agreed with MSN's prior assessment that the API in its pitavastatin calcium was

Form A; and that the API in Apotex's ANDA product is Form A of the '993 patent. (*See* Tr. 219:13–223:3, 179:19–181:5). He testified that he did not agree with MSN's subsequent characterization of the active ingredient as Form E. (Tr. 219:13–18).

298. Thus, by comparing these digitized versions of the Apotex Diffractograms, including both the whole pattern and the computer-generated peak data, to the characteristic pattern expressed in claims 1 and 24, and to Figure 1 referenced in claims 23 and 25, Dr. Kaduk concluded that the API in Apotex's proposed ANDA product would infringe claims 1, 23, 24, and 25 of the '993 patent. (Tr. 212:13–218:5; *see* Tr. 212:21–25 ("So the documentation tells us that [the API is] pitavastatin calcium. The raw data and the text in the ANDA describes it as crystalline polymorph. [] MSN concluded it was form A. I concluded it was crystalline form A. So we certainly have crystalline polymorph A of pitavastatin calcium.")). Dr. Kaduk applied the plain and ordinary meaning to all claim terms. (Tr. 192:16–22).

iii. Dr. Sacchetti's Analysis and Conclusions

299. In asserting non-infringement, Apotex relies on Dr. Sacchetti, its expert.[41]

300. Dr. Sacchetti testified that "to have infringement in this case, we have to have a match both in terms of two-theta values and relative intensity;" in other words, Dr. Sacchetti understood both as separate individual claim limitations. (Tr. 586:10–11, *see* Tr. 648:1–5).

301. Dr. Sacchetti did not create any computer-generated overlays in conducting his analysis, despite testifying in his deposition that chemists, in determining polymorphic forms, generally look at an entire XRPD pattern overlaid with an existing pattern to compare the two; and when asked "In terms of overlaying patterns, is that something that you do visually?" Dr. Sacchetti

[41] Defendants offered Dr. Mark Sacchetti as an expert in "solid state chemistry and solid state chemical testing, including characterization of crystal forms by X-ray powder diffraction." (Tr. 578:13–15).

responded: "Correct. And you can also use computer-aided software for comparison of polymorphic forms. That's actually what I meant when I said – when you said visually – it would be done on software." (Tr. 635:8–9, 11–14; *see* Tr. 634:4–8, 634:15–635:6).

302. Instead, Dr. Sacchetti visually compared Figure 1 of the '993 patent and the claimed characteristic peaks for Form A to the XRPD patterns and associated peak lists of the Three MSN Batches and the Reference Batch, and the XRPD pattern of the Apotex Sample Batch. (Tr. 595:25–596:2, 603:23–604:12, 605:2–12, 608:13–609:15, 634:6–8).

303. In assigning peak positions for the peak lists of the Three MSN Batches, Dr. Sacchetti accounted for what he identified as a "systemic shift" in two-theta values of 0.1-0.2 due to specimen displacement. (Tr. 595:11–596:24). Dr. Sacchetti also used an experimental error for relative intensity rate of 20%, which he deemed appropriate based on his identification of an approximately 20% difference in relative intensity variability among the Apotex Diffractograms; the fact that Apotex's and MSN's sample preparation procedures both called for grinding to minimize preferred orientation before testing; and the 1995 USP stating that "relative intensities between sample and reference may vary up to 20 percent." (Tr. 596:25–599:25; Apotex-138 (1995 U.S. Pharmacopeia 23, Ch. 941 X-Ray Diffraction (1995) at ORIENT00202435). The 2002 USP, which Dr. Sacchetti did not use in his analysis, modified this relative intensity error language to "may vary considerably due to preferred orientation." (Apotex-139 (U.S. Pharmacopoeia 25, Ch. 941, X-Ray Diffraction (2002) ("2002 USP") at PITADEF00019045); *see* Tr. 629:21–633:8). Dr. Sacchetti testified however, that he did not use the ±20% as a strict cutoff; and that his non-infringement conclusions would withstand higher error rates. (Tr. 603:2–8).

304. From this analysis, Dr. Sacchetti drew three major conclusions. First, he opined that six "relative intensity discrepancies between the accused API and claimed form A are too significant and consistent across five batches to be regarded as experimental error" (Tr. 603:13–16; *see* 603:23–620:6). Second, he concluded that "characteristic peaks [are] missing in the accused API peak list and diffractograms." (Tr. 603:17–18; *see* Tr. 620:8–621:21). Finally, Dr. Sachetti identified "some peak shape and pattern characteristics in the diffractograms" different from those of Figure 1 of the '993 patent. (Tr. 603:19–20; *see* Tr. 621:22–624:1).

305. Dr. Sacchetti concluded that the API in Apotex's ANDA product has a different crystal structure than, and does not meet the limitations of, claimed Form A; and that Apotex does not infringe the Asserted Claims. (*See* Tr.579:3–10; 603:21–22, 624:2–625:1).

iv. Claims 1 and 24

306. The Court credits Dr. Kaduk's testimony, which confirms that a POSA would identify the "characteristic X-ray diffraction pattern with characteristic peaks expressed in 2θ at 5.0 (s), 6.8 (s), 9.1 (s), 10.0 (w), 10.5 (m), 11.0 (m), 13.3 (vw), 13.7 (s), 14.0 (w), 14.7 (w), 15.9 (vw), 16.9 (w), 17.1 (vw), 18.4 (m), 19.1 (w), 20.8 (vs), 21.1 (m), 21.6 (m), 22.9 (m), 23.7 (m), 24.2 (s), 25.2 (w), 27.1 (m), 29.6 (vw), 30.2 (w), 34.0 (w)" in the Apotex Diffractograms representing the Apotex API; and would recognize the presence of Form A, as claimed in claims 1 and 24 therein. (*See* Tr. 213:11–214:18)

307. As an initial matter, the Court does not agree with Dr. Sacchetti's argument that fourteen characteristic peaks are "missing" from the Three MSN Batches and the Reference Batch. (*See* Tr. 620:8–621:21). The Court instead credits Dr. Kaduk's rebuttal testimony, in which he demonstrated, by magnifying the diffractogram patterns, that all fourteen characteristic peaks can be optically observed within expected variability of intensity. (Tr. 1591:17–1597:17).

Though Dr. Sacchetti testified that his analysis did not "just rely on the peak tables," he explained that he identified these peaks as "missing" by first consulting the associated peak lists, and only "as a last step" used the Apotex Diffractogram patterns to "confirm" his conclusions. (Tr. 620:21–23). But as explained, and as exemplified by Dr. Kaduk's demonstrative testimony, peak-picking algorithms may "miss" or "inconsistently" identify or locate peaks that actually may exist at varied relative intensities. (Tr. 641:25–642:9; *see* Tr. 205:24–206:11, 1592:10–16). Further, a POSA would review for characteristic peaks knowing that relative intensities may vary considerably. (Tr. 170:13–171:16, 179:17–181:5, 1647:19–22).

308. Regardless, Dr. Sacchetti's first two conclusions – that (1) a combined fourteen characteristic peaks are "missing" from the Three MSN Batches and Reference Batch (Tr. 620:8–621:21); and (2) there are six "peak pairs" across all five Apotex API batches with relative intensities inconsistent to those recited in claims 1 and 24 (Tr. 603:23–620:6), means that the Apotex API does not meet the limitations of claims 1 and 24 – rely on his understanding that each and every 2θ value and relative intensity recited in claims 1 and 24 are individual claim limitations. (Tr. 586:10–11, 648:1–5). But this is an erroneous understanding of the plain and ordinary meaning of claims 1 and 24.

309. As explained *supra*, a POSA would understand the limitations of claims 1 and 24 not to require an exact match of every peak position and relative intensity; but would rather understand the limitations to be met if the claimed Form A can be identified in the experimental XRPD data by reference to the characteristic reference pattern set forth in claims 1 and 24. As explained in detail herein, every characteristic peak need not be present, nor be a precise match (in terms both of 2θ position and relative intensity), in the sample for a POSA to do so.

310. A POSA, in determining whether the claimed Form A is present in the Apotex API, would thus review for the characteristic pattern by assessing the Apotex Diffractograms in their entirety and taking experimental errors into account. As Dr. Roberts conceded, a skilled artisan would "look at the totality of the data, the positions, and the peaks, and it would be a mistake to pick on one peak." (Tr. 853:10–12, *see also* Tr. 312:2–5, 1616:3–15). Dr. Sacchetti himself agreed with this concept. (Tr. 647:11–13 ("We use the whole x-ray powder diffraction pattern [to identify crystalline forms]. The most common way that we do that to make it definitive is to compare the whole pattern.")). This is especially true where an XRPD pattern is available. (*See* Tr. 1647:24–1648:5 (Apotex's withdrawn expert Dr. Eckhardt deposition testimony) ("Q: To determine whether a polymorph is the same as a polymorph depicted in a diffractogram, a person of ordinary skill in the art looks at the pattern as opposed to an individual specific peak or set of peaks; isn't that right, doctor? A: If you are lucky enough to have the entire diffractogram, yes.")).

311. The Court does not credit Dr. Sacchetti's testimony that the fact that a small subset of isolated peaks are "missing" (a conclusion with which, as stated above, the Court does not agree) means that the limitations of claims 1 and 24 are not met.

312. For the same reasons, the Court does not credit Dr. Sacchetti's testimony that the limitations of claims 1 and 24 are not met because there are six "peak pairs" with conflicting relative intensities across all five Apotex batches. (Tr. 603:23–620:6). To draw this conclusion, Dr. Sacchetti compared the claimed relative intensity of one of the 26 claimed characteristic peaks to another; and then compared that "pair" of relative intensities to the peaks at the same 2θ peak positions in the five Apotex batches. (*See id.*).

313. But the 26 characteristic peaks of Form A create a total of 325 "peak pairs;" and relative intensity discrepancies in six of those 325 is insufficient for the Court to conclude that the Form A is not present in the Apotex API. (*See* Tr. 1591:2–16). Again, claims 1 and 24 do not require an exact match; a POSA would review for the claimed characteristic pattern by analyzing the XRPD data and pattern as a whole, not just isolated "peak pairs;" and would know that relative intensities often vary tremendously due to experimental variations or errors. (Tr. 147:15–20, 152:20–153:6, 312:2–5, 647:11–13, 853:10–12, 1616:3–15; 1647:24–1648:5).

314. The Court finds that Plaintiffs have proved by a preponderance of the evidence that the API in Apotex's proposed ANDA product meets the limitations of claims 1 and 24 because a POSA would identify Form A in the Apotex Diffractograms by reference to the characteristic pattern with characteristic peaks and intensities set forth in claims 1 and 24 of the '993 patent.

v. Claims 23 and 25

315. For the same reasons explained above, the Court finds that Dr. Sacchetti's conclusions regarding the "missing" peaks and six "peak pair" relative intensity discrepancies are insufficient bases to conclude that the Apotex Diffractograms are not "substantially as depicted" in Figure 1; and the Court notes that Dr. Sacchetti did not specifically explain why or how these conclusions means that the Apotex API does not meet the limitations of claims 23 and 25. (*See* Tr. 603:10–22; *see also* Tr. 648:13–649:6 (Court sustaining Plaintiffs' objection to Dr. Sacchetti testifying, on re-direct examination, about claim 25 as beyond the scope of his direct testimony)).

316. Dr. Sacchetti's third major conclusion – that the Apotex Diffractograms contain distinctive "peak patterns" different from the claimed characteristic peaks of the '993 patent – also relies on an improperly narrow understanding of the claim limitations of claims 23 and 25.

(*See* Tr. 621:23–624:1 (finding, for example, a "staircase" pattern in the Apotex Diffractograms where the '993 patent claims discernible peaks)).

317. A POSA would understand the limitations of claims 23 and 25 to be satisfied if the XRPD pattern of the substance in question is as substantially, or approximately, as depicted in Figure 1 of the '993 patent, viewing the patterns in totality and taking into account experimental errors and variation associated with XRPD analysis. Thus, a POSA would review the Apotex Diffractograms for the *characteristic pattern* as depicted in Figure 1 to determine whether Form A is present.

318. The Court credits Dr. Kaduk's testimony that a POSA would find substantial identity between the Apotex Diffractograms and Figure 1; and would recognize the presence of Form A in Apotex's API as reflected by the Apotex Diffractograms submitted in its ANDA. (*See* Tr. 216:20–218:5).

319. The Court finds that Plaintiffs have proved by a preponderance of the evidence that the API in Apotex's proposed ANDA product meets the limitations of claims 23 and 25 because a POSA would detect the presence of Form A in the Apotex Diffractograms' patterns by finding them substantially or approximately as depicted in Figure 1 of the '993 patent.

vi. Claim 22

320. Claim 22 reads: "A pharmaceutical composition comprising an effective amount of the crystalline polymorph or amorphous form according to claim 1, and a pharmaceutically acceptable carrier." (PTX-1063). Claim 22 depends on claim 1, and thus "includes all the limitations of" claim 1. (*Wahpeton Canvas Co., Inc. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989); *see Coconut Grove Pads, Inc. v. Mich & Mich TGR, Inc.*, 222 F. Supp. 3d 222, 231 (E.D.N.Y. 2016) ("Independent claims stand alone and do not reference any other claim, whereas

dependent claims reference broader independent or dependent claims and commonly express particular embodiments."); Tr. 324:13–14).

321. Dr. Byrn, using the plain and ordinary meaning of the claim terms, analyzed claim 22, using Apotex's ANDA submissions and Dr. Kaduk's expert report and testimony. (Tr. 322:3–19; *see generally* Tr. 322–33).

322. Based on Apotex's proposed label for its ANDA product, Dr. Byrn concluded that Apotex seeks to market an effective amount of the product. (Tr. 330:16–331:4). Dr. Byrn then reviewed Section 2.3.P.1 of Apotex's ANDA submission, which discloses the composition of 1, 2, and 4 mg pitavastatin calcium tablets; lists pitavastatin calcium as the active ingredient; and lists anhydrous lactose and other components, which Dr. Byrn testified are pharmaceutically acceptable carriers. (Tr. 328:14–330:4). Finally, Dr. Byrn opined that the form of pitavastatin calcium in Apotex's ANDA product is Form A; and explained that in reaching this opinion, he reviewed (and agreed with) Dr. Kaduk's expert reports, exhibits, and in-court testimony, for which he was present. (Tr. 331:5–332:11). Thus, Dr. Byrn concluded that Apotex infringes claim 22 of the '993 patent. (Tr. 323:24–25).

323. The Court credits Dr. Byrn's testimony; and finds that Plaintiffs have demonstrated, by a preponderance of the evidence, that Apotex's proposed ANDA product meets the limitations of claim 22.

c. Conclusion Regarding Infringement

324. The Court credits the testimony of Dr. Kaduk, concluding that Apotex's ANDA product infringes claims 1, 23, 24 and 25; and the testimony of Dr. Byrn, concluding that Apotex's ANDA product infringes claim 22. (*See* Tr. 212:17–218:6; 323:24–25).

325. Plaintiffs have shown by a preponderance of the evidence that Apotex's proposed ANDA product meets all limitations of the Asserted Claims. (*Dynacore*, 363 F.3d at 1273). Based on the extensive testimony and evidence presented, the Court is satisfied that "it is 'more likely than not' that some quantity, however miniscule," of the claimed Form A is present in the Apotex API. (*Cephalon*, 769 F. Supp. 2d at 778).

326. Plaintiffs have met their burden of proving, by a preponderance of the evidence, that Apotex's proposed ANDA product literally infringes the Asserted Claims. (*Siemens*, 637 F.3d at 1279).

CONCLUSION

For the foregoing reasons, the Court concludes that:

1. Defendants have failed to prove by clear and convincing evidence that claims 1, 22, 23, 24, and 25 of the '993 patent are invalid.

2. The '993 patent is valid.

3. Plaintiffs have proved, by preponderance of the evidence, that Apotex's proposed ANDA product literally infringes, or contributes to the infringement of, claims 1, 22, 23, 24, and 25 of the '993 patent.

Plaintiffs are directed to submit a proposed judgment by October 6, 2017, on five days' notice to Defendants.

The Court previously issued its Findings of Fact and Conclusions of Law regarding U.S. Patent No. 5,856,336, finding it valid. (*Kowa Co., Ltd. v. Amneal Pharm., LLC*, No. 14-CV-2758 (PAC) (S.D.N.Y. Apr. 11, 2017)).

The Clerk of Court is directed to enter final judgment on all claims in 14-CV-2758 and in 14-CV-7934.

In accordance with the parties' April 26, 2017 e-mail to the Court requesting deferred briefing on attorney fees until after entry of judgment on the '993 patent, Plaintiffs shall submit a proposed deadline for filing of a motion requesting attorney fees.

Dated: New York, New York
September 19, 2017

SO ORDERED

PAUL A. CROTTY
United States District Judge