IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BONE CARE INTERNATIONAL, L.L.C. and GENZYME CORPORATION, Plaintiffs, v. ROXANE LABORATORIES, INC., SANDOZ, INC., and ANCHEN PHARMACEUTICALS, INC., Defendants.	)	C.A. No. 09-cv-285 (GMS) (Consolidated)

MEMORANDUM

I. INTRODUCTION

In this consolidated patent infringement action, plaintiffs Bone Care International, L.L.C. and Genzyme Corporation (collectively, "the plaintiffs") allege that the pharmaceutical products proposed by defendants Anchen Pharmaceuticals, Inc., Roxane Laboratories, Inc., and Sandoz, Inc. (collectively, "the defendants") infringe the asserted claim of the patent-in-suit. (D.I. 1.) The court held a five-day bench trial in this matter on November 14, 2011 through November 18, 2011. (D.I. 231-235.) Presently before the court are the parties' post-trial proposed findings of fact and conclusions of law concerning the validity of the patents-in-suit and whether the defendants' proposed products infringe the patent-in-suit. (D.I. 218; D.I. 219.)

Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire record in this case and the applicable law, the court concludes that: (1) the defendants' proposed products induce infringement of the asserted claim of the patent-in-suit and Sandoz's proposed products contributorily infringe the asserted claim; (2) the asserted claim of the patent-in-suit is not invalid as inoperative; (3) claim 7 of the '116 Patent is entitled to a 1988 priority filing date;

(4) the asserted claim of the patent-in-suit is not invalid due to obviousness; and (5) the plaintiffs' Rule 52(c) motion is granted and the defendants' Rule 52(c) motion is denied. These findings of fact and conclusions of law are set forth in further detail below.

II. FINDINGS OF FACT[1]

A. The Parties

1. Plaintiff Bone Care International, L.L.C. ("Bone Care") is a limited liability company organized and existing under the laws of the State of Delaware, having a principal place of business at 500 Kendall Street, Cambridge, Massachusetts 02142.

2. Plaintiff Genzyme Corporation ("Genzyme") is a corporation organized and existing under the laws of the Commonwealth of Massachusetts, having a principal place of business at 500 Kendall Street, Cambridge, Massachusetts 02142.

3. Defendant Anchen Pharmaceuticals, Inc. ("Anchen") is a corporation organized and existing under the laws of the State of California, having its principal place of business at 9601 Jeronimo Road, Irvine, California 92618.

4. Defendant Mylan Pharmaceuticals, Inc. ("Mylan") is a corporation organized and existing under the laws of the State of West Virginia, having a principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26505.

5. Defendant Roxane Laboratories, Inc. ("Roxane") is a corporation organized and existing under the laws of the State of Nevada, having its principal place of business at 1809 Wilson Road, Columbus, Ohio 43228.

6. Defendant Sandoz, Inc. ("Sandoz") is a corporation organized and existing under the laws of the State of Colorado, having a principal place of business at 506 Carnegie Center, Suite 400, Princeton, New Jersey 08540.

7. Anchen, Roxane, and Sandoz are collectively referred to herein as "the defendants."[2]

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[1] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 194, Ex. 1.) The court takes most of its findings of fact from the parties' uncontested facts. Where necessary, the court has overruled objections to the inclusion of these facts. The court has also reordered and renumbered some paragraphs, corrected some spelling and formatting errors, and made minor edits for the purpose of concision and clarity that it does not believe alters the meaning of the paragraphs from the Pretrial Order. Otherwise, any differences between this section and the parties' statement of uncontested facts are unintentional.

The court's findings of fact with respect to matters that were the subject of dispute between the parties are included in the Discussion and Conclusions of Law section of this opinion, preceded by the phrase "the court finds" or "the court concludes."

[2] The plaintiffs also filed suit against Mylan Pharmaceuticals, Inc. ("Mylan"), but stipulated to the dismissal of Mylan with prejudice on November 13, 2011. (D.I. 213.) The court so ordered the parties' proposed stipulation on November 14, 2011. (D.I. 214.) Consequently, the term "defendants," as used in this Memorandum

8. The court has subject matter jurisdiction, as well as personal jurisdiction over all parties.

B. Background

9. End-stage renal disease ("ESRD") is a chronic kidney disease, which requires patients suffering from it to undergo chronic dialysis or a kidney transplant in order to survive. Secondary hyperparathyroidism ("SHPT") is a disorder that is secondary to, or caused by, ESRD and involves the parathyroid glands, kidneys, and bones.

10. The parathyroid glands make and secrete parathyroid hormone ("PTH"), a hormone that signals bones to release calcium into the blood and directs the kidneys to make calcitriol, which is a form of Vitamin D. Calcitriol, among other functions, helps the body maintain normal calcium levels by stimulating the intestines to absorb dietary calcium into the bloodstream.

11. In healthy individuals, the parathyroid glands detect low levels of calcium in the blood and respond by increasing the secretion of PTH. PTH then, in turn, stimulates the release of calcium from bone into the bloodstream and signals the kidneys to produce calcitriol, which stimulates the intestines to absorb dietary calcium. With more calcium entering the bloodstream, calcium levels can return to normal and the parathyroid glands respond by decreasing PTH secretion. Thus, Vitamin D plays a critical role in signaling the parathyroid gland to stop secreting PTH.

12. In patients with ERSD, however, the kidneys cannot make sufficient amounts of calcitriol to raise blood calcium levels to normal through increased absorption of dietary calcium and, as a result, below-normal calcium levels persist. These below-normal calcium levels are known as "hypercalcemia."

13. Persistent hypercalcemia is problematic because the parathyroid glands continue to produce and secrete PTH, a problem called "hyperparathyroidism," and the resulting constant state of elevated PTH can lead to bone disease. Specifically, because the PTH acts as a constant signal for the bones to release stored calcium, bone density is reduced. In addition, it can result in the hardening of tissues such as the heart and lungs through calcification.

14. SHPT is a chronic condition and treatment of it requires not only lowering PTH levels, but also maintaining lowered PTH levels over time.

15. "PTH target range" refers to the desired level of PTH suppression, at which PTH levels are maintained. This level corresponds to PTH levels that allow for normal bone health in patients with ESRD.

16. Vitamin D compounds were used in 1988 to treat bone diseases and were employed to treat patients with ESRD and SHPT. In 1988, calcitriol and alfacalcidol were the principal drugs

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and Order, refers only to defendants Anchen Pharmaceuticals, Inc. ("Anchen"), Roxane Laboratories, Inc. ("Roxane"), and Sandoz, Inc. ("Sandoz").

available for the treatment of these two conditions. Hypercalcemia, however, was a problem associated with the use of calcitriol and alfacalcidol as of 1988.

17. There are two types of Vitamin D: Vitamin D_2 and Vitamin D_3, and there any many forms, or "analogs," of each. Calcitriol and alfacalcidol are characterized as Vitamin D_3 analogs, while doxercalciferol is a Vitamin D_2 analog.

18. 1α,25-$(OH)_2$-VitaminD_3 ("calcitriol") is the active pharmaceutical ingredient in Rocaltrol® (capsules), which was approved by the FDA in 1978 and Calcijex® (injection), which was approved by the FDA in 1986. Both Rocaltrol® and Calcijex® are currently marked in the United States.

19. 1α-OH-Vitamin D_3 ("alfacalcidol") has not been FDA approved for use in the United States, but is approved and marketed in other countries.

20. 1α-OH-Vitamin D_2, also known as "doxercalciferol," is a synthetic Vitamin D_2 analog, which was first synthesized in 1974.

21. Doxercalciferol is also known by other names, including 1-α-hydroxyvitamin D_2, 1-α-OH Vitamin D_2, 1αD_2, 1-α(OH)-D_2, 1αOHD_2, and 1-hydroxyergocalciferol.

22. Doxercalciferol is the active pharmaceutical ingredient in the Hectorol® injection and capsule products.

C. The Patent-in-Suit[3]

23. United States Patent Number 5,602,116 ("the '116 Patent"), titled "Method For Treating and Preventing Secondary Hyperparathyroidism," was issued by the United States Patent and Trademark Office (the "PTO") on February 11, 1997 and names Joyes C. Knutson, Charles W. Bishop, and Richard B. Mazess as inventors.

24. The '116 Patent and United States Patent Number 6,903,083 ("the '083 Patent") are listed in the Food and Drug Administration (the "FDA") publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") in connection with the Hectorol® injection and capsule products.

25. United States Patent Numbers 5,707,980 ("the '980 Patent") and 7,148,211 ("the '211 Patent") are listed in the Orange Book in connection with the Hectorol® injection (vial) product.

26. Plaintiff Genzyme has requested that the FDA de-list the '083 Patent and the '980 Patent from the Orange Book. (09-cv-524, D.I. 13, Ex. 1.)

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[3] The plaintiffs originally asserted claims of U.S. Patent Numbers 7,148,211 ("the '211 Patent") and 6,903,083 ("the '083 Patent") against defendant Sandoz. The plaintiffs and Sandoz settled their claims related to these patents, however, and, as a result, the court does not address either in this section.

27. U.S. Application No. 415,488 ("the '488 Application"), which issued as the '116 Patent, was filed with the PTO on April 3, 1995. The '116 Patent is related, through a chain of continuation and continuation-in-part patent applications, to U.S. Application No. 07/227,371 ("the '371 Application"), which was filed on August 2, 1988.

28. The '488 application is a continuation of U.S. Application No. 08/119,895 ("the '895 Application"), filed with the PTO on September 10, 1993, now U.S. Patent No. 5,403,831 ("the '831 Patent"), which is a continuation of U.S. Application No. 07/812,056 ("the '056 Application"), filed with the PTO on March 5, 1992, now abandoned, which is a continuation of U.S. Application No. 07/569,412 ("the '412 Application"), filed with the PTO on August 17, 1990, now U.S. Patent No. 5,104,864 ("the '864 Patent"), which is a continuation of the '371 Application, filed with the PTO on August 2, 1988, now abandoned.

29. The '116 Patent is assigned on its face to Bone Care and was later assigned to Genzyme, which owns all right, title, and interest to the '116 Patent. The '116 Patent expires on February 11, 2014.

30. Genzyme sells doxercalciferol commercially in the United States under the trade name Hectorol® pursuant to New Drug Application ("NDA") Numbers 021027 (injection) and 020862 (capsule).

31. Bone Care submitted the original NDAs for Hectorol® injection and capsule.

32. The FDA approved Hectorol® capsules on June 9, 1999 and Hectorol® injection on April 6, 2000.

33. Hectorol® is indicated "for the treatment of secondary hyperparathyroidism in patients with Stage 3 or Stage 4 chronic kidney disease" (capsules) and "for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis" (capsules and injection).

34. The FDA completed the Medical Officer's Review of NDA 20-862 for Hectorol® capsules on May 20, 1999.

35. Plaintiffs assert only claim 7 of the '116 Patent, a method-of-use claim, against all defendants in the above-captioned action.

1. The Asserted Claim

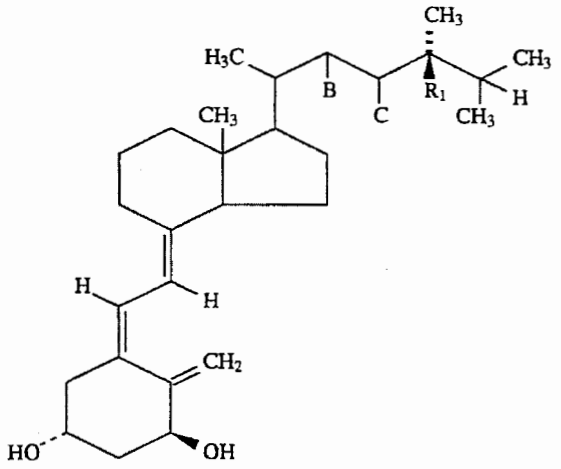
36. The plaintiffs assert claim 7 of the '116 Patent against all defendants.

37. The plaintiffs allege that the defendants' proposed products infringe claim 7 of the '116 Patent by inducement and/or will contribute to infringement of it.[4]

38. Claim 1, upon which claim 7 depends, reads:

[4] The plaintiffs do not allege direct infringement in this action. (D.I. 183, Ex. 1 at ¶ 20.)

A method of lowering or maintaining lowered serum parathyroid hormone in human patients suffering from hyperparathyroidism secondary to end stage renal disease, comprising: administering to said patients an effective amount of a vitamin D analog to lower and maintain lowered serum parathyroid hormone levels, said analog comprising formula (I):



(I)

wherein B and C are either hydrogen or a carbon-carbon double bond between C_{22} and C_{23}; and R_1 is hydrogen or hydroxyl provided that when B and C are a double bond, R_1 is hydrogen.

a dependent claim, incorporates the limitations of the claims 1 and 2, upon which it relies.

39. Claim 2, upon which claim 7 depends, reads: The method according to claim 1, wherein said analog of formula (I) is 1α,24(R)-$(OH)_2$-vitamin D_4.

40. Claim 7 reads: The method of claim 2, wherein said analog is 1α-OH-vitamin D_2.

41. The parties agree that asserted claim 7, when re-drafted to incorporate the limitations of claims 1 and 2, provides:

> A method for lowering or maintaining lowered serum parathyroid hormone in human patients suffering from hyperparathyroidism secondary to end stage renal disease, comprising: administering to said patients an effective amount of 1α-OH-vitamin D_2 to lower and maintain lowered serum parathyroid hormone levels.

(D.I. 183, Ex. 1 at 4.)

42. The parties agreed that the claim term "lowering or maintaining lowered serum parathyroid hormone" means "lowering and maintaining lowered blood concentrations of parathyroid hormone." (D.I. 55.)

43. The parties agreed that the claim term "suffering from" means "having." (*Id.*)

44. The parties agreed that the claim term "hyperparathyroidism" means "increased (i.e., above normal) secretion of PTH by the parathyroid gland." (*Id.*)

45. The parties agreed that the claim term "secondary to" means "as a result of." (*Id.*)

46. The parties agreed that the claim term "end stage renal disease" means "a disease wherein the patients' kidneys no longer function at a level necessary to sustain life and thus require chronic dialysis or kidney transplantation." (*Id.*)

47. The court held a *Markman* hearing on January 11, 2011 and, on February 3, 2011, issued an order construing the term "effective amounts of 1α-OH-vitamin D_2 to lower and maintain lowered serum parathyroid hormone levels" to mean:

> An amount of 1α-OH-vitamin D_2 sufficient to lower and maintain lowered blood concentrations of PTH with a lower incidence of hypercalcemia than would result from using 1α,25-$(OH)_2$-Vitamin D_3 or 1α-OH-vitamin D_3 to achieve the same level of PTH suppression.

(D.I. 119.)

2. The Accused Products

i. *ANDA No. 20-1518 Submitted by Anchen*

48. Anchen sent the plaintiffs a letter dated April 26, 2010 ("Anchen's Notice Letter") stating that it had submitted ANDA No. 20-1518 to the FDA under § 505(j)(2)(B)(i) and (ii) of the Federal Food, Drug and Cosmetic Act ("the Act") and Title 21 of the Code of Federal Regulations, seeking approval to engage in the commercial manufacture, use, or sale of the product described in ANDA No. 20-1518.

49. Anchen's Notice Letter stated that Anchen's ANDA contained a certification that the '116 Patent is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the drug product described in Anchen's ANDA.

50. The plaintiffs brought suit against Anchen on June 10, 2010, within forty-five days of receiving Anchen's Notice Letter, alleging infringement of the '116 Patent.

51. On August 20, 2010, Anchen answered the Complaint and filed counterclaims for declaratory judgment of non-infringement and invalidity of the '116 Patent.

52. The 30-month stay imposed by 21 U.S.C. § 355(j)(5)(B)(iii) on the FDA with respect to granting final approval of ANDA 20-1518 expires on or around October 27, 2012.

53. ANDA No. 20-1518 seeks FDA approval for the commercial manufacture, use, or sale of a generic capsule product containing doxercalciferol (the "Anchen Generic Product") prior to expiration of the '116 Patent.

ii. *ANDA No. 91-433 Submitted by Roxane*

54. Roxane sent the plaintiffs a letter dated June 17, 2009 ("Roxane's June 2009 Notice Letter") stating that it had submitted ANDA No. 91-433 to the FDA under § 505(j) of the Act seeking approval to engage in the commercial manufacture, use, or sale of the 0.5 and 2.5 mcg doxercalciferol capsule products described in ANDA No. 91-433.

55. When Roxane submitted ANDA No. 91-433 to the FDA, the '116 Patent was listed in the Electronic Orange Book for doxercalciferol 2.5 mcg capsules, but not for doxercalciferol 0.5 mcg capsules.

56. Roxane's June 2009 Notice letter stated that Roxane's ANDA contained a certification that, *inter alia*, the claims of the '116 Patent are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the drug product described in Roxane's ANDA.

57. Plaintiffs brought suit against Roxane on July 31, 2009, within forty-five days of receiving Roxane's June 2009 Notice Letter alleging infringement of the '116 Patent ("2009 Complaint").

58. Roxane sent the plaintiffs a letter dated August 21, 2009 ("Roxane's August 2009 Notice Letter") notifying the plaintiffs that Roxane was filing an amendment to ANDA No. 91-433. When Roxane submitted its ANDA amendment to the FDA, the '116 Patent was listed in the Electronic Orange Book for doxercalciferol 0.5 mcg and 2.5 mcg capsules. Roxane's ANDA amendment added a paragraph IV certification directed to the '116 Patent with respect to Roxane's 0.5 mcg doxercalciferol capsule product.

59. Roxane's August 2009 Notice Letter stated that Roxane's ANDA amendment contained a certification that the claims of the '116 Patent are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of Roxane's 0.5 mcg doxercalciferol capsules product described in Roxane's ANDA.

60. On September 16, 2009, Roxane filed an Answer to the plaintiffs' 2009 Complaint.

61. Roxane sent the plaintiffs a letter dated June 9, 2010 ("Roxane's 2010 Notice Letter") stating that it had filed with the FDA an amendment to ANDA No. 91-433 to add a 1.0 mcg capsule product. Roxane's 2010 Notice Letter also stated that Roxane's ANDA contains a paragraph IV certification directed to the '116 Patent.

62. The plaintiffs brought suit against Roxane on July 23, 2010, within forty-five days of receiving Roxane's 2010 Notice Letter, alleging infringement of the '116 Patent ("2010 Complaint").

63. On August 13, 2010, Roxane filed an Answer to the plaintiffs' 2010 Complaint.

64. The 30-month stay imposed by 21 U.S.C. § 355(j)(5)(B)(iii) on the FDA with respect to granting final approval of ANDA No. 91-433 expires on or around December 18, 2011 for Roxane's 2.5 mcg doxercalciferol capsule product and December 10, 2012 for Roxane's 1.0 mcg doxercalciferol capsules product. No 30-month stay applies to Roxane's 0.5 mcg doxercalciferol capsules product because the '116 Patent was not listed in the Orange Book for doxercalciferol 0.5 mcg capsules when Roxane submitted its ANDA for 0.5 mcg capsules.

65. ANDA No. 91-433 seeks FDA approval for the commercial manufacture, use, and sale of a generic capsule product containing doxercalciferol (the "Roxane Generic Product"), prior to the expiration of the '116 Patent.

iii. *ANDA No. 91-333 Submitted by Sandoz*

66. Sandoz sent the plaintiffs a letter dated June 1, 2009 ("Sandoz's 2009 Notice Letter") stating that it had submitted ANDA No. 91-333 to the FDA under § 505(j) of the Act seeking approval to engage in the commercial manufacture, use, or sale of the product described in ANDA No. 91-333.

67. Sandoz's 2009 Notice Letter stated that Sandoz's ANDA No. 91-333 contained a certification that, *inter alia*, the '116 Patent is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the drug product described in Sandoz's ANDA.

68. The plaintiffs brought suit against Sandoz within forty-five days of receiving Sandoz's 2009 Notice Letter alleging infringement of the '116 Patent.

69. On October 5, 2009, Sandoz filed counterclaims for declaratory judgment of, *inter alia*, non-infringement and invalidity of the '116 Patent.

70. ANDA No. 91-333 seeks FDA approval for the commercial manufacture, use, and sale of an injection generic product containing doxercalciferol, more specially in an ampule form (the "Sandoz Ampule Product") prior to the expiration of the '116 Patent.

iv. *ANDA No. 200926 Submitted by Sandoz*

71. Sandoz sent the plaintiffs a letter dated April 7, 2010 ("Sandoz's 2010 Notice Letter") stating that it had submitted ANDA No. 200926 to the FDA under § 505(j) of the Act seeking approval to engage in the commercial manufacture, use, or sale of the product described in ANDA No. 200926.

72. Sandoz's 2010 Notice Letter stated that Sandoz's ANDA contained a certification that, *inter alia*, the '116 Patent is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the drug product described in Sandoz's ANDA.

73. The plaintiffs brought suit against Sandoz on May 21, 2010, within forty-five days of receiving Sandoz's 2010 Notice Letter, alleging infringement of the '116 Patent.

74. On July 23, 2010, Sandoz answered the Complaint and filed counterclaims for declaratory judgment of non-infringement and invalidity of the '116 Patent.

75. The 30-month stay imposed by 21 U.S.C. § 355(j)(5)(B)(iii) on the FDA with respect to granting final approval of ANDA No. 200926 expires on or around October 8, 2012.

76. ANDA No. 200926 seeks FDA approval for the commercial manufacture, use, and sale of a generic product containing doxercalciferol prior to the expiration of the '116 Patent.

D. Procedural History

77. The plaintiffs filed their Complaint for patent infringement against Mylan on April 23, 2009, in what was labeled 09-cv-285 and has since been dismissed with prejudice via a stipulation the plaintiffs filed on November 13, 2011. (09-cv-285, D.I. 213.)

78. In separately-captioned actions, the plaintiffs filed complaints for patent infringement against Sandoz, 09-cv-524 and 10-cv-429,[5] on July 16, 2009 and May 12, 2010, respectively; Roxane, 09-cv-567 and 10-cv-627, on July 31, 2009 and July 23, 2010, respectively; and Anchen, 10-cv-512, on June 10, 2010.

79. The plaintiffs' actions 09-cv-285, 09-cv-524, and 09-cv-567, were consolidated on February 17, 2010, and 10-cv-512 was later consolidated with these actions on October 5, 2011.

80. The court held a five-day bench trial in this matter on November 14, 2011 through November 18, 2011. (D.I. 231-235.)

III. DISCUSSION AND CONCLUSIONS OF LAW

The court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1338, and 2201. The parties have consented to personal jurisdiction and venue in this court for the purpose of adjudicating the present dispute. (D.I. 183, Ex. 1 at 2.) After having considered the entire record in this case, the substantial evidence in the record, the parties' post-trial submissions, and the applicable law, the court concludes that: (1) the defendants' proposed products induce infringement of the asserted claim of the patent-in-suit and Sandoz's proposed

[5] The plaintiffs' claims against Sandoz in the 10-cv-429 action related to its proposed generic vial product and alleged infringement of its '211 and '083 Patents. These claims are no longer involved in the action due to stipulation of dismissal filed by the parties and, therefore, the court does not address these claims in its Memorandum and Order.

products contributorily infringe the asserted claim; (2) the asserted claim of the patent-in-suit is not invalid as inoperative; (3) claim 7 of the '116 Patent is entitled to a 1988 priority filing date; (4) the asserted claim of the patent-in-suit is not invalid due to obviousness; and (5) the plaintiffs' Rule 52(c) motion is granted and the defendants' Rule 52(c) motion is denied.[6] The court's reasoning follows.

A. Infringement

As noted, the plaintiffs contend that the defendants infringe claim 7 of the '116 Patent, which is a method claim, by inducement and/or contribute to infringement of it. (D.I. 218.) As construed by the court, claim 7 has four limitations: (1) administering an amount of doxercalciferol; (2) to patients with ESRD and SHPT; (3) sufficient to lower and maintain lowered PTH levels; (4) with a lower incidence of hypercalcemia than would result from using calcitriol or alfacalcidol to achieve the same level of PTH suppression. (D.I. 119). The plaintiffs argue that the defendants' proposed generic products "provide explicit instructions to doctors and caregivers concerning how to administer doxercalciferol to patients with ESRD and SHPT to lower and maintain lowered PTH levels." (D.I. 219 at 2.) The plaintiffs also argue that the "lowering and maintaining of lowered PTH levels" is accomplished by administering doxercalciferol because doxercalciferol "results in a lower incidence of hypercalcemia than would result from using calcitriol or alfacalcidol to achieve the same level of PTH suppression." (*Id.*) Thus, the plaintiffs contend that the defendants' proposed products meet each claim

[6] The court notes that, prior to trial, Sandoz voluntarily dismissed its inequitable conduct counterclaims. (D.I. 203.) Roxane, the only other defendant to allege inequitable conduct, did not adduce evidence in connection with this affirmative defense at trial. The court, therefore, does not address inequitable conduct in this Memorandum and Order.

limitation of claim 7 of the patent-in-suit simply through use of these products pursuant to their proposed labels.[7] (*Id.* at 28.)

Conversely, the defendants maintain that the plaintiffs have failed to prove infringement because doxercalciferol does not, in fact, result in a lower incidence of hypercalcemia than calcitriol or alfacalcidol and, therefore, the defendants' proposed products cannot infringe the claim. In support of this position, the defendants assert that: (1) the plaintiffs' expert, Dr. Langman, in reaching his conclusion that doxercalciferol causes a lower incidence of hypercalcemia, compared studies that employed different dosing patterns and, further, did not take into account such inconsistencies across clinical trials as PTH arrays, baseline PTH, or the type of dialysis used, such that his conclusions are unreliable; (2) the Wesseling-Perry study, the only study to conduct a head-to-head comparison involving doxercalciferol and calcitriol or alfacalcidol, found no differences in the incidences of hypercalcemia across these drugs; and (3) the FDA did not allow the plaintiffs to include a superiority claim in its commercial labeling indicating that doxercalciferol is safer than calcitriol/alfacalcidol because the plaintiffs did not, as required to promote a superiority claim, conduct two, adequate head-to-head clinical trials. Thus, overall the defendants assert that the plaintiffs' statistical and comparative analysis of available clinical trials, coupled with the Wesseling-Perry Study data, confirms that the defendants' proposed products do not infringe the asserted claim of the patent-in-suit. (D.I. 218 at 5-26.)

In consideration of the evidence adduced at trial and the applicable law, the court finds, for the reasons that follow, that the defendants' proposed products infringe the asserted claim of

[7] The plaintiffs note that the defendants' ANDA products copy the Hectorol® label and that the use of Hectorol® pursuant to its label meets all limitations of claim 7. In particular, the first three limitations—(1) administering of doxercalciferol, (2) to patients with ESRD and SHPT, (3) sufficient to lower and maintain lowered PTH levels—are explicitly found in the Hectorol® label and the fourth element is the result of performing the first three. (D.I. 219 at 28 (citing Tr. at 162:24-163:10 (Langman)).)

the patent-in-suit by inducement and that Sandoz's proposed product contributes to infringement of it. For the purpose of clarity, the court first addresses whether the defendants' proposed products "directly" infringe each element of the asserted claim for inducement and contributory infringement purposes. Second, the court evaluates the defendants' noninfringement argument that its produce have substantial, noninfringing uses.[8]

1. The Legal Standard

The application of a patent claim to an accused product is a fact-specific inquiry. *See Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1332 (Fed. Cir. 2001). The determination of whether an accused method infringes a claim in a patent has two steps: (1) construction of the claim to determine its meaning and scope; and (2) comparison of the properly construed claim to the method at issue. *See Tanabe Seiyaku Co. v. United States Int'l Trade Comm'n*, 109 F.3d 726, 731 (Fed. Cir. 1997) (citing *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd* 517 U.S. 370 (1996)). The patent owner has the burden of proving by a preponderance of the evidence that "every limitation of the patent claim asserted to be infringed is found in the accused [method], either literally or by equivalent." *SmithKline Diag., Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988). Per this standard, a patent owner does not have to produce "definite" proof of infringement, but must instead demonstrate that "infringement was more likely than not to have occurred." *See Warner-Lambert Co. v. Teva Pharms., USA, Inc.*, 418 F.3d 1326, 1341 n.15 (Fed. Cir. 2005) (citing *Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys., Inc.*, 261 F.3d 1329, 1336 (Fed. Cir. 2001)).

[8] The defendants raise a number of other noninfringement arguments, which the court addresses, due to the nature of these arguments, in its consideration of whether the defendants' proposed products indirectly infringe each element of the asserted claim.

In the ANDA context, 35 U.S.C. § 271(e)(2)(A) provides that it shall be an act of infringement to submit an ANDA "if the purpose of such submission is to obtain approval . . . to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent." 35 U.S.C. § 271(e)(2)(A). Here, courts are tasked with assessing what the ANDA will likely market if its application is approved—recognizing that this has not yet occurred—and, in so doing, requires examining the ANDA application and the extensive materials submitted in its support. To this end, the infringement analysis is hypothetical and requires comparing the asserted claims against the product that is likely to be sold should the FDA approve the application. *Bayer AG*, 212 F.3d at 1248-49.

More specifically, as it relates to the instant matter, 35 U.S.C. § 271(b) states that "[w]hoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). Inducement requires "actively and knowingly aiding and abetting another's direct infringement." *C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc.*, 911 F.2d 670, 675 (Fed. Cir. 1990). In the Hatch-Waxman context, "[s]tatements in a package insert that encourage infringing use of a drug product are alone sufficient to establish intent to encourage direct infringement" for purposes of inducement to infringe under 35 U.S.C. § 271(b). *See 3M Co. v. Chemque, Inc.*, 303 F.3d 1294, 1305 (Fed. Cir. 2002) (defendant who is aware of a patent and supplies a product to a customer with instructions for use, which when followed lead to infringement, has encouraged acts constituting direct infringement).

Importantly, however, mere knowledge of possible infringement does not constitute inducement. Rather, the patentee must prove that the defendant's actions "induced infringing acts and that [the defendant] knew or should have known that [its] actions would induce actual

infringement." *See Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990). In ANDA cases, the "pertinent question is whether the proposed label instructs users to perform the patented method," as well as "promote[s] or "encourage[s]" others to practice the patented method. *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (citing *Vita-Mix Corp. v. Basic Holdings, Inc.*, 581 F.3d 1317, 1329 n.2 (Fed. Cir. 2009)); *see also Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003).

With respect to contributory infringement, under 35 U.S.C. § 271(c), "[w]hoever offers to sell or sells within the United States or imports into the United States a component of patented . . . manufacture, combination or composition, or a material . . . for use in practicing a patented process, constituting a material part of the infringement, knowing the same to be especially made or especially adapted for use in infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use," shall be considered "a contributory infringer." The Federal Circuit has clarified that, to establish contributory infringement, the patent owner must prove that: (1) there is direct infringement; (2) the accused infringer had knowledge of the patent at issue; (3) the component has no substantial noninfringing uses; and (4) "the component is a material part of the invention." *See Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010); *Lucent Techs. Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1320 (Fed. Cir. 2009).

2. <u>The "Administering of Doxercalciferol" and "To Patients with ESRD and SHPT" Elements of the Asserted Claim</u>

As noted, the asserted claim of the patent-in-suit requires administration of doxercalciferol to patients with ESRD and SHPT. The defendants do not dispute that their ANDAs and proposed product labels are indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease. (D.I. 218); *see also, e.g.*, PDTX-

215; PDTX-216; PDTX-219. The defendants correctly assert that they cannot directly infringe the asserted claim of the patent-in-suit as a matter of law because they are pharmaceutical companies that do not treat ESRD or SPHT and, instead, would sell their products to wholesalers or pharmacists, "who in turn sell the drugs to patients possessing prescriptions from physicians." *See Warner-Lambert Co.*, 316 F.3d at 1363 n.7. Thus, the defendants cannot directly infringe claim 7 because they will not administer doxercalciferol to human patients for the treatment of ESRD and SHPT. The plaintiffs do not contest this point, and the court agrees.

The plaintiffs argue, however, that the defendants' proposed products induce infringement of claim 7 because the defendants' proposed product labels instruct users to perform each element of this claim of the patented method. The plaintiffs also contend that the defendants' proposed products contribute to infringement of claim 7 because their proposed labels would contribute to direct infringement of the asserted claim and the defendants' products have no substantial noninfringing uses. The defendants argued at trial and in their post-trial briefing, however, that they cannot infringe the asserted claim by inducement or contribute to infringement of it because: (1) there is no evidence that doxercalciferol results in a lower incidence of hypercalcemia and, therefore, the plaintiffs cannot prove an underlying act of direct infringement as required to prove inducement or contributory infringement; and (2) their proposed products have "substantial non-infringing uses." (D.I. 218 at 44.) Specifically, and with regard to their noninfringing use arguments, the defendants assert that their proposed doxercalciferol products can be administered: for the treatment of SHPT in chronic kidney disease patients in a manner that "lowers and maintains lowered blood concentrations of PTH *without* a lower incidence of hypercalcemia than would result from using doses of calcitriol or alfacalcidol that achieve the same level of PTH suppression" (*id.* (emphasis added)); and for the

treatment of patients with Stage 3 or 4 chronic kidney disease, which would not infringe claim 7 because claim 7 is limited to patients with Stage 5 chronic kidney disease on dialysis (*id.* at 44.)

The court highlights the defendants' arguments here because both, and the latter in particular, relate to the noninfringement arguments they advance in connection with the first two elements of claim 7. As noted, however, the court will evualte these substantial, noninfringing use arguments after assessing, in this subsection and those to follow, whether each of the defendants' proposed products labels would, on its face, induce or contribute to infringement of claim 7.

With respect to the first element of claim 7, the defendants' ANDAs call for the administration of doxercalciferol to patients with ESRD and SHPT. Specifically, the defendants' proposed labels instruct medical professionals to administer doxercalciferol. Tr. at 156:3-4 (Langman). That administration can be done by a physician, a medical professional, or the patient themselves, either orally or by injection. *Id.* at 154:21-155:1. Thus, the defendants' proposed ANDAs satisfy the first element of claim 7 for inducement and/or contributory infringement purposes because they call for the administering of doxercalciferol.

Moreover, the Hectorol® capsule and injection labels set forth that doxercalciferol should be administered "for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis." *Id.* at 156:5-12; *id.* at 589:15-25 (Morris); *see also* PDTX-107; PDTX-108. As Dr. Langman explained, patients with chronic kidney disease on dialysis suffer from ESRD and the majority of patients with ESRD also suffer from SPHT. Tr. at 156:12 (Langman). Dr. Langman also testified, and the court agrees, that the defendants' proposed labels do not differ from the Hectorol® labels in any relevant way. (D.I. 219 at 28 n.5 (citing Tr. at 155:8-18 (Langman)).) Thus, the court concludes, based on a comparison of the Hectorol®

labels to the defendants' proposed product labels, that the second element of claim 7 is also met for inducement and/or contributory infringement purposes.[9]

3. The "Sufficient to Lower and Maintain Lowered PTH Levels" and "With a Lower Incidence of Hypercalcemia Than Would Result from Using Calcitriol or Alfacalcidol To Achieve the Same Level of PTH Suppression" Elements of the Asserted Claim

With respect to the "sufficient to lower and maintain lowered PTH levels" element of claim 7, the defendants do not meaningfully dispute that their proposed generic products' labels call for administering doxercalciferol to patients with SHPT and ESRD to lower PTH into a target range and to maintain these lowered PTH levels. (D.I. 219 at 29 (citing PDTX-107; PDTX-108; Tr. at 156:20-157:9 (Langman)); D.I. 218 at 44).) The defendants' proposed labels specify a target PTH range of 150 to 300 pg/mL and, like the Hectorol® labels, report data from Frazao and Maung which indicate that, if doxercalciferol is administered according to the product label, PTH levels will be lowered and maintained.[10] (D.I. 219 at 29 (citing PDTX-107 at 2; PDTX-108 at 3; Tr. at 158:24-160:9 (Langman)).) The court, therefore, concludes that the defendants' proposed labels recite this element.

Regarding the "lower incidence of hypercalcemia than would result from using calcitriol or alfacalcidol to achieve the same level of PTH suppression" element, the plaintiffs assert that the defendants' proposed products meet this element—including Sandoz's proposed labels which does not reference a "low rate" of hypercalcemia—because, doxercalciferol, by lowering and

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[9] Again, the court notes that it makes this determination without considering whether the practice of claim 7 of the patent-in-suit results in a lower incidence of hypercalcemia than calcitriol and alfacalcidol at the same level of PTH suppression. This element is discussed in the subsections to follow.

[10] As Dr. Langman explained, the defendants' proposed product labels report, for instance, that:

> Hectorol injection treatment resulted in a clinically significant reduction (at least 30 percent) from baseline in mean PTH levels during the 12-week open label treatment period in more than 92 percent of the 70 treated patients. In fact, 37 of 79 patients, 53 percent, had plasma PTH levels within the targeted range during Weeks 10 to 12.

See PDTX-107 at 2. Dr. Langman testified that this data demonstrates that PTH levels are lowered and maintained at lower levels and that the defendants' labels reflect this data. Tr. at 158:24-160:9 (Langman).

maintaining lowered PTH levels, results in a lower incidence of hypercalcemia. To this end, the plaintiffs assert that performance of the first three elements, explicitly found in the defendants' proposed labels, results in the performance of this fourth element, such that, if the defendants' proposed products are administered pursuant to their proposed labels, the products will practice all limitations of claim 7. (*Id.* at 28 (citing Tr. at 162:24-163:10 (Langman)).) In further support of this argument, the plaintiffs note that the absence of the words "lower incidence of hypercalcemia" does not render the use of the defendants' proposed products "off label" because they are directed to the same FDA-approved medical use as the patent-at-issue. Tr. at 371:24-372:23 (Drezin).

The defendants argue, in the main, that the plaintiffs have failed to show that their products meet the "with a lower incidence of hypercalcemia than would result from using calcitriol or alfacalcidol to achieve the same level of PTH suppression" element of the asserted claim because: (1) doxercalciferol does not, in fact, cause a lower incidence of hypercalcemia and, as a result, their ANDAs do not seek approval for the method of use in claim 7; and (2) this element of claim 7 was not FDA approved and, thus, there can be no infringement.[11] (D.I. 218 at 5-26.) To this end, the defendants assert that they cannot infringe claim 7 because their proposed products do not infringe each element of the asserted claim. As noted at the outset of this infringement analysis, the defendants cite a number of propositions in support of this contention. The court examines the defendants' arguments and the plaintiffs' positions with respect to each

[11] The court notes that it includes the third and fourth elements of claim 7—(1) sufficient to lower and maintain lowered PTH levels" and (2) "with a lower incidence of hypercalcemia than would result from using calcitriol or alfacalcidol to achieve the same level of PTH suppression"—because the two elements are closely related. Specifically, and as is discussed more fully in connection with the obviousness analysis, skilled artisans at the time of the claimed invention equated toxicity, i.e., incidences of hypercalcemia, with PTH levels. Relevant literature discussed in this subsection likewise demonstrated a connection between these two elements. Thus, because lowering and maintaining lowered PTH levels is directly relevant to toxicity and, as a result, much of the available literature on and clinical studies of doxercalciferol discuss these elements in concert, the court does the same.

below. For the reasons that follow, the court concludes that the defendants' proposed product labels would, in fact, infringe this element of claim 7 for inducement and contributory infringement purposes.

a. The Methods and Dosing Strategies Employed in the Calcitriol/Alfacalcidol Studies and the Bone Care Doxercaliferol Trials Compared to Demonstrate This Element

At trial, the plaintiffs' expert, Dr. Langman, testified that, based upon his review of relevant evidence, doxercalciferol lowers and maintains lowered PTH levels with a lower incidence of hypercalcemia than would result from using calcitriol or alfacalcidol to achieve the same level of PTH suppression. The defendants assert that Dr. Langman's conclusion is misguided because he derived this finding from comparing results of disparate clinical trials and failed to recognize the influence that divergent dosing strategies have on hypercalcemia occurrence. (*Id.*) With regard to the former assertion, the defendants allege that Dr. Langman based his findings on disparate clinical trials and did not take into account or control for differences between and among these trials in rendering his conclusion. Specifically, the defendants note that Dr. Langman compared the results of the "Bone Care Doxercalciferol Trials,"[12] a collection of trials and articles conducted and authored by the inventors between 1997 and 2001, with the results of the "Calcitriol/Alfacalcidol Studies," which were conducted and reported between 1978 and 1997 and employed different clinical parameters. (*Id.* at 5 (citing Tr. at 813:6-815:8 (Holick)).) This comparison, the defendants allege, is improper because, as

[12] The "Bone Care Doxercalciferol Trials" are comprised of: Tan, A.U., Levine B.S., et al., *Effective Suppression of Parathyroid Hormone by 1alpha-hydroxyvitamin D2 in Hemodialysis Patients With Moderate to Severe Secondary Hyperparathyroidism*, KIDNEY INT'L 51:317-323 (1997) ("the Tan article"); Frazao, J.M., Elangovan, L., et al., *Intermittent Doxercalciferol (1alpha-hydroxyvitamin D(2)) Therapy for Secondary Hyperparathyroidism*, AM. J. KIDNEY DIS. 36:550-561 (2000) ("the Frazao article"); and Maung, H.M., Elangovan, L., et al., *Efficacy and Side Effects of Intermittent Intravenous and Oral Doxercalciferol (1-hydroxyvitamin D2) in Dialysis Patients With Secondary Hyperparathyroidism: A Sequential Comparison*, AM. J. KIDNEY DIS. 37:532-543 (2001).

the defendants' expert Dr. Holick explained, "one cannot draw reliable conclusions regarding the incidence of hypercalcemia by comparing [these] results because many different variables in these studies effect whether, and to what extent, hypercalcemia occurs." (*Id.* (citing Tr. at 815:12-17, 838:3-840:20 (Holick); Tr. at 225:7-228:15 (Langman)).)

In particular, the defendants assert that Dr. Langman: (1) "failed to account for differences in phosphate binders when comparing the incidence of hypercalcemia"[13] between the selected studies and relied on trials from the mid-1990s that used aluminum hydroxide binders which, it was later learned, can cause adynamic bone disease and contribute to hypercalcemia[14]; and (2) did not consider the type of PTH assay used,[15] baseline PTH levels,[16] calcium intake,[17] the definition of hypercalcemia,[18] interpatient variability,[19] or the type of dialysis the patients involved in the clinical trials were undergoing.[20]

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[13] As explained in greater detail at trial, phosphate binders are "chemical compounds ingested by ERSD patients to bind dietary phosphates and prevent their absorption into the blood." (D.I. 218 at 10 (citing Tr. at 836:7-837:20 (Holick)).) The use of phosphate binders in the treatment of kidney disease is necessary because poorly functioning kidneys do not adequately eliminate phosphates from the blood, leading to elevated phosphate levels. These elevated levels can ultimately contribute to soft tissue calcification, leading to heart disease and heart attacks. (*Id.* (citing Tr. at 835:23-836:6 (Holick)).)

[14] Dr. Holick explained that the use of phosphate binders has changed since the 1990s as physicians have learned how particular binders affect blood calcium levels. (*Id.* (citing Tr. at 837:7-24 (Holick)).) Dr. Holick testified that Dr. Langman relied on multiple trials that employed the use of aluminum hydroxide, rather than calcium carbonate, the phosphate binder employed in the Bone Care Doxercalciferol Trials. (*Id.* (citing Tr. at 837:3-6 (Holick); Tr. at 227:8-16 (Langman)).) Per Dr. Holick's testimony, calcium carbonate does not contribute to hypercalcemia like aluminum hydroxide and, in fact, the Bone Care Doxercalciferol Trials excluded participants who used aluminum hydroxide binders within twelve months of enrolling in the study. (*Id.* (citing Tr. at 836:17-837:2 (Holick); PDTX-125 at 318; PDTX-186 at 551)).)

[15] The defendants argue that, per Dr. Holick's testimony, Dr. Langram could not reliably compare the Calcitriol/Alfacalcidol Studies and the Bone Care Doxercalciferol Trials because the older N-terminal and C-terminal assays used in the former trials only measured fragments of the PTH molecules, while the latter doxercalciferol trials used a newer and more accurate PTH assay, intact assay, which detects the entire PTH molecule. (*Id.* at 12 (citing Tr. at 838:5-22 (Holick)).)

[16] Here, the defendants note that "comparing patient populations with different baseline PTH levels is unreliable" because patients that experience renal disease for a short period of time may respond differently to treatment than a patient who has had ESRD for decades. (*Id.* (citing Tr. at 818:10-17, 838:23-839:5 (Holick)).)

[17] The defendants assert that Dr. Langman erred in comparing the incidence of hypercalcemia in studies whose subjects have different levels of dietary calcium intake because Vitamin D analogs increase calcium absorption and, as a result, different dietary calcium intake can result in different levels of serum calcium and hypercalcemia. (*Id.* (citing Tr. at 818:18-21, 839:6-12 (Holick)).)

[18] Dr. Holick testified that many of the Calcitriol/Alfacalcidol Studies elevated serum calcium levels because it was thought to sufficiently lower PTH levels. Conversely, the Bone Care Doxercalciferol Trials targeted

In addition, the defendants argue that Dr. Langman's failure to consider the different dosing strategies employed in the Calcitriol/Alfacalcidol Studies and the Bone Care Doxercalciferol Trials render his conclusion unreliable. Specifically, the defendants assert, relying on Dr. Holick's testimony, that dosing strategy has a "significant influence on whether hypercalcemia is observed in a given clinical study" and has changed over the years. (*Id.* at 6 (citing Tr. at 811:23-24, 815:12-817:8, 835:3-17 (Holick)).) For instance, Dr. Holick testified that the dosing strategy used in the Calcitriol/Alfacalcidol Studies attempted to suppress PTH levels into the range found in normal, healthy individuals, by raising serum calcium to above-normal levels. (*Id.* (citing Tr. at 815:19-816:2, 816:21-817:3 (Holick)).) As a result, the dosing strategy had the effect of contributing to hypercalcemia in two ways: (1) causing oversuppression[21]; and (2) purposely elevating serum calcium levels to above normal levels. (*Id.* (citing Tr. at 818:24-819:4 (Holick)).)

To demonstrate this effect, Dr. Holick explained that the Berl study, a study on which the plaintiffs' experts relied, described a dosing strategy wherein the trial attempted to elevate serum calcium to above normal levels to decrease PTH to the level found in normal, healthy individuals. *See* PDTX-137; *see also* Tr. at 843:24-844:12 (Holick). In keeping with this

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higher PTH levels and serum calcium levels were expected to be in the normal range, such that dosing was stopped when "marked hypercalcemia" was observed. (*Id.* at 13 (citing Tr. at 817:4-8, 818:22-819:4 (Holick)).)

[19] The defendants note that "[c]omparing the incidence of hypercalcemia in different studies without accounting for interpatient variability with respect to, for example, Vitamin D status, length of time with ESRD, or patient age, can yield unreliable results because patient population characteristics can significantly impact results." (*Id.* (citing Tr. at 840:3-13 (Holick)).) For example, Dr. Holick testified that in the Andress calcitriol study upon which Dr. Langram relied as a comparator, patients were selected because they did not respond to oral calcitriol. (*Id.* (citing Tr. at 844:20-845:22 (Holick)).)

[20] The defendants assert that Dr. Langram's failure to consider the type of dialysis used in each study undermines his conclusion because "the type of dialysis may impact the incidence of hypercalcemia in a given study." (*Id.* (citing Tr. at 840:3-13 (Holick)).)

[21] Dr. Holick testified that it is now known that healthy bone function in ESRD patients requires higher PTH levels than levels required in healthy individuals. (*Id.* (citing Tr. at 830:14-18 (Holick)).) To this end, by suppressing PTH in ESRD patients to levels found in healthy individuals, the dosing strategy ultimately caused oversuppression which can result in adynamic bone disease and increase the risk of hypercalcemia. (*Id.* (citing Tr. at 821:1-23 (Holick)).)

strategy, "if serum calcium concentrations remained below 9.5 mg/dl for two consecutive measurements, the medication was increased not to exceed . . . 1.5 μg/day of [calcitriol]. If a patient developed significant hypercalcemia (serum calcium, >11.5 mg/dl), the test medication was decreased to one capsule every other day." PDTX-137 at 775. Thus, the Berl study did not decrease the dose of calcitriol unless serum calcium exceeded 11.5 mg/dl. Tr. at 818:24-819:4 (Holick). Dr. Holick testified that the modern view in dosing strategy is that a serum calcium level of ≥10.2 mg/dl is hypercalcemic.

The defendants argue that, contrary to the strategy implemented in Berl and other trials, the modern dosing strategy calls for patients to receive less Vitamin D. Specifically, the Bone Care Doxercalciferol Trials sought to achieve a PTH level in ESRD patients that is between two and nine times the upper limit of that found in healthy individuals. This strategy, the defendants assert, avoids PTH oversuppression and the resulting adynamic bone disease that increases the risk of hypercalcemia. *Id.* at 821:22-822:7. The defendants also note that the 2009 Kidney Disease Improving Global Outcomes Guidelines ("the KDIGO Guidelines"), which are evidence-based recommendations drafted by international experts addressing the treatment of various kidney diseases, recommend this modern dosing strategy and do not express a preference for doxercalciferol over calcitriol or alfacalcidol.[22] *Id.* at 823:11-12, 823:20-824:3, 825:10-20.

The defendants further highlight that, unlike the Calcitriol/Alfacalcidol Studies, the Bone Care Doxercalciferol Trials used this modern dosing strategy to avoid oversuppression and cite the Tan, Frazao, and Maung reports as evidence of this proposition. Specifically, the Tan trials

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[22] Specifically, the 2009 KDIGO Guidelines recommend that:

> In patients with [chronic kidney disease] stage 5D, we suggest maintaining iPTH levels in the range of approximately two to nine times the upper normal limit for the assay (2C). We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range.

DTX-471 at S70; *see also* Tr. at 825:21-826:5 (Holick). The defendants also note that these Guidelines "do not express a preference for any particular [V]itamin D drug or indicate that calcitriol is more hypercalcemic than doxercalciferol or any other [V]itamin D drug." (D.I. 218 at 14 (citing Tr. at 855:13-856:9 (Holick)).)

dosed doxercalciferol "to achieve a serum iPTH level within the specific target range of 130 to 250 pg/ml," which is approximately two to three times the upper limit of the PTH range found in normal, healthy individuals.[23] PDTX-125 at 318. The Tan authors noted that they selected this dosing strategy to achieve, unlike earlier trials, "a specific range of intact PTH levels that have been associated with normal or minimally increased rates of bone formation." PDTX-125 at 320. The Tan authors further explained that the targeted "iPTH range was chosen because it is most commonly associated with normal rates of bone turnover in patients with end-stage renal disease." *Id.* at 318. The defendants contend that these statements demonstrate: "(1) the importance of avoiding PTH oversuppression in ESRD patients and (2) that normal rates of bone remodeling in ESRD patients are achieved at PTH levels above the normal range for healthy individuals." (D.I. 218 at 8-9 (citing Tr. at 82:16-21, 829:19-830:2 (Holick). The defendants note that the Frazao and Maung's Bone Care Doxercalciferol Trials employed similar dosing strategies.[24] (*Id.* at 9.)

In sum, the defendants argue that Dr. Langman's conclusion that physicians using calcitriol and alfacalcidol faced a "therapeutic dilemma"[25]—i.e., that physicians had to either (1)

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[23] The Tan article noted that:

> The treatment with [doxercalciferol] was stopped in patients whose serum iPTH decreased below 130 to 150 pg/ml. When this occurred, the serum iPTH was monitored weekly until it rose above 300 pg/ml, at which time treatment with [doxcercalciferol] was resumed at a dose reduced by one step (Table 1).

PDTX-125 at 318; *see also* Tr. at 828:7-829:4 (Holick).

[24] Specifically, the Frazao article noted that: "the design of the present study and our earlier trials with [doxercalciferol] differ from clinical trials using [V]itamin D sterols to manage secondary hyperparathyroidism in that dose adjustments were targeted to reduce iPTH levels to a specific range of 150 to 300 pg/mL." PDTX-186 at 558-59. Similarly, the Maung article, published in 2001 as the third Bone Care Doxercalciferol Trial, adjusted the doxercalciferol dose to "bring plasma iPTH levels into the target range of 150 to 300 pg/mL" and discontinued dosing "if the iPTH level decreased to less than 150 pg/mL." PDTX-101 at 534; *see also* Tr. at 833:7-834:4 (Holick).

[25] Specifically, Dr. Langman described that physicians:

> Were left . . . with a therapeutic dilemma. I think that is a term that is very apt. We were faced in a way with a double-edged sword with the use of the prior art. If we effectively treated the secondary hyperparathyroidism and lowered PTH, we end up producing hypercalcemia. And . . . as we reduce the calcitriol to get rid of the hypercalcemia, we have lost control of the secondary

raise serum calcium levels to dangerously high levels and increase the risk of hypercalcemia, or (2) lower PTH less and increase the risk of bone problems resulting from SHPT—is unreliable. Specifically, the defendants assert that Dr. Langman's finding that doxercalciferol results in a lower incidence of hypercalcemia should be attributed to differences in the methods and dosing strategies employed in the clinical trials he compared and subsequent improved treatment protocols, rather than to any specific attribute or characteristic of the Vitamin D analog used. (*Id.* at 10.)

The plaintiffs, however, dispute each of the defendants' arguments and assert that they have proved, by a preponderance of the evidence, that the defendants' proposed products infringe this element of claim 7. First, and with respect to the defendants' contention that Dr. Langman's conclusions are unreliable because he did not account for variations in trial parameters, the plaintiffs clarify that Dr. Langman "did not calculate and compare incidences of hypercalcemia associated with doxercalciferol and the prior art" because this comparison was not relevant or required. (D.I. 219 at 19.) Instead, Dr. Langman presented evidence demonstrating that, "irrespective of the specific methodology [used], calcitriol and alfacalcidol have never been associated with the lowering and maintaining of lowered PTH levels without concomitant hypercalcemia, whereas doxcercalciferol has." (*Id.* (citing Tr. at 124:11-125:9 (Langman)).) To this end, Dr. Langman's conclusions were not directed to comparing hypercalcemia incidences of doxercalciferol versus calcitriol or alfacalcidol, but rather were derived from his assessment that, across all relevant prior art references, calcitriol and alfacalcidol have not been shown capable of lowering and maintaining lowered PTH levels.

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hyperparathyroidism. So we are doing a ying-yang approach to the care of the patient. So we are unable to lower and maintain lowered levels of PTH with the prior art because of this finding.

See Tr. at 87:11-22 (Langman).

In addition, the plaintiffs assert that even if Dr. Langman's examination were based on such a comparative assessment of hypercalcemia, Dr. Holick overstated the "interstudy variability" between and among the Calcitriol/Alfacalcidol Studies and the Bone Care Doxercalciferol Trials. (*Id.*) Specifically, the plaintiffs highlight that the Quarles, Malberti, and Gonella studies Dr. Langman evaluated, and that were included in the Calcitriol/Alfacalcidol Studies, employed the same type of "(a) phosphate binder (calcium-based), (b) dialysis (hemodialysis), and (c) PTH assay (intact) as those used in the Bone Care studies." (*Id.* (citing PDTX-162 at 705; PDTX-186 at 55; PDTX-160 at 350-51; PDTX-159 at 1711; PDTX-125 at 318; Tr. at 96:20-97:24, 111:25-122:12 (Langman)).) Moreover, Dr. Holick did not cite any evidence that the studies evaluated differed in any of the other ways he suggested. (*Id.*)

The plaintiffs also challenged Dr. Holick's statement that calcitriol failed to lower and maintain lowered PTH levels in certain studies Dr. Langman cited because those patients had severe SHPT (high baseline PTH levels) and were, as a result, untreatable. (*Id.* (citing Tr. at 838:23-839:5, 844:21-845:22 (Holick)).) Specifically, the plaintiffs note that Malberti concluded in 1996 that "the refactoriness to calcitriol has been related to the development of [] hypercalcemia that requires a reduction in calcitriol dose which limits the efficacy of treatment." (*Id.* (citing PDTX-162 at 704; Tr. at 96:23-97:17 (Langman)).) Thus, the plaintiffs assert that Malberti's conclusion that such patients could not be treated confirms Dr. Langman's assessment, discussed in the Bone Care Doxercalciferol Trials, that while calcitriol is unable to lower and maintain lowered PTH levels, doxercalciferol "effectively and safely suppressed plasma iPHT levels, even in patients with very severe SHPT." (*Id.* (citing PDTX-186 at 558; Tr. at 121:22-122:2 (Langman)).)

Finally, the plaintiffs note that many of the variables Dr. Holick discussed would actually be expected to increase the incidence of hypercalcemia. (*Id.*) In particular, Dr. Holick testified that aluminum phosphate binders, which were used in studies before 1988, were associated with higher incidences of hypercalcemia. (*Id.* (citing Tr. at 836:7-837:6 (Holick)).) However, the plaintiffs argue that calcium-based phosphate binders, which were used in place of aluminum phosphate binders in studies like the Bone Care Doxercalciferol Trials, actually increased the risk of hypercalcemia. Specifically, and as Dr. Slatopolsky noted in his 1990 '789 Patent:

> Hypercalcemia is compounded by the fact that calcium carbonate is currently the preferred compound for binding of intestinal phosphorous. . . . Unfortunately, the simultaneous administration of large doses of calcium carbonate and calcitriol frequently induces sever hypercalcemia, thus precluding the administration of therapeutic doses of calcitriol.

PDTX-142 at col. 1, ll. 62 – col. 2, ll. 1-5; *see also* Tr. at 93:5-96:7 (Langman). Gonnella likewise questioned, in 1995, whether calcitriol should be used in conjunction with calcium-based phosphate binders due to the increased risk of hypercalcemia. (D.I. 219 at 21 (citing PDTX-160 at 352; Tr. at 96:8-19 (Langman)).) The KDIGO Guidelines similarly listed hypercalcemia as a side effect of calcium-based phosphate binders. (*Id.* (citing DTX-471 at S52).) Nevertheless, as Tan reported, doxercalciferol is "safe despite exclusive use of calcium-based phosphate binders." (*Id.* (citing PDTX-125 at 137; Tr. at 111:16-21 (Langman)).) In view of the foregoing, the court finds that Dr. Langman's conclusions are not undermined by any failure to consider interstudy variability.

The court is also not persuaded by Dr. Holick's argument that the lower incidence of hypercalcemia reported in the Bone Care Doxercalciferol Trials should be attributed to its "modern" dosing strategy, rather than to attributes of the Vitamin D analog. As noted, Dr. Holick testified that the "old" dosing strategy used in the Calcitriol/Alfacalcidol Studies

suppressed PTH levels to within the normal range of healthy individuals—thus, oversuppressing PTH—regardless of hypercalcemia, while the "modern" dosing strategy in the Bone Care Doxercalciferol Trials lowered PTH into a target range higher than normal to avoid oversuppression. Tr. at 815:12-816:20 (Holick). However, as the plaintiffs correctly note, Dr. Holick failed to present a single publication to support his conclusions that: "(1) calcitriol and alfacalcidol were actually dosed to suppress PTH into the normal range for healthy individuals in the clinical studies cited by Dr. Langman; or (2) that dosing calcitriol and alfacalcidol to a given PTH target range lowers the incidence of hypercalcemia." (D.I. 219 at 17 (citing Tr. at 886:16-887:19 (Holick)).)

In fact, the two clinical trials that Dr. Holick referenced in his testimony to support his dosing strategy argument, the Berl and Andress studies, reflect that PTH should not be lowered to the PTH range appropriate for normal, healthy individuals with ESRD and SHPT patients. (*Id.* (citing PDTX-127; PDTX-155).) In particular, the 1978 Berl study recognized that levels of PTH above the normal PTH range for healthy individuals was beneficial for patients with ESRD and the 1989 Andress study was cited in Wesseling-Perry as the basis for their PTH range of 300-400 pg/mL. (*Id.* (citing Tr. at 110:8-14, 88:17-20, 143:20-144:14 (Langman); PDTX-204 at G00530798).) Dr. Holick also testified that he changed his own dosing strategy from trying, in the early 1980s, to "get the PTH into [the] normal range," to attempting to "get [his patients'] PTH levels within that targeted range" by the "mid-to-late[] 1980s" to avoid hypercalcemia. (*Id.* (Tr. at 842:8-22 (Holick)).)

Moreover, Dr. Langman highlighted two studies, not addressed by Dr. Holick, which demonstrated that calcitriol and alfacalcidol are not effective when dosed to avoid "PTH oversuppression" and hypercalcemia. Specifically, the Quarles and Malberti studies both

targeted a PTH range of three to four times the upper limit of normal while attempting to maintain calcium in the normal range. Both were unable to achieve the desired levels, despite the fact that these were the same levels targeted in the Bone Care Doxercalciferol Trials, wherein doxercalciferol proved successful.[26] (*Id.* at 17-18 (citing PDTX-159 at 1717-18; PDTX-162 at 706-07; Tr. at 89:10-23, 90:25-92:19, 96:23-24, 97:18-99:1, 110:15-19 (Langman)).)

Finally, the plaintiffs challenged, via Dr. Langman's testimony, the validity of Dr. Holick's statement that the Tan authors confirmed his dosing strategy argument by reporting that their study "differs from earlier trials with [V]itamin D sterols in that treatment was adjusted to achieve a specific range of intact PTH levels." Specifically, Dr. Langman explained, in testimony the court finds persuasive, that this statement in the Tan study does not indicate that the authors were implementing a new dosing strategy. Rather, the statement highlights that the Tan trial was the first to "achieve" such a targeted range—an accomplishment that distinguished doxercalciferol from the prior art. (*Id.* at 19 (citing Tr. at 110:20-111:13 (Langman)).)

In consideration of the evidence presented, the court finds that Dr. Langman's conclusion that doxercalciferol results in a lower incidence of hypercalcemia using calcitriol or alfacalcidol to achieve the same level of PTH suppression is not undermined by failure to account for interstudy variability or the dosing strategies employed.

b. The Need for a Head-To-Head Clinical Study of Doxercalciferol and Calcitriol/Alfacalcidol & The Wesseling-Perry Study

[26] Specifically, the Quarles study reported no change in PTH in over half of its patients and Malberti reported that PTH increased or remained unchanged in fourteen of the thirty-five patients and observed persistent hypercalcemia in six patients despite reduction in calcitriol doses to only 2 µg per week. (D.I. 219 at 18 (citing PDTX-159 at 1717-18; PDTX-162 at 706-07; Tr. at 98:15-99:1 (Langman)).) Conversely, in the Frazao study, doxercalciferol was reported to decrease PTH by more than fifty-percent in ninety-two percent of patients even though calcium levels remained within the normal range throughout the study. In addition, Frazao reported that there were no increases in hypercalcemia when doxercalciferol was increased to a 60 µg per week dose. (*Id.* (citing PDTX-196 at 270-71; Tr. at 126:11-21 (Langman)).)

The defendants next assert that the evidence shows that a head-to-head study is required to demonstrate that doxercalciferol results in fewer episodes of hypercalcemia than calcitriol or alfacalcidol, and that the only such head-to-head study, the Wesseling-Perry Study, found that doxercalciferol does not result in a lower incidence of hypercalcemia than calcitriol or alfacalcidol when dosed to achieve the same level of PTH suppression. (*Id.* at 3.) The court addresses each argument separately below.

i. *The Need for a Head-to-Head Study & Conclusions as To Doxercalciferol's Ability to Lower and Maintain Lowered PTH Levels With a Lower Incidence of Hypercalcemia*

In support of their argument that a head-to-head study of doxercalciferol and calcitriol or alfacalcidol is needed to establish this element of claim 7, the defendants assert that its expert, Dr. Holick, the '116 Patent inventors, the plaintiffs' expert, Dr. Langman, the KDIGO Guidelines, peer-reviewed literature, and the FDA, all recognized the need for such a head-to-head comparison in order to "reliably determine whether there is a difference with the incidence of hypercalcemia" that is not attributable to trial parameter variations or dosing strategies, among other factors. (*Id.* at 15 (citing Tr. at 846:11-847:4, 846:11-847:4 (Holick)).)

Regarding the '116 Patent inventors specifically, the defendants note that both the Tan and Frazao articles stated that it is necessary to conduct a head-to-head comparison of doxercalciferol and calcitriol or alfacalcidol to determine if doxercalciferol is, in fact, safer. (*Id.*) For instance, the Tan article noted that "future studies comparing the efficacy and safety of [doxercalciferol] with either calcitriol or [alfacalcidol] are clearly warranted,"[27] and the Frazao article stated that "[w]hether [doxercalciferol] will be less calcemic than [alfacalcidol] or calcitriol in clinical trials in patients must await studies with direct comparisons of these

[27] *See* PDTX-125 at 322.

sterols."[28] The defendants also cite to the Frazao article's statements that "[h]ow [doxercalciferol] compares with calcitriol, alfacalcidol[], or paricalcitol in terms of efficacy and safety cannot be answered without direct comparisons with these sterols" and that "[i]n the future, studies that directly compare [doxercalciferol] with other [V]itamin D sterols will be needed to provide proof of relative safety." *See* PDTX-186 at 559.

The defendants also cite a book chapter Dr. Langman coauthored, wherein, the defendants assert, he acknowledged that a head-to-head study was needed by reporting that:

> The clinical effectiveness of doxercalciferol has been demonstrated with both intravenous and oral administration in hemodialysis, and by oral administration in [chronic kidney disease] Stages 3 and 4. However, the claim of lower calcemic action compared to calcitriol has not been demonstrated definitely.

See DTX-95 at 127. Likewise, the defendants note that the KDIGO Guidelines recommended further clinical investigation of doxercalciferol by posing the question: "In a prospective [randomized clinical trial] to assess the current dialysis population, do laboratory outcomes differ for newer [V]itamin D analogs vs. doses of calcitriol or alfacalcidol, which are equipotent for PTH lowering?" DTX-471 at S82. The defendants contend that this statement demonstrates that, as of 2009 when these Guidelines were written, the "question of whether doxercalciferol causes less hypercalcemia . . . when dosed to achieve the same level of PTH suppression was an open question." (D.I. 218 at 16 (citing Tr. at 853:11-854:21 (Holick)).) Additionally, the defendants cite two peer-reviewed articles, the Dennis article and the Palmer article, both of which called for head-to-head studies between doxercalciferol and calcitriol or alfacalcidol to "differentiate its place in therapy,"[29] "clearly distinguish if it provides "a clear advantage in

[28] *See* PDTX-186 at 557.

[29] *See* PDTX-357 at 1955. The Dennis article, "Doxercalciferol Treatment of Secondary Hyperparathyroidism," published in the Annals of Pharmacology, states that doxercalciferol "has not demonstrated a lower incidence of hypercalcemia and/or hyperphosphatemia in relation to other vitamin D therapies," and that "comparative randomized studies are needed to differentiate its place in therapy." The defendants argue that this

relation to the occurrence of hypercalcemia,"[30] and definitively "assess whether newer vitamin D agents [such as doxercalciferol] have similar or different effects . . . than established compounds."[31] (*Id.* at 17-18 (citing PDTX-357; DTX-479)).)

Finally, the defendants note that the FDA requires patentees asserting superiority claims, i.e., claims indicating that one compound is safer than another, to provide "substantial evidence" of this superiority "in the form of two adequate and well controlled head-to-head studies which compare the two drugs." (*Id.* at 18-19 (citing Tr. at 363:8-12 (Drezin); Tr. at 572:17-21 (Morris)).) The defendants' expert regarding FDA and Division of Drug and Marketing, Advertising, and Communications ("DDMAC")[32] matters, Dr. Morris, testified that a claim comparing "safety or efficacy is referred to as a comparative claim" and a "claim that one drug is safer or more effective than another drug is referred to as a superiority claim." (*Id.* at 18 (citing Tr. at 572:7-16 (Morris); Tr. at 363:13-15 (Drezin)).)

Both parties' experts testified that the plaintiffs originally included language in their promotional materials that would be considered a superiority claim. The DDMAC reviewed Bone Care's promotional materials and, on August 24, 1999, issued an advisory opinion finding that the inclusion of a superiority claim "would be misleading because it is an unsubstantiated superiority claim." *See* PDTX-92 at G00044194; *see also* Tr. at 362:7-363:4 (Drezin). Specifically, while the FDA recognized that the clinical studies relied upon in the Hectorol® NDA showed lower rates of hypercalcemia and hyperphosphatemia than published data on

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shows that doxercalciferol's alleged "lower incidence of hypercalcemia" was not established by November 2006 when this article was published.

[30] *See supra* note 29.

[31] The defendants note that the Palmer article, "KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder," is a meta-analysis that combines data from multiple studies and attempts to account for differences in interstudy variables. (D.I. 218 at 17.) Palmer ultimately concluded that the lack of head-to-head trials "makes it difficult to assess" whether newer Vitamin D analogs have "similar or different effects" than older Vitamin D analogs. *See* DTX-471 at 849.

[32] The DDMAC is the division of the FDA that is charged with reviewing and regulating prescription drug advertising. Tr. at 356:14-357:3 (Drezin); *see also id.* at 570:4-6 (Morris).

calcitriol treatment, Bone Care could not, without conducting two adequate head-to-head clinical trials, assert superiority. *See* DTX-553; *see also* Tr. at 600:20-23, 601:12-603:4 (Morris). The DDMAC also sent a letter to Bone Care in September 2000 indicating that a claim that "Hectorol is equally efficacious but 5-10 fold less calcemic than calcitriol" was misleading because it did not meet the superiority claim substantiation requirements. *See* DTX-45 at G00044197. As a result of these advisory opinions, Bone Care deleted its superiority claim from its Hectorol® promotional materials and, as a result, there is no information on Hectorol®'s capsule or injection product labels detailing the incidence of hypercalemia in patients using doxercalciferol as compared to calcitriol or alfacalcidol. *See* PDTX-93; PDTX-107; PDTX-108; Tr. at 576:4-8, 577:2-5 (Morris); Tr. at 386:10-387:1 (Drezin). Thus, the defendants argue that the plaintiffs did not have sufficient head-to-head studies to assert a lower incidence of hypercalcemia than calcitriol and alfacalcidol at the same level of PTH suppression and that, because such a study was needed, the FDA did not approve claim 7 for a comparative or superiority claim that it has a lower incidence of hypercalcemia. (D.I. 218 at 38.)

The plaintiffs dispute each of the defendants' arguments. First, the plaintiffs assert that while head-to-head studies are needed to support an FDA superiority claim, they are not required, as Dr. Holick opined, to demonstrate that doxercalciferol lowers and maintains lowered PTH levels with a lower incidence of hypercalcemia than calcitriol or alfacalcidol at the same level of PTH suppression. (D.I. 219 at 21-27.) In support of this contention, the plaintiffs assert that the defendants have selectively quoted the inventors, Dr. Langram, and the KDIGO Guidelines, among others, and, in so doing, misrepresent what is required to demonstrate what was understood about these elements. (*Id.*) As an outset matter, the plaintiffs note that Dr. Langman testified that physicians commonly make medical judgments, based on information

available at the time, about whether one drug is "in some way better than another" even in the absence of head-to-head data. (*Id.* at 21 (citing Tr. at 125:10-20 (Langman)).) Specifically, Dr. Langman testified that such medical judgments are necessary because "[i]f I were waiting for that one or two head-to-head studies, I would really be paralyzed for the care of that patient. That's not what physicians do. We make decisions all the time using available evidence and weighing the risks and benefits." Tr. at 125:10-20 (Langman). Likewise, the defendants' expert, Dr. Charytan, a nephrologist, testified that he has also made medical judgments in selecting which drug to use without the benefit of head-to-head studies. (D.I. 219 at 21 (citing Tr. at 469:25-470:23-471:4 (Charytan)).)

Moreover, the plaintiffs note, as an example of the defendants' misrepresentation of Tan and Frazao's statements, that these inventors actually explained that head-to-head studies are needed only to meet the standard of "absolute certainty" or "95% confidence." (*Id.* (citing Tr. at 733:15-25 (Bishop)).) In consideration of both parties' arguments and the testimony adduced at trial, the court finds the plaintiffs' assertion that a head-to-head study is not required to assess and make conclusions regarding the benefits and/or risks of a particular drug persuasive. Specifically, the court finds credible Dr. Langman's testimony that medical professionals and physicians do not wait for head-to-head studies to be conducted before evaluating whether a drug would prove beneficial in treatment, particularly if information in the available literature speaks to such advantages. Consequently, the court agrees with the plaintiffs and concludes that head-to-head studies, though useful in demonstrating "absolutely certainty," are not required.

Second, the plaintiffs argue that, having established that a head-to-head trial was not needed, the information available on doxercaliferol demonstrated that the Vitamin D analog was effective in lowering and maintaining lowered PTH levels with a lower incidence of

hypercalcemia than calcitriol or alfacalcidol at the same level of PTH suppression. Specifically, Dr. Bishop, one of the inventors of the claimed invention, testified that, even in the absence of a head-to-head study, Tan and Frazao's data convinced him and Bone Care that they could run a successful head-to-head study against calcitriol demonstrating doxercalciferol's lower incidence of hypercalcemia. (*Id.*) The plaintiffs point out that Tan, Frazao, and Maung reached similar conclusions. In particular, Tan outlined that "[c]onventional therapy with daily oral calcitriol is limited by the occurrence of hypercalcemia" and that doxercalciferol "is highly effective in lowering [PTH] levels with a very low incidence of hypercalcemia." (*Id.* at 23 (citing PDTX-125 at 317; Tr. at 111:14-21 (Langman)).) Similarly, the Frazao authors, including Dr. Bishop, reported:

> [T]he sustained administration of large doses of doxercalciferol effectively and safely suppressed plasma iPTH levels even in patients with very severe secondary hyperparathyroidism. Importantly, there was no increase in the number of hypercalcemic episodes when the dosage of doxercalciferol was increased to 60 micrograms per week; such observations provide evidence of a favorable safety profile for [doxercalciferol].

(*Id.* (citing PDTX-186 at 558; Tr. at 121:22-122:7, 169:1-23 (Langman)).) Indeed, as the plaintiffs note, even the defendants' expert, Dr. Holick, testified that these reported results were "favorable." (*Id.* (citing Tr. at 848:2-17, 905:18-19, 906:6-15 (Holick)).)

Dr. Bishop also testified that patient data from the H-106 gave him confidence that doxercalciferol would outperform calcitriol with respect to incidences of hypercalcemia at the same level of PTH suppression. (*Id.* at 24 (citing Tr. 732:2-733:25 (Bishop); PDTX-125 at 322).) Specifically, Dr. Bishop explained that the H-106 patients treated with calcitriol had average PTH levels of 502 pg/mL, while, following twelve weeks of treatment with doxercalciferol, those same patients had their PTH levels lowered to 292 pg/mL. (*Id.* (citing Tr. at 734:23-738:12, 748:17-18 (Bishop); PDTX-400).) Additionally, the patient results indicated

that even those individuals thought untreatable with calcitriol had their PTH levels lowered and maintained with doxercalciferol. (*Id.* (citing Tr. at 738:13-740:25 (Bishop)).) Consequently, Dr. Bishop concluded that doxercalciferol would perform better than calcitriol in a head-to-head study and that such a study was "clearly warranted." (*Id.* (citing Tr. at 732:2-733:25 (Bishop)).)

Moreover, the plaintiffs cite to a number of other articles and clinical studies reported in the 1988 and post-1988 literature indicating that calcitriol and alfacalcidol are ineffective and that doxercalciferol compared favorably to both, including: (1) Quarles' study in 1994, which concluded that "intermittent intensive calcitriol therapy, regardless of administration route, is poorly tolerated . . . and has limited ability to achieve sustained serum PTH reductions" (PDTX-159 at 1710); (2) Bone Care's first human clinical trial, H-101, which tested doxercalciferol in postmenopausal osteoporosis women under the same study design and with the same patient population as a calcitriol trial, and demonstrated that doxercalciferol caused less hypercalcemia than calcitriol, even at high doses (PDTX-177 at G00485980, G00486222)[33]; (3) the 1994 Bone Care H-106 trial, which reported, in Tan, that PTH levels fell in all patients and reached the PTH target range in twenty-one out of twenty-four patients, despite only "modest increments" in serum calcium (PDTX-125 at 319-21); (4) the 2000 Frazao publication of Bone Care's clinical trial, which reported that eighty-three percent of their doxercalciferol-treated patients had PTH levels lowered to within the target PTH range in less than six weeks, while the average calcium

[33] Dr. Bishop's testified that the H-101 trial patient group, postmenopausal women with osteoporosis, involve similar low levels of calcitriol and cooresponding elevated levels of PTH as those exhibited in SHPT. (D.I. 219 at 7 (citing Tr. at 713:9-715:10 (Bishop)).) H-101 was intended to determine the dose of doxercalciferol at which side effects (primarily hypercalcemia) occur, as well as compare doxercalciferol to calcitriol by using the same study design, principal investigator, clinical site, and patient population as an earlier calcitriol study. (*Id.* (citing Tr. at 712:2-713:8 (Bishop)).) The study was conducted dosing patients at 5 ug per day and did not result in side effects, which exceeded the inventors' expectations. As a result, Bone Care sought and received FDA permission to administer even higher doses of 8 and 10 ug per day. (*Id.* (citing Tr. at 717:22-720:7 (Bishop)).). To receive approval, Bone Care presented the FDA with a comparison of the results it obtained with doxercalciferol and results obtained from the earlier calcitriol study. This comparison demonstrated that doxercalciferol was less likely to cause hypercalcemia than calcitriol and the FDA approved the higher doses. (*Id.* (citing Tr. at 720:8-722:13 (Bishop)).)

levels remained in the normal range (PDTX-186 at 553-54); and (5) the 2001 Maung publication detailing the results of another Bone Care clinical trial wherein doxercalciferol was reported to lower and maintain lowered PTH levels with a very low incidence of hypercalcemia (PDTX-101 at 536-37).

The plaintiffs also cite nine articles in the literature written by authors who, relying on the same Bone Care studies Dr. Langman examined in formulating his opinion, all concluded that treatment with doxercalciferol lowers and maintains lowered PTH levels with a lower incidence of hypercalcemia than calcitriol or alfacalcidol when doses to achieve the same level of PTH suppression.[34] The plaintiffs argue that the articles and trials discussed in this subsection, read in conjunction with the cited studies, demonstrate that the literature did, in fact, confirm Dr. Langman's conclusion.[35]

Finally, and in response to the defendants' assertions that Dr. Langman's book chapter and the KDIGO Guidelines show that doxercalciferol was not recognized for its purported benefits, the plaintiffs argue that the defendants again mischaracterize these sources. Dr. Langman testified that while he and his coauthors did state that "the claim of lower calcemic

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[34] *See* PDTX-130 at 1234 (noting that doxercalciferol "effectively decrease[s] PTH with a decreased incidence of hypercalcemia"); PDTX-190 at S525 (finding "markedly less potency to induce hypercalcemia"); PDTX-192 at S55 (noting "less hypercalcemic episodes prior to attaining target PTH levels"); PDTX-193 at 46 (stating that doxercalciferol has "[r]educed PTH levels effectively" and "produced less hypercalcemia"); PDTX-194 at 291 (noting "less toxicity than calcitriol"); PDTX-195 at 293 (noting "fewer hypercalcemic effects"); PDTX-196 at 271 (noting that doxercalciferol "selectively depress[es] the parathyroid gland with a lower incidence of hypercalcemia when compared to current agents"); PTDX-197 at 120-21 (concluding that doxercalciferol is "able to lower PTH more effectively with a lower incidence of hypercalcemia than calcitriol"); PDTX-198 at 580 ("cause[s] less hypercalcemia and hyperphosphatemia than traditional calcitriol").

[35] In support of this conclusion, the plaintiffs also challenge the defendants' interpretation of the Palmer and Dennis articles. Specifically, the plaintiffs charge that the defendants selectively quoted from these articles and that a full reading of each shows that: (1) Palmer "confirms the existence of a therapeutic dilemma with 'established' vitamin D compounds (calcitriol and alfacalcidol) by noting that these compounds are associated with increased risk of hypercalcemia, but not a statistically significant reduction in PTH levels" (D.I. 219 at 24 (citing DTX-479 at 842; Tr. at 248:5-17 (Langman)); (2) Palmer did not "specifically analyze the incidence of hypercalcemia as between doxercalciferol, calcitriol, and alfacalcidol" (*id.* (citing Tr. at 246:18-247:24)); and (3) Dennis' comparison of doxercalciferol and calcitriol was "economic in nature and, nevertheless, resulted in the recommendation that '[d]oxercalciferol should be maintained as a formulary alternative for patients unresponsive to or intolerant of calcitriol'" (*id.* (citing PDTX-357 at 1962; Tr. at 128:23-130:24 (Langman)).

action [of doxercalciferol] compared to calcitriol has not been demonstrated definitely" in the book chapter the defendants' cited, this statement was made less than five years after Hectorol®'s launch and before there was "accumulated experience by practicing and treating physicians," other than the authors, "to have real-world experience to back up the published literature." Tr. at 254:14-21 (Langman). In the absence of this accumulated experience, Dr. Langman testified that he did not want to "definitely" conclude that there was a lower incidence of hypercalcemia, though he believed this to be the case. *Id.* Further, Dr. Langman testified that the defendants' reference to this statement, in isolation, fails to recognize that the chapter also: (1) noted that the recent introduction of novel drugs, including active Vitamin D analogs such as doxercalciferol "should lead to improved clinical management of [renal osteodystrophy]"; and (2) contained several algorithms, reproduced from the KDIGO guidelines, instructing physicians to change to a "less calcemic" (e.g., doxercalciferol) analog when PTH levels remain high with the use of calcitriol. (*Id.* at 26 (citing DPTX-364A at 131; Tr. at 257:6-258:2 (Langman)).)

The plaintiffs also assert that the defendants' argument regarding the KDIGO Guideline's failure to suggest the use of doxercalciferol because it did not have a head-to-head study misrepresents the scope and purpose of those Guidelines. (*Id.*) Specifically, the plaintiffs note that the KDIGO Guidelines aim to recommend "uniform protocols" for the treatment of kidney disease "worldwide." Thus, because doxercalciferol is only available in the United States and Canada, the plaintiffs argue that the absence of a KDIGO Guideline recommendation for the use of doxercalciferol cannot be viewed as a judgment on its ability to lower and maintain lowered PTH levels with a lower incidence of hypercalcemia. (*Id.* (citing PDTX-364A at foreword; Tr. at 255:4-256:22, 259:17-261:7 (Langman)).) Notably, Dr. Holick even agreed that the KDIGO

Guidelines "[don't] say, one way or the other," whether doxercalciferol results in lower incidences of hypercalcemia. (*Id.* at 26 n.22 (citing Tr. at 854:11-21 (Holick)).)

Based on its review of the inventors' statements, the Bone Care Doxercalciferol Trials' results, peer-reviewed literature cited by both parties, among other sources, and the expert testimony presented, the court concludes that the collective knowledge about doxercalciferol, calcitriol, and alfacalcidol demonstrated that: (1) calcitriol and alfacalcidol were associated with hypercalcemia, even at low doses; (2) doxercalciferol was able to lower and maintain lowered PTH levels; and (3) doxercalciferol evidenced a lower incidence of hypercalcemia than calcitriol or alfacalcidol at the same level of PTH suppression.

The court notes that this finding is not undermined by the defendants' argument that the FDA denied Hectorol®'s superiority claim and, therefore, did not approve its method of use with respect to these elements. (*Id.* at 26; D.I. 218 at 38.) Specifically, the FDA's approval of an NDA includes the approval of drug labeling. (*Id.* (citing Tr. at 358:13-19 (Drezin)).) The plaintiffs note that the FDA-approved labeling for Hectorol® explicitly states that the incidence of hypercalcemia is "low," referencing "four adequate and well-controlled studies." (*Id.* (citing PDTX-108; Tr. at 357:22-358:12 (Drezin); Tr. at 593:17-595:4 (Morris); Tr. at 161:15-25 (Langman)).) The FDA-approved labeling for the Hectorol® injection also detailed the incidence of hypercalcemia as approximately once every two years, which is low. (*Id.* at 27 (citing PDT-108; Tr. at 359:1-13 (Drezin); Tr. at 161:3-14 (Langman)).) In accordance with its FDA-approved labels, Genzyme's promotional materials also advertise Hectorol® products as having a "low" incidence of hypercalcemia. (*Id.* (citing PDTX-94; PDTX-100; Tr. at 370:19-371:3 (Drezin)).)

The plaintiffs' expert, Dr. Drezin, and the defendants' expert, Dr. Morris, both agreed that the FDA would not have approved the use of the term "low" in Hectorol®'s label if it believed this statement to be misleading. (*Id.* at 26 (citing Tr. at 593:17-594:4 (Morris); PDTX-108)).) Moreover, the plaintiffs cite to a statement of Dr. Sobel, who served as director of the Division of Metabolic and Endocrine Drug Products at the FDA when Hectorol® capsules were approved in 1999. Dr. Sobel explained, with regard to Hectorol®, that:

> In four controlled clinical studies the incidence of hypercalcemia and hyperphosphatemia increased during Hectorol therapy. The incidence rates of hypercalcemia (>11.2 mg/dl) increased form greater or equal to 0.4 episodes per 100 patient-weeks to 3.6 episodes per 100 patient-weeks. No cases of severe hypercalcemia with symptomology were observed. These rates are lower than published data on calcitriol treatment.

(*Id.* at 27-28 (citing DTX-543 at G1373552; Tr. at 599:18-601:12, 602:19-603:3 (Morris)).) Thus, the plaintiffs argue that the FDA's rejection of its superiority claim was due to their failure to submit two adequate, well-controlled head-to-head clinical studies, rather than to an FDA assessment that doxercalciferol does not result in a lower incidence of hypercalemia. (*Id.* (citing Tr. at 362:7-363:15 (Drezin); Tr. at 581:24-582:24 (Morris); PDTX-92).) The court agrees and, as noted in connection with the plaintiffs' prior argument, concludes that clinical studies with doxercalciferol demonstrate that it can lower and maintain lowered PTH levels with a lower incidence of hypercalcemia than calcitriol or alfacalcidol. Thus, the court rejects the defendants' argument that the FDA did not approve Hectorol®'s claimed method of use as recited in claim 7.

ii. *The Wesseling-Perry Study's Findings*

As noted, the defendants also assert that the plaintiffs cannot prove infringement by a preponderance of the evidence because, the Wesseling-Perry Study—the only head-to-head study comparing the incidence of hypercalcemia associated with doxercalciferol and calcitriol at the same PTH suppression—found no difference in the incidence of hypercalcemia between the

two analogs.[36] (D.I. 218 at 20-26 (citing Tr. at 866:13-25 (Holick)).) The Wesseling-Perry Study ("the Study") was published in 2010 in the peer-reviewed journal, Kidney International, and reported the findings of a trial conducted at the Pediatric Nephrology Center at the UCLA School of Medicine.[37] (*Id.* at 21 (citing PDTX-69; Tr. at 867:22-868:4 (Holick)).) This trial randomly allocated patients into four treatment groups: (1) patients treated with doxercalciferol and calcium carbonate (a phosphate binder); (2) patients treated with doxercalciferol and sevelamer (a phosphate binder); (3) patients treated with calcitriol and calcium carbonate; and (4) patients treated with calcitriol and sevelamer. *See* PDTX-69 at 6. The defendants' expert, Dr. Holick, testified that the Study employed a modern dosing strategy wherein the trial administrators adjusted doses of doxercalciferol and calcitriol every four weeks to achieve a target PTH level of between 300 and 400 pg/ml, while maintaining serum calcium in the normal range of 8.4 to 10.2 mg/dL and phosphorous between 4 and 6 mg/dL. *See* PTDX-69 at 6; *see also* Tr. at 872:8-22 (Holick).

In support of their assertion that the Study demonstrates there is no difference in the incidence of hypercalcemia resulting from use of doxercalciferol or calcitriol, the defendants cite the Study's explicit statement that "[n]o differences in serum calcium levels or episodes of hypercalcemia were found between calcitriol and [doxercalciferol] therapies." (D.I. 218 at 22 (citing PDTX-69 at 3).) The defendants also contend that the Study achieved the same level of PTH suppression in the doxercalciferol and calcitriol treatment groups, as is evidenced by its

[36] The defendants also note that the Wesseling-Perry Study ("the Study") was conducted and its results were published outside the context of litigation and, therefore, were not influenced by "litigation-induced arguments." (D.I. 218 at 24.) The defendants further state that Dr. Salusky, a board member of Genzyme Corporation, and Bone Care provided "unrestricted support" for the Study. (*Id.* (citing PDTX-69 at 7 (disclosures & acknowledgements)).)

[37] The defendants note that the authors of the Wesseling-Perry Study "include internationally recognized and highly-respected experts in their respective fields: pediatric nephrologist Dr. Isidro Salusky, endocrinologist Dr. Harald Jupper, and biostatistician Dr. Robert Elashoff." (D.I. 218 at 21 (citing Tr. at 867:12-21 (Holick); Tr. at 489:14-23 (Pagano)).)

reports that: (1) "doxercalciferol and calcitriol were equivalent in controlling bone turnover" and "suppressing parathyroid hormone" (*id.* (citing PDTX-69 at 1 (title))); (2) "serum phosphate concentrations were controlled equally well by both binders, but serum calcium levels increased during treatment with calcium carbonate, and serum parathyroid hormone levels were decreased by 35% in all groups" (*id.* (citing PDTX-69 at 1 (abstract))); (3) "doxercalciferol is as effective as calcitriol in controlling serum parathyroid hormone levels and suppressing bone formation rate" (*id.* (citing PDTX-69 at 1 (abstract))); (4) PTH "values had declined by an average of 34% . . . in all treatment groups" (*id.* (citing PDTX-69 at 3 (Figure 3a-3b))); and (5) "serum PTH and alkaline phosphatase levels were suppressed to a similar degree in all groups despite differences in serum calcium levels" (*id.* (citing PDTX-69 at 5 (discussion))).

The defendants further assert that the Study's conclusion that there is no difference in the incidence of hypercalcemia that results from the use of doxercalciferol or calcitriol at the same level of PTH suppression is statistically supported. Specifically, Dr. Holick's testified that Figures 3a and 3b of the Study show that there was no relevant statistically significant difference in PTH suppression between any of the treatment groups at any point during the trial.[38] In addition, the defendants' statistical expert, Dr. Pagano, testified that the Study discloses its statistical design and contains a statistical analysis of serum calcium, serum phosphate, plasma PTH, plasma FGF-23, and Vitamin D sterol. Tr. at 484:9-487:10 (Pagano); *see also* PDTX-69 at Fig. 1-5. The defendants note that the Study specifically states that "48 episodes of hypercalcemia (serum calcium $\geq$10.2 mg/dl) occurred in $CaCO_3$-treated subjects as compared with 17 episodes in those receiving Sevelamer ($P<0.01$)." PDTX-69 at 3. The defendants assert that the disclosure of a P value indicates that this conclusion is supported by a statistical analysis

[38] Dr. Holick qualified this statement by noting that the only statistically significant difference shown in Figure 3a is that between months five and eight all treatment groups had mean PTH levels that were statistically different from the baseline mean PTH level. *See* PDTX-69 at 4; *see also* Tr. at 875:20-876:7 (Holick).

and that the conclusion was found to be statistically significant. *See* Tr. at 487:22-489:12 (Pagano). Moreover, the Study disclosed an identical number of episodes of hypercalcemia, twenty-nine, in each of the doxercalciferol and calcitriol arms of the trial, which, the defendants argue, is consistent with the Study conclusion that "[n]o differences in . . . episodes of hypercalcemia were found between calcitriol and [doxercalciferol] therapies." PDTX-69 at 3.

The plaintiffs, however, argue that the defendants misrepresent the Study's findings because its data and conclusions actually demonstrate that doxercalciferol can lower and maintain lowered PTH levels, resulting in a lower incidence of hypercalcemia than calcitriol or alfacalcidol at the same level of PTH suppression. The court agrees. First, the plaintiffs note that Dr. Salusky, in developing the Study protocol, stated that calcitriol resulted in "frequent episodes of hypercalcemia" and that the development of Vitamin D analogs such as doxercalciferol had the potential, based on the Tan and Frazao findings, to "lower serum PTH levels without substantially increasing serum calcium." PTDX-204 at G00530795. Dr. Salusky also recognized that because doxercalciferol had not yet been tested in children—who, unlike adults, still experience bone growth—the Study would require "careful evaluation," despite promising early results in adult studies, to determine if doxercalciferol would suppress bone formation rates less than treatment with calcitriol. *Id.* In light of this consideration, Dr. Salusky adjusted the target PTH range for both doxercalciferol and calcitriol to 300-400 pg/mL. *Id.* at G00530789; Tr. at 143:18-144:8 (Langman).

The plaintiffs note that a 2003 abstract reporting the trial's early results indicated that calcium levels increased in the calcitriol-treated patients, thereby increasing the risk of hypercalcemia, but decreased in those patients receiving doxercalciferol. (D.I. 219 at 9 (citing PDTX-207; Tr. at 144:20-145:2, 145:23-146:19 (Langman)).) Thus, contrary to the Study's

2010 conclusion that "no differences in serum calcium levels or episodes of hypercalcemia were found between calcitriol and [doxercalciferol] therapies," the 2003 results found that doxercalciferol resulted in lower calcium levels than calcitriol. *(Id.)* The plaintiffs argue that these results, rather than the 2010 Study conclusion, accurately reflect the trial's head-to-head comparison. Specifically, the plaintiffs contend that the calcium level differences observed in 2003 were ultimately eliminated from the trial through steps aimed directly at reducing hypercalcemia for the purpose of permitting the administration of high enough doses of calcitriol to lower its PTH levels into the predetermined target range of 300-400 pg/mL. (*Id.* (citing Tr. at 147:4-148:12 (Langman)).)

In addition, the plaintiffs contend that, even discounting the 2003 abstract results, the 2010 Study's data and findings show that doxercalciferol results in a lower incidence of hypercalcemia than calcitriol or alfacalcidol at the same level of PTH suppression. To support this assertion the plaintiffs make several arguments in connection with the Study's results. First, the plaintiffs note that hypercalcemia "prevented the average PTH level of the calcitriol/calcium carbonate-treated patients from being lowered into the [PTH level] target range." (*Id.* (citing Tr. at 148:13-149:16 (Langman)).) According to the plaintiffs, this result is consistent with those seen in the Wesseling-Perry clinical trials in 1998, wherein the authors observed no change in PTH levels in patients treated with calcitriol when calcium levels were kept in the normal range. (*Id.* (citing PDTX-70 at 109; Tr. at 136:2-24 (Langman)).) Importantly, however, the doxercalciferol/calcium carbonate treated patients' average PTH levels were lowered into the target range by approximately the fourth month of the study and were maintained within the target range until the trials' conclusion. (*Id.* (citing PDTX-69 at Fig. 3a; Tr. at 148:16-149:16

(Langman)).) Dr. Holick similarly recognized that the Study was unable to lower the calcitriol-treated patients into the predetermined PTH target range. (*Id.* (citing Tr. at 889:2-18 (Holick)).)

The plaintiffs next challenge Dr. Holick's conclusion that the Study showed no relevant statistically significant difference between PTH levels, as is required by claim 7.[39] (D.I. 219 at 10 (Tr. at 898:15-899:1 (Holick)).) As noted, Dr. Holick qualified his statement by noting that the statistically significant difference shown in Figure 3a between months five and eight supported the conclusion that all treatment groups had mean PTH levels that were statistically different from the baseline mean PTH level. *See* Tr. at 875:20-876:7 (Holick). Thus, Dr. Holick concluded that, because there was "no difference between the groups," the level of PTH suppression was the same. *Id.* at 876:2-15. Conversely, the plaintiffs' statistical expert, Dr. Cremieux, testified that the average PTH level between months four and eight for the calcitriol/calcium carbonate-treated patients was 627 pg/mL compared to 383 pg/mL for the doxercalciferol/calcium carbonate-treated patients, and that these values represent a statistically significant difference between the two groups. *Id.* at 288:10-289:25 (Cremieux).

In view of the foregoing and based on examination of the Study's findings and the parties' expert testimony, the court agrees with the plaintiffs and concludes that calcitriol and doxercalciferol were not used to "achieve the same level of PTH suppression," either statistically or clinically.[40] Thus, because the PTH levels of doxercalciferol and calcitriol were not both lowered into the target PTH level and maintained at the same level of PTH suppression, as required by claim 7, the Study's finding that patients treated with doxercalciferol and calcitriol experience the same raw number of hypercalcemic events, does not demonstrate that these two

[39] Dr. Holick agreed that, "[i]n the context of this claim, 'to achieve the same level of PTH suppression,'" "means to have a lowering of PTH that statistically is not different" for the doxercalciferol and calcitriol or alfacalcidol groups. Tr. at 898:20-899:2 (Holick).

[40] As both Drs. Langman and Holick recognized, the calcitriol/carbonate-treated patients were unable to reach or to stay within the PTH target range in the Study. Tr. at 148:16-149:16 (Langman); *id.* at 899:2-18 (Holick).

analogs cause similar incidences of hypercalcemia as the defendants maintain. *See id.* at 268:18-269:23, 291:20-292:16. In fact, the court agrees with Dr. Langman's conclusion that had the calcitriol-treated patient group's PTH levels been lowered into the target range, these patients would have needed to receive higher doses of calcitriol and, therefore, would have demonstrated a higher incidence of hypercalcemia. (D.I. 219 at 11 (citing Tr. at 149:17-24)).)

In addition, the court notes that it is clear from Figure 3a that the doxercalciferol/calcium carbonate-treated patient group was the only group that had its PTH levels lowered into the target range. (PDTX-69 at Fig. 3a.) Both Drs. Langman and Holick agreed with this assessment, and Dr. Holick's recognition of this fact negates his conclusion that there were no differences among the four treatment groups because the authors "already [] achieved what they wanted to, which was to get the PTH levels into [the] targeted range." *See* Tr. at 148:16-149:16 (Holick); *id.* at 87:2-13, 899:7-18 (Holick).

The court also notes its agreement with Drs. Cremieux and Langman's testimony that the Study's statement that doxercalciferol and calcitriol are "equivalent" in suppressing PTH does not parallel the definition of equivalence required for claim 7 of the '116 Patent. *Id.* at 149:17-24, 148:16-149:16 (Langman). The court concludes that, based on the Study's findings, "equivalent" in suppressing PTH "is not the same as comparing treatment with doxercalciferol and calcitriol at the same level of PTH suppression." (D.I. 219 at 11-12 (citing PDTX-69 at 1; Tr. at 287:11-290:16 (Cremieux); Tr. at 218:5-8 (Langman)).) Specifically, as used in the Study context, the term "equivalent" directly refers to the fact that the average reduction in PTH for the four patient groups at the end of the study was thirty-four percent. PDTX-69 at 4. Notably, however, equivalence in the Study was assessed at the end, rather than throughout, a point that

Dr. Langman noted and Dr. Holick acknowledged[41] impedes meaningful evaluation of whether there is a lower incidence of hypercalcemia at the same level of PTH suppression. (D.I. 219 at 12 (citing Tr. at 216:5-217:2 (Langman); Tr. at 290:1-291:19, 353:14-20 (Cremieux)).)

In particular, Dr. Langman testified that it is necessary to know when individual incidences of hypercalcemia occur because this allows trial administrators to ascertain whether incidences of hypercalcemia in each group occur at the same level of PTH suppression. Thus, assessing equivalence at the end of the study without review of the underlying patient data precludes examination of the PTH suppression level that corresponds to each hypercalcemic incident. Dr. Holick did not review the Study's underlying patient data in determining that the incidence of hypercalcemia is the same for doxercalciferol and calcitriol. Tr. at 900:1-9 (Holick). Dr. Langman did review this underlying data, however, and found that the doxercalciferol/calcium carbonate-treated patients did not experience a single episode of hypercalcemia until after PTH levels were lowered the below the target range. *See id.* at 151:1-152:1 (Langman). In contrast, the calcitriol/calcium carbonate-treated patients experienced incidences of hypercalcemia above, within, and below the target range. *Id.* at 152:2-153:4. The court finds Dr. Langman's testimony and findings on this issue instructive and credible.[42] Thus,

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[41] In his deposition testimony, Dr. Holick acknowledged "[t]hat would make sense," in response to the plaintiffs' question: "if the question being asked is, is there a lower incidence of hypercalcemia at the same level of PTH suppression . . . don't we need to know when the individual episodes of hypercalcemia occurred?" Tr. at 901:5-9 (Holick). Though Dr. Holick testified at trial that he did not understand the question during his deposition, he also testified in response to the same question that, "in general, if you are just asking in general about either individual or in a group of subjects, it's reasonable." *Id.* at 901:20-25.

[42] The court's conclusion is not undermined by the defendants' argument that: (1) Drs. Langman and Cremieux erred in evaluating only the doxercalciferol and calcitriol calcium carbonate trials and excluding those trials with sevelamer (D.I. 218 at 24-25); (2) Dr. Cremeiux's opinions are inherently inconsistent because he critiqued the Study as having "too few observations," yet excluded the sevelamer half of the trial (*id.* at 25); and (3) Dr. Cremieux's re-analysis of the patient level data in the Study is flawed because he "did not have all of the data that the Wesseling-Perry nephrologists and biostatisticians had during their review, did not verify whether patients who dropped out of the study did so for random or medical reasons, and failed to use the correct "interaction term" in concluding that doxercalciferol results in a lower incidence of hypercalcemia (*id.*).

Specifically, and with regard to the first two arguments, the plaintiffs' experts' exclusion of the sevelamer groups is not problematic for two reasons. First, and as Dr. Langman testified, only the doxercalciferol/calcium

the court concludes that the Study did not demonstrate that doxercalciferol and calcitriol have the same incidence of hypercalcemia when used to achieve the same level of PTH suppression.

c. Use of Doxercalciferol versus Calcitriol in Clinical Practice

In addition to the foregoing, the plaintiffs introduced testimony of Ms. McCann, a renal dietician who has treated patients with ESRD for the past forty years and has used both doxercalciferol and calcitriol. (D.I. 219 at 14-15 (citing Tr. 394:1-395:11, 399:14-22 (McCann)).) Ms. McCann also serves as a member of an executive team at a dialysis service provider, Satellite Healthcare ("Satellite"), where she advises Satellite on what drugs to purchase and administer to its approximately 5,000 patients. (*Id.*) Ms. McCann has also written all of Satellite's treatment protocols over the past twenty years. (*Id.*) In response to questions related to her experience using doxercalciferol versus calcitriol, Ms. McCann testified that she observed a "sawtooth" treatment pattern with calcitriol. (*Id.* at 15 (citing Tr. at 416:6-17, 418:7-22 (McCann)).) This pattern, described by Dr. Langman in his testimony, refers to "pattern of repetitive hypercalcemia," wherein there is a "lowering of PTH with increasing calcium levels when calcitriol is administered, followed by increased PTH levels and a drop in calcium levels

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carbonate-treated patients had their average PTH levels lowered and maintained within the PTH target range as required by claim 7. Additionally, sevelamer was not available at the time of the invention, which means that the calcium carbonate patients were the only ones that were clinically and/or legally relevant. (D.I. 219 at 13 (citing Tr. at 149:25-150:2 (Langman)).) Second, the plaintiffs' experts testified that, even if the sevelamer arms of the Study were included, the data from all four groups show, under standard statistical analysis, that the patients treated with calcitriol are two-and-a-half times more likely to experience hypercalcemia than patients treated with doxercalciferol when PTH levels are above the PTH target range and "when relevant clinical variables are controlled for." (*Id.* (citing Tr. at 269:24-271:3, 299:25-300:12, 302:1-13, 321:7-322:3 (Cremieux)).) Dr. Cremieux also testified that patients treated with calcitriol were seven-and-a-half times more likely to experience hypercalcemia than those treated with doxercalciferol when PTH is within the target range, which is a statistically significant value. (*Id.* (citing Tr. at 303:21-24, 307:12-20 (Cremieux)).)

The court finds Dr. Cremieux's testimony and findings to be reliable and notes that Dr. Cremieux consulted with Dr. Langman for clinical guidance and conducted analyses to verify his findings. (*Id.* at 13 n.14 (citing Tr. at 288:10-289:25, 297:17-299:24, 308:12-310:12, 313:2-314:9, 318:22-321:10, 353:24-354:23 (Cremieux)).) The court also rejects the defendants' assertion that Dr. Cremieux's failure to take into account variables such as patient dropout render his results unreliable because it finds credible Dr. Cremieux's testimony that he did not need to consider these factors for the reasons he advanced. The court also notes that Dr. Pagano, the defendants' statistical expert, did not test the validity of his criticisms of Dr. Cremieux's analysis and did not obtain guidance from a clinician in reaching his conclusions. (*Id.* (citing Tr. at 520:18-521:3, 538:7-13, 555:17-558:12 (Pagano)).)

when calcitriol is withheld due to hypercalcemia." (*Id.* at 14 (citing Tr. at 100:13-102:21 (Langman)).) Dr. Langman described this patter as "sawtooth[ed]" because it repeats when calcitriol is again administered in order to control PTH. (*Id.* (citing Tr. at 103:1-104:19 (Langman); *see also* Tr. at 124:15-125:9, 162:1-5 (Langman)).)

While Ms. McCann observed this pattern in her use of calcitriol, she testified that she did not observe the same when using doxercalciferol. (*Id.* at 15 (citing Tr. at 416:6-17, 418:7-22 (McCann)).) Based on these observations, Ms. McCann testified that doxercalciferol has become Satellite's drug of choice, as it is "less burdensome" for clinicians than calcitriol because hypercalcemia is infrequent and, therefore, allows for continuous dosing and maintenance of desired PTH levels. (*Id.*) Dr. Langman likewise confirmed Ms. McCann's observations, noting that, in his treatment of over 500 patients with ESRD and SHPT over the past thirty years, he encountered frequent hypercalcemia with the use of calcitriol regardless of his efforts to avoid it. (*Id.* at 14 (citing Tr. at 124:15-125:9 (Langman)).) With doxercalciferol, however, Dr. Langman explained that he was able to lower and maintain lowered PTH levels due to the lower incidences of hypercalcemia. (*Id.* (citing Tr. at 103:1-104:19, 124:15-125:9, 162:1-5 (Langman)).)

Ms. McCann also testified that, despite new Medicare "bundling" rules, which allegedly provide a financial incentive for dialysis service providers to use less expensive drugs such as calcitriol, none of the large dialysis service providers in the United States, including Satellite, have switched their in-center patients from the more expensive doxercalciferol to calcitriol.[43] (*Id.* (citing Tr. at 414:21-25, 419:9-24, 421:12-23 (McCann); Tr. at 456:22-457:12 (Charytan)).)

[43] Ms. McCann explained that the majority of ESRD and SHPT patients are treated at in-center dialysis clinics with injectable Vitamin D drugs, and that a much smaller portion are treated at home using oral Vitamin D drugs. (D.I. 219 at 15 (citing Tr. at 409:24-412:25 (McCann)).) Due to the significant difference in cost of the oral medications, Satellite recently approved a trial of oral calcitriol in its smaller group of home dialysis patients, with "some very strong safety nets in place." (*Id.* (citing Tr. at 420:11 (McCann)).) However, Ms. McCann testified that for those patients whose physicians allowed a switch to calcitriol, there has been an increase in incidences of hypercalcemia and physicians are switching back to doxercalciferol. (*Id.* (citing Tr. at 419:25-421:2 (McCann)).)

Thus, in light of Ms. McCann and Dr. Langman's testimony, the plaintiffs maintain it is clear that the majority of caregivers treat patients with doxercalciferol—despite financial incentives to use calcitriol—thus showing that practicing physicians and medical personnel find doxercalciferol able to lower and maintain lowered PTH levels with a lower incidence of hypercalcemia than calcitriol or alfacalcidol at the same level of PTH suppression. (D.I. 219 at 14-16.)

In response, the defendants presented testimony from Dr. Holick, who indicated that he had successfully treated SHPT patients with calcitriol and did not experience problems with hypercalcemia, thus disproving Dr. Langman's "therapeutic dilemma."[44] (D.I. 218 at 15 (citing Tr. at 841:15-24 (Holick)).) The defendants' nephrologist expert, Dr. Charytan, countered that drug selection is largely driven by financial considerations and noted that recent publications indicate that "bundling" will result in a shift from the use of more expensive drugs like Hectorol®, to less expensive drugs like calcitriol. (*Id.* (citing Tr. at 450:18-451:20, 450:18-469:2 (Charytan); DTX-715; DTX-716; DTX-717; DTX-720)).) Finally, the defendants challenged Ms. McCann's testimony as unreliable because: (1) her own company has switched from Hectorol® to less expensive drugs due to the new Medicare "bundling" law; and (2) she did not know the prices that her company or other companies pay for Hectorol® or calcitriol. (*Id.* (citing Tr. at 415:1-419:24 (McCann)).)

In view of the foregoing and in consideration of the evidence adduced at trial, the court rejects the defendants' arguments. First, the court notes that Dr. Holick acknowledged on cross examination that treating ESRD and SHPT patients has never been his primary work and he has,

[44] Specifically, Dr. Holick testified that he has not experienced a "therapeutic dilemma" despite using calcitriol in patients with chronic kidney disease and ESRD for more than thirty years. Dr. Holick noted that he has "been very careful in [his] dosing of the drug to make sure that they don't become hypercalcemic . . . [y]et . . . been able to get their PTH levels into that targeted range." Tr. at 841:18-24 (Holick).

in fact, never worked with doxercalciferol. Tr. at 881:22-25 (Holick). Dr. Holick testified that he treats approximately four to six ESRD and SHPT patients per year and has never treated with Hectorol®. Based on Dr. Holick's relatively limited experience treating ESRD and SHPT and his lack of experience with doxercalciferol, the court finds Dr. Langman's testimony regarding his doxercalciferol and calcitriol observations more credible. Second, although Dr. Charytan testified that he anticipates there will be shift from doxercalciferol to calcitriol due to financial considerations implicit in the Medicare "bundling' laws, he was unaware of any dialysis service provider that has switched from Hectorol® to calcitriol and was not proffered as an expert on the new "bundling rules." (D.I. 219 at 15-16 (citing Tr. at 477:3-6 (Charytan); *see also* Tr. at 445:21-446:4).) Moreover, Dr. Charytan's conclusion has not, to date, proved correct. In actuality, data from Dialysis Outcomes Practice Patient Survey ("DOPPS") illustrates that the use of injectable calcitriol to treat patients with ESRD has not increased since the "bundling" rules took effect and remains virtually abandoned. (*Id.* at 16 (citing Tr. at 130:2-132:6, 132:21-133:1 (Langman)).) The plaintiffs also note that even The Kidney Center where Dr. Charytan treats patients does not stock calcitriol. (*Id.* (citing Tr. at 477:7-18 (Charytan)).)

Finally, the court disagrees with the defendants' critique of Ms. McCann's conclusions for the reasons they advance. Specifically, and as Ms. McCann explained, while it is true that Satellite started using calcitriol in lieu of Hectorol®, it did so in very limited trials and physicians have seen an increase in hypercalcemia since using calcitriol. Thus, the defendants' argument is not persuasive. Moreover, the court does not find that Ms. McCann's conclusions are undermined by the fact that she did not know the prices of Hectorol® and calcitriol, because, in keeping with her testimony, Ms. McCann concluded that the primary concern of caregivers in

selecting Vitamin D drugs is to provide the best outcome for patients, rather than financial considerations. (*Id.* (citing Tr. at 407:21-408:18 (McCann)).)

Thus, the court finds the plaintiffs have successfully demonstrated that practitioners and medical professionals have found that doxercalciferol is able to lower and maintain lowered PTH levels with a lower incidence of hypercalcemia than calcitriol or alfacalcidol at the same level of PTH suppression and that, for this reason, it is favored over calcitriol despite its higher cost.

d. Conclusion

As noted, the court finds that the defendants' proposed product labels instruct users to administer doxercalciferol to patients with ESRD and SHPT, thus infringing the first two elements of claim 7.[45] In view of the foregoing analysis, the court further concludes that: the plaintiffs have produced sufficient evidence to show that doxercalciferol can lower and maintain lowered PTH levels with a lower incidence of hypercalcemia than calcitriol or alfacalcidol used to achieve the same level of PTH suppression; and the defendants' noninfringement arguments have failed to rebut this evidence. Specifically, the court finds the testimony of Drs. Langman and Drezin and Ms. McCann to be credible and, in light of their testimony and the court's own independent review of the evidence presented, concludes that: (1) doxercalciferol has been demonstrated to lower and maintain lowered PTH levels; (2) results in a lower incidence of hypercalcemia; and (3) the practicing of the first three elements of claim 7 necessarily results in a lower incidence of hypercalcemia than would occur from using calcitriol or alfacalcidol to achieve the same level of PTH suppression.[46]

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[45] *See supra* Sections III.A.2.

[46] *See* Tr. at 157:10-163:15 (Langman); *see also* PTDX-215; PDTX-216; PDTX-26; PDTX-219; PDTX-220; PDTX-221. The court notes that, in reaching this conclusion, it rejects defendant Sandoz's argument that its proposed products do not infringe the "lower incidence of hypercalcemia" element of claim 7 because its proposed product labels do not include the term "low rate." (D.I. 219 at 44.) Sandoz asserts that Dr. Langman relied on this "low rate" language in concluding that the Sandoz proposed products meet each element, and specifically element four, of claim 7. (*Id.*) However, the court finds that the absence of this language from Sandoz's proposed product

Thus, the court finds that the plaintiffs have shown, by a preponderance of the evidence, that the defendants' proposed products would indirectly infringe claim 7 of the patent-in-suit and, therefore, that the underlying direct infringement required to satisfy the inducement and contributory infringement causes of action, is met. With this finding established, the court next assesses whether the plaintiffs have presented evidence sufficient to prove, by a preponderance of the evidence, that the defendants' proposed products induce infringement of and/or contributorily infringe the asserted claim of the patent-in-suit. For the reasons that follow, the court finds that each of the defendants' proposed products induces infringement of claim 7 and that Sandoz's proposed products contributorily infringe this asserted claim.

a. The Defendants' Proposed Products Induce Infringement of the Asserted Claim of the Patent-in-Suit

As noted, the "pertinent question" in ANDA cases, with respect to induced infringement, is "whether the proposed label instructs users to perform the patented method," and "promote[s] or "encourage[s]" others to practice that method. *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (citation omitted). Here, the court has found, for the reasons stated above, that the defendants' proposed product labels would instruct users to perform each element of the patented method detailed in claim 7. The Federal Circuit has clarified, however, that satisfaction of this element, without more, is insufficient to prove inducement. Instead, the

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labels does not rebut the plaintiffs' infringement evidence because it has concluded, for the reasons discussed more fully above, that the first three elements of claim 7 necessarily result in performance of the "lower incidence of hypercalcemia" element.

The court also notes that, in further support of this conclusion, Dr. Langman explained that the absence of the "low rate" language from the Sandoz proposed labels is not dispositive in the infringement analysis because the labels include data demonstrating the "lower incidence of hypercalcemia" element. Specifically, Dr. Langman noted that each label includes a table displaying the results of "two Phase 3 studies with doxercalciferol injection" wherein it is reported that the "incidence or rate of hypercalcemia expressed per 100 patient weeks for the two studies labeled as open table" is one episode of hypercalcemia "roughly . . . every two years or so." Tr. at 251:8-252:25 (Langman)). Dr. Langman testified that this reported rate "would inform someone reading the label that [there] is a very low frequency of hypercalcemia with doxercalciferol." *Id.* at 252:2-4. The court agrees and finds that, even in the absence of the "low rate" language, Sandoz's proposed products infringe the "lower incidence of hypercalcemia" element for inducement and contributory infringement purposes.

patentee must also present evidence that the defendant "knew or should have known that his actions would induce actual infringement"[47] and "that the induced acts constitute patent infringement."[48] To this end, the patentee must first show that the accused infringer had actual knowledge of the patent or was willfully blind to its existence. *See Global-Tech.*, 131 U.S. at 2067-68. With respect to this requirement, it is clear from the defendants' paragraph IV certification letters that each was aware of the patent-in-suit.

The defendants argue, however, that the plaintiffs cannot show that they knew their proposed products would induce actual infringement and, therefore, cannot demonstrate, as required, that the defendants "knowingly aided and abetted another's infringement." (D.I. 218 at 42 (citing *Rodime PLC v. Seagate Tech., Inc.*, 174 F.3d 1294, 1306 (Fed. Cir. 1999))). Specifically, the defendants assert, in addition to those arguments already addressed,[49] that "intent to induce infringement cannot be inferred when there are substantial noninfringing uses for the [accused] drug." (*Id.* at 44 (citing *Warner-Lambert*, 316 F.3d at 1365).) The court is not persuaded by the defendants' assertion that "lower[ing] and maintain[ing] lowered blood concentrations of PTH *without* a lower incidence of hypercalcemia" constitutes a noninfringing use, given its conclusion that the first three elements of claim 7 result in the performance of the fourth element. The matter does not end there, however, because the defendants also present an additional noninfringing use argument. Specifically, defendants Anchen and Roxane assert that their products may be administered for the treatment of SHPT in patients with Stage 3 and Stage 4 chronic kidney disease, and that this use would not infringe claim 7, which is limited to the treatment of Stage 5 chronic kidney disease. (*Id.*) Defendant Sandoz does not assert this

[47] *See DSU Med. Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006).

[48] *See Global-Tech Apppliances, Inc. v. SEB S.A.*, 131 U.S. 2060, 2068 (2011).

[49] As established above, the court rejects the defendants' arguments that: (1) doxercalciferol has not been demonstrated to lower and maintain lowered PTH levels with a lower incidence of hypercalcemia than would result from using calcitriol or alfacalcidol to achieve the same level of PTH suppression; and (2) the FDA did not approve claim 7 for the method of use recited, such that the defendants cannot infringe the asserted claim.

noninfringing use because its proposed products are directed to the injection form of doxercalciferol and the Hectorol® injection is approved only for the treatment of Stage 5 chronic kidney disease.[50]

With respect to this noninfringing use argument, the defendants elicited testimony from Dr. Langman on cross examination that, because the '116 Patent is approved, in capsule form, for the treatment of Stage 3 and Stage 4 chronic kidney disease and the asserted claim 7 is directed only to Stage 5, a product directed to the treatment of Stages 3 and 4 would not infringe claim 7. The defendants thus maintain that because their products have a substantial noninfringing use, the plaintiffs cannot show that they possessed the specific intent necessary to induce infringement as they did not know that the induced acts would constitute patent infringement or would encourage and promote others' infringement. (*Id.* at 41-44.)

Notably, while the plaintiffs seemingly address Anchen and Roxane's substantial, noninfringing use argument in connection with contributory infringement,[51] they do not discuss this argument in their proposed findings and conclusions on induced infringement. The court finds the plaintiffs' failure to address this argument in its post-trial briefing unsurprising. In fact, the defendants explicitly address this argument in only one sentence of their Proposed Findings of Fact and Conclusions of Law,[52] and instead focus their briefing on the evidence they presented

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[50] Sandoz argues, in support of its contention that it does not induce infringement of claim 7, that its proposed product labels do not include the language "low rate" and, therefore, do not indirectly infringe element 4 of the asserted claim. (D.I. 218 at 44.) This argument is unavailing for the reasons stated above. *See supra* note 46. In addition, the Federal Circuit has recognized that inducement can be established even if the patented use is not expressly stated in a product label, provided that the patented use is implicit. *See AstraZeneca*, 633 at F.3d at 1057-58. Consequently, because the court rejects this argument and Sandoz does not present any noninfringing use or other defense to negate the intent element, the court concludes, for the reasons detailed below, that Sandoz induces infringement of claim 7.

[51] In their Proposed Findings and Fact and Conclusions of Law, the plaintiffs assert that only defendant Sandoz contributorily infringes claim 7 and, therefore, seemingly concede that Anchen and Roxane's products do not contributorily infringe the asserted claim because each have a substantial, noninfringing use. (D.I. 219 at 46-47.)

[52] Specifically, the defendants assert, in the only paragraph of their Proposed Findings of Fact and Conclusions of Law addressing their Stage 3 and Stage 4 treatment noninfringing use argument, that:

at trial in support of the contention that their products' noninfringing use is lowering and maintaining lowered PTH levels without a lower incidence of hypercalcemia. (D.I. 218 at 40-46.) In fact, the trial transcript contains only a single reference to the defendants' noninfringing use Stages 3 and 4 treatment argument—a question posed to Dr. Langman on cross examination[53]—testimony which the defendants did not deem of sufficient import to even cite in their Proposed Findings of Fact or Conclusions of Law to support this assertion. Tr. at 230:14-231:3 (Langman); *see also* D.I. 218 at 44. Thus, while the defendants' argument has some logical appeal in the inducement analysis, the assertion of this noninfringement defense, both at trial and in the defendants' post-trial briefing appears as a secondary and markedly undeveloped defense, which, the court concludes, is insufficient to rebut the plaintiffs' infringement evidence.

Put simply, and in view of the record before it, the court finds that the plaintiffs have shown, by a preponderance of the evidence, that the defendants' proposed products induce infringement of the asserted claim of the patent-in-suit. As noted, in the Hatch-Waxman context, "[s]tatements in a package insert that encourage infringing use of a drug product are alone sufficient to establish intent to encourage direct infringement" for purposes of induced infringement under 35 U.S.C. § 271(b). *See 3M Co.*, 303 F.3d at 1305. The Federal Circuit has

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"Doxercalciferol may also be administered for the treatment of SHPT in patients with Stage 3 or Stage 4 [chronic kidney disease], which would not infringe claim 7 of the '116 [P]atent because claim 7 is limited to patients with Stage 5 [chronic kidney disease]." (*Id.*)

[53] The defendants' cross examination of Dr. Langman on this issue consisted of the following exchange:

Q: [Chronic Kidney Disease] Stage 1 through 5 do not require dialysis. Correct?
A: That's correct.
Q: That would be, obviously, patients with Stage 3 or Stage 4 chronic kidney disease would not require dialysis. Correct?
A: That's true.
Q: They would be pre-dialysis patients. Is that true?
A: That's correct.
Q: In fact, the oral form of doxercalciferol is approved for pre-dialysis patients as well. Correct?
A: Yes, it is.
Q: So those patients wouldn't fall within Claim 7 because they don't have ESRD. Correct?
A: That's true.

Tr. at 230:14-231:3 (Langman).

stated, however, that inducement in the ANDA context should not be decided according to the tenets of strict liability action.[54] Instead, a court assessing an inducement claim should determine whether the proposed label "instructs users to perform the patented method"[55] and "teach[es] an infringing use . . . such that we are willing to infer from those instructions an affirmative intent to infringe the patent."[56] Here, each of these requirements is met.

As explained in detail above, the court finds that the defendants' proposed product labels would infringe each element of the asserted claim. The court also finds that, by instructing users to perform each element of this claim, the defendants' proposed products would induce infringement by teaching those who follow claim 7 to perform the patented method. With respect to the specific intent element of inducement, the court concludes that the plaintiffs have sufficiently shown that the defendants "knew or should have known [their] actions would induce actual infringements." *See DSU Med. Corp.*, 471 F.3d at 1306. In this case, all defendants filed ANDAs with the FDA seeking approval to market a doxercalciferol product that would be sold accompanied by information instructing physicians and medical professionals to administer doxercalciferol according to the method explained in claim 7 for treating SHPT in patients with ESRD. This FDA-approved indication is the same use set forth in claim 7 of the patent-in-suit and, pursuant to 21 C.F.R. § 314.94(1)(8)(iv), the labels of the defendants' proposed products are the same as the plaintiffs' Hectorol® labels. The court concludes that the defendants' argument that the specific intent element is not met based on their proposed products' noninfringing uses is unavailing.

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[54] *See Warner-Lambert*, 316 F.3d at 1364-65.

[55] *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (citing *Vita-Mix Corp. v. Basic Holdings, Inc.*, 581 F.3d 1317, 1329 n.2 (Fed. Cir. 2009)).

[56] *Vita-Mix Corp.*, 581 F.3d at 1329 n.2.

First, and with respect to the defendants' assertion that their proposed products can practice the claimed invention without resulting in a lower incidence of hypercalcemia because doxercalciferol has not been proven to do so, the court finds that the evidence adduced at trial supports a conclusion to the contrary. Specifically, and as detailed above, the court concludes that, based on the clinical trials and literature available, the defendants knew or should have known that doxercalciferol has been shown to lower and maintain lowered PTH levels with a lower incidence of hypercalcemia than would result from using calcitriol or alfacalcidol at the same level of PTH suppression. Thus, the court concludes that the defendants, in submitting their ANDAs, knew or should have known that their proposed products would induce actual infringement of claim 7. The court finds this level of intent sufficient for inducement purposes. *See Manvill Sales Corp.*, 917 F.2d at 553; *Vita-Mix Corp.*, 581 F.3d at 1329 n.2 (concluding that a defendant induced infringement where the "instructions teach an infringing use of the device such that we are willing to infer . . . an affirmative intent to infringe the patent").

Second, and with regard to Anchen and Roxane's contention that they did not have the requisite intent to induce infringement of claim 7 because their proposed products can be used to treat Stage 3 and Stage 4 chronic kidney disease, the court finds that this argument does not rebut the plaintiffs' infringement evidence. As noted, the defendants did not meaningfully assert this proposition at trial or present any evidence indicating that the Anchen and Roxane products were intended for the treatment of Stage 3 and Stage 4, but not Stage 5, chronic kidney disease. In fact, the defendants seek FDA approval for the use of doxercalciferol in treating SHPT in patients with ESRD, the same FDA-approved indication set forth in claim 7 of the '116 Patent.[57]

[57] The court notes that, to the extent that the defendants argue that their substantial noninfringing uses constitute "off-label use" that will not infringe the asserted claim under 38 U.S.C. § 271(e)(2), the court finds this argument unpersuasive as the defendants' ANDAs are directed to the treatment of the same disease as that addressed

While Anchen and Roxane's argument is relevant, as discussed below, in connection with contributory infringement as a noninfringing use, it fails to show that the defendants did not believe their products would infringe the asserted claim of the patent-in-suit. *See DSU Med. Corp.*, 471 F.3d at 1307 (finding that intent to induce infringement was not present where the accused infringer did not believe that its products infringed the claimed invention). Rather, the court finds that the plaintiffs have shown that the defendants were aware of the patented claim, knew or should have known that their proposed products would induce infringement of the asserted claim, and, nevertheless, provided instructions for use that would lead to infringement of that claim. Thus, the court concludes that each of the defendants' proposed product labels encourage users to perform the patented method, inducing infringement of the asserted claim. *See AstraZeneca*, 633 F.3d at 1060; *Vita-Mix Corp.*, 581 F.3d at 1329 n.2.

b. Sandoz's Proposed Products Contributorily Infringe Claim 7

As explained above, to establish contributory infringement, a patentee must show that: (1) there is direct infringement; (2) the accused infringer had knowledge of the patent at issue; (3) the component has no substantial noninfringing uses; and (4) "the component is a material part of the invention." *See Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d at 1326. Intent is presumed in a contributory infringement analysis. *See Metro-Goldwyn-Mayer Studios v. Grokster Ltd.*, 545 U.S. 913, 932 (2005). In light of the above analysis, the court finds that: the defendants' proposed products directly infringe claim 7 for purposes of this cause of action; each defendant had knowledge of the patent-in-suit; and the method of use recited in claim 7 and the use of doxercalciferol are each a material part of the claimed invention, as these elements direct how and to what end the Vitamin D analog is administered. Thus, the court's analysis with respect to

in claim 7. *See Warner-Lambert*, 316 F.3d at 1348, 1351-52 (distinguishing "off-label use" as commonly involving the treatment of a different disease); *see also* D.I. 219 at 43-44.

this cause of action centers on whether the defendants' proposed products have a substantial noninfringing use.

The plaintiffs' Proposed Findings of Fact and Conclusions of Law assert that Sandoz's proposed products contributorily infringe claim 7 of the patent-in-suit. (D.I. 219 at 46.) The plaintiffs do not assert, based on the evidence presented at trial, that Anchen or Roxane's proposed products contributorily infringe claim 7. (*Id.*) As noted, Anchen and Roxane assert that their proposed products—both of which are directed to the capsule use of doxercalciferol—can be used to treat Stage 3 and Stage 4 chronic kidney disease without infringing claim 7 because, while claim 7 is directed to treating Stage 5 chronic kidney disease, Hectorol® capsules are approved for the noninfringing use Anchen and Roxane advance. (D.I. 218 at 44.) The court agrees and concludes that, if the Anchen and Roxane products are used exclusively to treat Stage 3 and Stage 4, but not Stage 5, chronic kidney disease, they do not contributorily infringe claim 7.[58]

The court further concludes, based on the evidence before it, that Sandoz's proposed products infringe claim 7 of the patent-in-suit. Specifically, Sandoz seeks to sell its generic doxercalciferol injection products for the FDA-approved indication—treating SHPT in patients with ESRD. As stated above, Hectorol® injection is approved exclusively for the treatment of Stage 5 chronic kidney disease for patients on dialysis. As a result, unlike Anchen and Roxane's proposed products, which can be used for the treatment of Stage 3 and Stage 4 chronic kidney disease, Sandoz's proposed products can only be used for the treatment covered in claim 7. Consequently, because Sandoz's products have no substantial noninfringing use and all other

[58] As is clear from the analysis above, if Anchen or Roxane sought to use their proposed products for the treatment of Stage 5 chronic kidney disease, this use of would contributorily infringe claim 7, which is directed to that singular treatmenet purpose.

elements of contributory infringement are met, the court concludes that Sandoz contributorily infringes claim 7 of the patent-in-suit.

B. Utility

The defendants contend that claim 7 of the '116 lacks utility because it is inoperative. (D.I. 218 at 50.) It is well-established that "[l]ack of enablement and absence of utility are closely related grounds of unpatentability." *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1358 (Fed. Cir. 1999) (citation omitted). In this context, the Federal Circuit has concluded that, "if claims in an application fail to meet the utility requirement because the invention is inoperative, they also fail to meet the enablement requirement because a person skilled in the art cannot practice the invention." *In Re Swartz*, 232 F.3d 862, 863 (Fed. Cir. 2000). Moreover, the Federal Circuit has further clarified that, "[w]hen a claim recites incorrect science in one limitation, the entire claim is invalid, regardless of the combinations of the other limitations recited in the claim." *EMI Group North America, Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1349 (Fed. Cir. 2001) (internal citations omitted). Post-filing evidence may be relied on to establish a lack of enablement if that evidence constitutes "later knowledge about art-related facts existing on the filing date." *In re Hogan*, 559 F.2d 595, 605 (C.C.P.A. 1977).

Importantly, however, the Federal Circuit has established that an issued patent is presumed valid by statute. *See* 35 U.S.C. § 282. That presumption can be overcome only by clear and convincing evidence, which is defined as evidence the "proves in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] highly probable." *Intel Corp. v. U.S. Int'l Trade Comm'n*, 946 F.2d 821, 830 (Fed. Cir. 1991).

In support of their contention that claim 7 fails because its "lower incidence of hypercalcemia than calcitriol or alfacalcidol at the same level of PTH suppression" element is inoperative, the defendants advance essentially the same arguments they raised in defending against the plaintiffs' infringement allegations. Specifically, the defendants assert that: (1) the Wesseling-Perry Study demonstrated that doxercalciferol and calcitriol, when dosed to achieve the same level of PTH suppression, exhibit no difference in incidences of hypercalcemia (D.I. 218 at 37 (citing PDTX-69; Tr. at 872:23-873:19 (Holick)); (2) because alfacalcidol is converted to calcitriol in the body, alfacalcidol would also show no difference in its incidence of hypercalcemia as compared to doxercalciferol at the same level of PTH suppression (*id.* (citing Tr. at 812:3-23 (Holick)); and (3) there are no clinical studies with human patients demonstrating that doxercalciferol causes fewer incidences of hypercalcemia than calcitriol or alfacalcidol when dosed to the same level of PHT suppression (*id.* (citing Tr. at 879:13-17 (Holick)). Based on these arguments, the defendants contend that claim 7 is inoperative and cannot be practiced because "when dosed to achieve the same level of PTH suppression, doxercalciferol does not result in a lower incidence of hypercalcemia than calcitriol or alfacalcidol, as required by the claim." (*Id.* (citing PDTX-69 at 3).) In sum, the defendants maintain that claim 7 is based on incorrect science with respect to the "lower incidence of hypercalcemia than calcitriol or alfacalcidol at the same level of PTH suppression" element and, therefore, that the entire claim should be deemed invalid for lack of enablement. (*Id.* at 50.)

Conversely, the plaintiffs assert that, should the court find in its favor on infringement, as it has, the defendants cannot establish that claim 7 is inoperable. The court agrees. As addressed more fully in the preceding section on infringement, the court finds the defendants' arguments unavailing as they relate to the "lower incidence of hypercalcemia than calcitriol or alfacalcidol

at the same level of PTH suppression" element of claim 7. Specifically, and for the reasons cited in the infringement examination, the court disagrees with the defendants' contentions that: (1) Dr. Langman's conclusions with respect to this element are unreliable for failure to consider interstudy variability and the alleged effect of dosing strategies; (2) the Wesseling-Perry Study constitutes a doxercalciferol/calcitriol head-to-head study demonstrating equal occurrence of hypercalcemia; (3) calcitriol and alfacalcidol have been shown in the prior art and by physician practice to be capable of lowering and maintaining lowered PTH levels and, therefore, controlling hypercalcemia; and (4) practitioners and medical professionals are guided by financial considerations in selecting patient treatment and calcitriol will replace doxercalciferol as the primary Vitamin D ESRD and SHPT treatment because of the financial incentives created by Medicare "bundling." Thus, for the reasons fully examined in its infringement analysis, the court that the defendants have not proved by clear and convincing evidence that this element of claim 7 is inoperable.

C. Priority

The parties contest the priority filing date to which claim 7 of the '116 Patent is entitled. Because identification of this date is necessary to ascertain the level of ordinary skill in the art at the time of the claimed invention, a finding critical to the obviousness analysis, the court will first examine the parties' arguments in connection with this issue. For the reasons that follow the court agrees with the plaintiffs and finds that the asserted claim of the patent-in-suit is entitled to a priority filing date of August 2, 1988.

1. The Legal Standard

To establish that an asserted claim of a patent-in-suit is entitled to the priority filing date of an earlier parent application, the patentee has the burden of proving that the written

description in that earlier application supports the later-filed claim. *See Tech Licensing Corp. v. VideoTek*, 545 F.3d 1316, 1327 (Fed. Cir. 2008). Continuation-in-part patent applications are entitled to the priority date of the parent application for those claims that have an adequate written description in that parent application. *See Go Med. Indus. Pty, Ltd. v. Inmed Corp.*, 471 F.3d 12 64, 1270 (Fed. Cir. 2006). To comply with the written description requirement of 35 U.S.C. § 112, the patent disclosure must convey with reasonable clarity to a person of ordinary skill in the art that the inventor was in possession of the claimed invention at the time of the earlier application. *See Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc).

The test for "reasonable conveyance" is a flexible one, "requir[ing] an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art" to determine whether, by reading the original disclosure, that person could "immediately discern the limitation at issue in the claims." *Id*; *see also Perdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). Importantly, however, *in haec verba* disclosures using the same language of the claim are not required. *Ariad Pharms, Inc.*, 598 F.3d at 1352. Moreover, the application "does not have to describe exactly the subject matter claimed." *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 2000). Rather, the requirement is met if a person of ordinary skill in the art would find it is "reasonably clear what the invention is and that the patent specification conveys that meaning." *All Dental Prodx, L.L.C. v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002). To this end, "a description that merely renders the invention obvious does not satisfy the requirement," and support in the written description must be based on what actually is disclosed, not on an "obvious variant" of what is disclosed. *See Ariad Pharms, Inc.*, 598 F.3d at 1352; *Lockwood v. American Airlines*, 107 F.3d 1565, 1571

(Fed. Cir. 1997). However, the failure to "specifically mention a limitation that later appears in the claims is not fatal when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented." *All Dental Prodx, Inc.*, 309 F.3d at 774. In sum, the written description must "actually or inherently disclose each element of the claim." *Power Oasis, Inc. L.L.C. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1307 (Fed. Cir. 2008).

The Federal Circuit has also clarified that where, as here, the earlier application details a prophetic example, such examples "can be sufficient to satisfy the written description requirement," if the disclosure has a "descriptive link" to the claimed invention. *Ariad Pharms, Inc.*, 598 F.3d at 1357. To this end, simply "mention[ing]" the "desired outcome" is insufficient. *Id.* Whether the written description requirement is met is a question of fact. *See Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1369-70 (Fed. Cir. 2009) (citation omitted). Once the plaintiff has shown "not only the existence of [an] earlier application, but why the written description in the earlier application supports the claim," including all limitations, the burden resides with the proponent of invalidity, who must "convince the court that [the patentee is] not entitled to the benefit of the earlier filing date." *Tech. Licensing Corp.*, 545 F.3d at 1328. To meet this burden, the invalidity proponent must persuade the court, by clear and convincing evidence, that it is correct. *Id.* (noting that the "ultimate burden[] of persuasion" never "shifts to the other party," and instead "the risk of decisional uncertainty stays on the proponent of the proposition").

2. The Parties' Contentions & Discussion

Here, the plaintiffs assert that claim 7's priority date is August 2, 1988, the filing date of the '371 application, because the '116 Patent claims priority to the '371 application and that

application would have reasonably conveyed the invention of claim 7 to a person of ordinary skill in the art as required by 25 U.S.C. § 112. (D.I. 219 at 31-34, 47.) The '371 application was drafted by Dr. Bishop, the inventor listed on the '116 Patent, and included four examples.[59] The plaintiffs cite specifically to Example 4[60] in the '371 application as the example reasonably conveying "each and every limitation of claim 7 of the '116 [P]atent" and, therefore, entitling it to the 1988 priority date. (*Id.* at 48.)

Conversely, the defendants argue that claim 7 of the '116 Patent is entitled only to an April 3, 1995 priority date because a person of ordinary skill in the art reading the '371 application in 1988 would not "have reasonably immediately discerned the limitations in claim 7 . . . or believed that the applicants possessed the alleged invention of claim 7." (D.I. 218 at 48.) Instead, the defendants argue that "only the new matter added to the '488 application in 1995 supports the contention that the applicants were in possession of the alleged invention in claim 7." (*Id.* (citing DTX-497; DTX-526; Tr. at 654:15-18, 652:3-6 (Friedman)).) In support, the

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[59] The '371 application examples include: Example 1, which reports the results of an actual human clinical trial of doxercalciferol in six post-menopausal osteoporotic women (hereinafter, "H-101"); Examples 2 and 3, which detailed prophetic clinical trials in which doxercalciferol was administered to treat women with osteoporosis; and Example 4, which described a prophetic clinical trial administered to treat ESRD.

[60] As is relevant to this analysis, Example 4 of the '371 application states:

> A twelve month double-blind placebo-controlled clinical trial is conducted with thirty men and women with renal disease who are undergoing chronic hemodialysis. All patients enter an 8-week control period during which time they receive a maintenance dose of Vitamin D_3 (400 IU/day). After this control period, the patients are randomized into two treatment groups: one group receives a constant dosage of 1α-Vitamin D_2 (u.i.d.; a dosage greater than 3.0 μg/day) and the other group receives a matching placebo. Both treatment groups receive a maintenance dosage of Vitamin D_3, maintain a normal intake of dietary calcium, and refrain from using calcium supplements. Efficacy is evaluated by pre- and post-treatment comparisons of the two patient groups with regard to (a) direct measurements of intestinal calcium absorption, (b) total body calcium retention, (c) radial and spinal bone mineral density, and (d) determinations of serum calcium and osteocalcin. Safety is evaluated by regular monitoring of serum calcium.
>
> Analysis of the clinical data shows that 1α-Vitamin D_2 significantly increases serum osteocalcin levels and intestinal calcium absorption, as determined by direct measurements using a double-isotope technique. Patients treated with this compound have normalized serum calcium levels, stable values for total body calcium, and stable radial and spinal bone densities relative to baseline values. In contrast, patients treated with placebo show frequent hypocalcemia, significant reductions in total body calcium and radial and spinal bone density. An insignificant incidence of hypercalcemia is observed in the treatment group.

PDTX-180 at 13-14.

defendants note that the '371 application was directed to osteoporosis treatment and did not: mention SHPT or measuring serum PTH, "a key factor in assessing SHPT"; teach or suggest a method of using doxercalciferol to treat SHPT; mention phosphate binders, which are needed for a patient taking doxercalciferol to treat SHPT; or discuss "conducting bone biopsies or analyzing chemical biomarkers," which are "relevant to assessing the effect of doxercalciferol on SHPT."[61] (*Id.* at 28-29 (citing Tr. at 650:19-651:15, 657:11-16, 658:3-5, 658:9-19, 658:23-659:18 (Friedman)).) Thus, the defendants argue that the '371 application contains no example "disclosing treating end-stage renal disease patients exhibiting secondary hyperparathyroidism." (D.I. 218 at 28 (citing Tr. at 654:11-14 (Friedman).)

As noted, the '116 Patent issued from the '448 application, which was filed on April 3, 1995 and was directed to the treatment of ESRD and SHPT patients. The '488 application was a continuation-in-part of the '895 application, which was itself a continuation of the '371 application, filed on August 2, 1988. The '371 application, though directed to the treatment of osteoporosis patients did, as both parties note, contain an example which the plaintiffs maintain would be read by a skilled artisan to disclose the invention in claim 7 of the '116 Patent. In consideration of the parties' arguments and the relevant law, the court concludes that an August 2, 1988 priority filing date is appropriate for claim 7 of the '116 Patent.

As an outset matter, the court notes that claim 7, per its *Markman* construction, can be divided into four elements, all of which need to be implicitly or explicitly disclosed in the '371 application to satisfy the 1988 priority filing date written description requirement: (1) administering an amount of doxercalciferol; (2) to patients with ESRD and SHPT; (3) sufficient

[61] On this last point, the defendants highlight that, per Dr. Friedman's testimony, "PTH levels or a bone biopsy would be used to determine whether the patient has the high bone turnover associated with SHPT (Friedman Direct 658:3-15, 658:25-659:14), and an analysis of biochemical markers (e.g., serum osteocalcin) would be used to demonstrate an improvement of bone health with treatment." (D.I. 218 at 29 n.13.) The defendants assert that "[n]one of these measurements are mentioned in Example 4—and, in fact, Example 4 describes the opposite of what would be expected." (*Id.* (citing DTX-497; Tr. at 659:15-660:13).)

to lower and maintain lowered PTH levels; (4) with a lower incidence of hypercalcemia than would result from using calcitriol or alfacalcidol to achieve the same level of PTH suppression. In consideration of the record before and the applicable law, the court finds that all four elements of claim 7 are disclosed in the '371 application.

First, Example 4 in the '371 application describes a prophetic twelve-month clinical trial. After an eight-week control period, the patients are randomized into a placebo group and a group that is administered doxercalciferol. Because the example explains that doxercalciferol is administered to half of the test group, the first element of claim 7 of the '116 Patent is met. Second, the court finds the plaintiffs' expert, Dr. Langman, to be persuasive in his explanation of how Example 4 discloses the second element of claim 7. Specifically, Dr. Langman explained that Example 4 describes a clinical trial anticipated to involve thirty men and women "with renal disease who are undergoing chronic hemodialysis." PDTX-180 at 13; *see also* Tr. at 911:3-8 (Langman). Dr. Langman testified that a person of ordinary skill in the art in 1988 would understand that patients undergoing chronic hemodialysis suffer from ESRD. Tr. at 911:3-8 (Langman). Moreover, a skilled artisan would also know that individuals who suffer from ESRD almost universally also suffer from SHPT. *Id.* at 911:8-14, 914:3-7.

Additionally, Dr. Langman explained that Example 4 is a randomized, double-blind, placebo-controlled study and that, in such studies, the results of the placebo group can be instructive in showing a person of ordinary skill in the art the disorder for which the patient group is being treated. *Id.* at 914:16-916:13. Here, the Example 4 placebo group is stated to show "frequent hypocalcemia" and "significant reductions in . . . radial and spinal bone density." *See* PDTX-180 at 13; *see also* Tr. at 916:14-22 (Langman). Frequent hypocalcemia in patients with ESRD results in increased secretion of PTH from the parathyroid glands. *Id.* As a result,

elevated PTH levels act as a constant signal for bones to release stored calcium, leading to a loss in bone density. *Id.* This loss in bone density, which, as Dr. Langman described, is technically known as hyperparathyroid bone disease, occurs mostly in the spine, but also in the long bones of the extremities, and was understood to be a symptom resulting from elevated PTH in untreated SHPT patients. *Id.* Dr. Langman testified that a person of skill in the art would have further understood that the treatment of patients with ESRD and SHPT involves the management of hypocalcemia to prevent loss of bone density. To demonstrate that this was known, Dr. Langman noted that the 1988 product label for oral calcitriol, Rocaltrol®, stated that it "is indicated in the management of hypolcalcemia and the resultant metabolic bone disease in patients undergoing chronic hemodialysis."[62] *See* PDTX-133 at 1737; *see also* Tr. at 918:17-919:20 (Langman). In consideration of the foregoing, Dr. Langman concluded, and the court finds credible, that a person of skill in the art would anticipate that the sample of individuals described in Example 4 have ESRD and SHPT, rather than osteoporosis as the defendants' expert Dr. Friedman opined.[63] *Id.*; *see also id.* at 910:17-911:14; *id.* at 651:2-15 (Friedman).

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[62] In support of his opinion that one of skill in the art in 1988 would have understood that treatment of ESRD and SHPT requires hypocalcemia management, Dr. Langman testified:

> Q: Do you have any support that in 1988 treatment of patients with secondary hyperparathyroidism involved the management of hypocalcemia and the underlying bone disease?
>
> A: Yes. . . . In that product label, we're told that the kidneys of uremic patients, of course, cannot adequately synthesize calcitriol, the active hormone formed from precursor Vitamin D. Resultant hypocalcemia and secondary hyperparathyroidism are a major cause of the metabolic bone disease and renal failure. So we learned the link between hypocalcemia and secondary hyperparathyroidism bone disease. Now, we also were taught in the label of Rocaltrol, it is indicated in the management of hypocalcemia and the resultant metabolic bone disease, referring to secondary hyperparathyroidism, in patients undergoing chronic renal dialysis, the same ones we're talking about in Example 4.
>
> Q: So the synthetic calcitriol that we've been talking about all week wasn't indicated for the treatment of secondary hyperparathyroidism in 1988?
>
> A: We used it to treat the secondary hyperparathyroidism, but it wasn't stated in those terms in the product label.

Tr. at 918:17-919:24 (Langman).

[63] Specifically, Dr. Friedman testified in direct examination that a person of ordinary skill in the art "would recognize that Example 4 describes an osteoporosis trial, not a trial for testing efficacy and toxicity on secondary hyperparathyroidism associated with ESRD." *Id.* at 651:12-15 (Friedman). However, as Dr. Langman explained in

Third, the court also finds persuasive Dr. Langman's conclusion that a person of ordinary skill in the art would have understood Example 4 to disclose that doxercalciferol treatment has the effect of lowering and maintaining lowered PTH levels. Specifically, Dr. Langman testified that Example 4's description of the control group patients as exhibiting "normalized serum calcium" and "stable radial and spinal bone density," indicates that the patients' PTH levels were lowered and maintained. *Id.* at 922:11-17 (Langman); *see also* PDTX-180 at 13. In support of this assertion, Dr. Langman explained that "normalized serum calcium" conveys that blood calcium levels were increased from below normal, which would occur during hypocalcemia, into a normal range. Tr. at 921:16-20, 92:25-923:4, 923:22-924:2 (Langman). Dr. Friedman concurred that an elevation in serum calcium levels would result in a decrease in PTH levels. *Id.* at 627:6-10 (Friedman). Thus, Example 4 indicates that PTH levels are lowered.

Moreover, Dr. Langman also explained, in testimony the court finds credible, that "stable radial and spinal bone density" is an example of improved bone health in patients with ESRD and SHPT, and that such improvements are associated with lowering and maintaining lowered PTH levels. *Id.* at 923:8-14; *see also* PDTX-180 at 13. Specifically, Dr. Langman testified, and Dr. Friedman agreed, that the PTH target range, which is the range where PTH level suppression should be maintained, corresponds to a stable bone density. Tr. at 107:23-110:7 (Langman); *id.* at 691:15-692:4 (Friedman). In light of this testimony, the court disagrees with Dr. Friedman's assertion that PTH levels must be measured to determine whether they are lowered and

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his testimony on this element, which included examination of the clinical test results projected in Example 4, a person of ordinary skill in the art in 1988 would:

> understand that patients had end-stage renal disease with secondary hyperparathyroidism. They were on chronic hemodialysis, so that denotes patients with end-stage renal disease. We mentioned that patients with end-stage renal disease have almost universally secondary hyperparathyroidism. And we went over the results of the placebo group to demonstrate that a person of ordinary skill in the art would recognize that those untreated patients for one year with frequent hypocalcemia and significant reductions in spinal and radial bone density must have secondary hyperparathyroidism.

Id. at 920:1-13 (Langman). The court finds Dr. Langman's testimony on this element credible.

maintained. *Id.* at 662:8-12 (Friedman). Rather, the court finds, based on the testimony adduced at trial, that a person of ordinary skill in the art would have viewed PTH levels to act as a proxy for bone density and understood that in order to maintain stable bone density, doxercalciferol would have to lower and maintain lowered PTH levels.[64] *Id.* at 922:11-923:14 (Langman). Thus, Example 4 relays to skilled artisans that doxercalciferol lowers and maintains lowered PTH levels and, therefore, discloses this element of claim 7 of the '116 Patent. *Id.* at 924:10-925:2.

Finally, the court finds that Example 4 also discloses the fourth element of claim 7 requiring doxercalciferol to result in a lower incidence of hypercalcemia than would result from using calcitriol or alfacalcidol to achieve the same level of PTH suppression. Specifically, Example 4 states that, "at the dosage ranges required for [calcitriol and alfacalcidol] to be truly effective, toxicity in the form of hypercalcemia and hypercalciuria becomes a major problem" and were only mildly beneficial. PDTX-180 at 4-5. Addressing this problem, Example 4 states that the use of doxercalciferol results in an "insignificant incidence of hypercalcemia." *Id.* at 14. Further, Example 4 also addresses the toxicity issue associated with hypercalcemia, stating that the '371 application examples "demonstrate that [doxcercalciferol] is effective in preventing or restoring the loss of bone mass or bone mineral content while being substantially less toxic than [alfacalcidol]." *Id.* at 4-5. In consideration of these Example 4 statements and Dr. Langman's

[64] Specifically, Dr. Langman testified:

> So let's take the[] results [from Example 4] . . . . Now, as we read in the example, that the serum calcium levels were normalized and the bone density was stable relative to the control period, and they're showing here a representation radiograph of what a normal spine would look like with that nice white skeleton. With stable bone density, a person of ordinary skill in the art would understand that for this to happen, the only way that this could happen with doxercalciferol treatment would be if there was a lowering and maintaining a lowered level of parathyroid hormone. So this is how a person of ordinary skill in the art would understand the results of the doxercalciferol treated group. . . . A person of ordinary skill in the art in 1988 would understand at once the invention in Claim 7, which is rather than with conventional Vitamin D_3-based therapy where the patients are hypercalcemic to have the PTH at this level, now with doxercalciferol, that could be achieved with a normal calcium and a stable bone density.

Tr. at 923:2-924:2 (Langman).

testimony that a person of ordinary skill in the art in 1988 understood that calcitriol and alfacalcidol were associated with hypercalcemia, the court finds that a skilled artisan would understand Example 4 to disclose a "lower incidence" of hypercalcemia than that associated with calcitriol or alfacalcidol at the same level of PTH suppression. Tr. at 925:9-21, 925:22-927:21 (Langman).[65]

The court notes that this conclusion is not undermined by the defendants' arguments that Example 4 does not mention the use of phosphate binders or that a patient in its control group suffering from SHPT would face a "significant risk of injury if they went without any vitamin D treatment for 52 weeks" in the placebo test group. (D.I. 218 at 29.) With respect to the defendants' first assertion, the court finds this argument rebutted by Dr. Langman's testimony that a person of ordinary skill in the art would understand that a phosphate binder would need to be used and, thus, that reference to a phosphate binder in the example is not necessary. Specifically, Dr. Langman testified that, in his view, "a person of ordinary skill in the art reading [Example 4] would understand that patients with end-stage renal disease would need phosphate control with binders. That was just standard practice." Tr. at 971:9-12 (Langman). The defendants seemingly concur with this assessment, noting in their Proposed Findings of Fact that "Example 4 does not mention the use of phosphate binders, and a [person of ordinary skill in the art] in 1988 would have known that it was necessary to administer a phosphate binder to a

[65] The court also notes that, in reaching this finding, it further concludes that the evidence in the record establishes a "descriptive link" between Example 4 in the '371 application and claim 7 of the '116 Patent sufficient to satisfy the written description requirement. Specifically, whereas in *Araid Pharmaceuticals, Inc. v. Eli Lilly & Co.*, the Federal Circuit found that this requirement was not satisfied because the disclosure in that case "mere[ly] mention[ed]" a "desired outcome," here, Example 4 identifies how the desired outcome would be obtained and the Vitamin D analogue that would be employed to achieve the desired result. *See Ariad*, 598 F.3d at 1356-57 (concluding that the patent asserted to constitute an earlier filed application for priority date purposes did not satisfy the written description requirement where the specification of that patent: provided no example molecules in the desired class; and did not establish whether the selected "dominantly interfering molecules" were "spatially distinct" as required). Consequently, because Example 4 details more than "a mere wish or plan for obtaining the claimed . . . invention" and, instead, identifies specific aspects of the invention disclosed in claim 7, the court finds that the 1988 priority date does not fail for lack of written description. *Id.*

patient taking doxercalciferol to treat SHPT." (D.I. 218 at 29 (citing Tr. at 835:21-836:16 (Holick).) The court, therefore, is not persuaded by the defendants' argument. *See All Dental Prodx, Inc.*, 309 F.3d at 774.

In addition, the court rejects the defendants' second assertion that Example 4 fails to disclose the elements of claim 7 of the '116 Patent because "[e]ven Dr. Langman recognized that . . . patient[s] with SHPT would face a significant risk of injury" if they participated in the placebo group described in Example 4. While the defendants are correct that Dr. Langman agreed a patient in the placebo control group of Example 4 could suffer bone breakages due to lower bone density, they do not reference the remainder of Dr. Langman's testimony on this question wherein he explained that such placebo control group tests were common in 1988, though they would not be ethically viable today. Specifically, Dr. Langman explained that, in his experience as chair of the Institutional Review Board at Northwestern University in the early-1990s, "there were long placebo-controlled trials,"[66] and that "it was an acceptable mode of research back then, but not now." Tr. at 968:6-18 (Langman). In light of this explanation regarding practices in and around 1988, the court rejects the defendants' argument that the nature of Example 4's trial was unethical and/or impossible to implement and, therefore, that the plaintiffs were not in possession of the invention in 1988.

Rather, the court concludes, for the reasons stated above, that claim 7 of the '116 Patent is entitled to an August 2, 1988 priority date because Example 4 of the '371 application would have reasonably conveyed to a person of ordinary skill in the art that the inventor had possession of claimed invention as of the filing date. The defendants have not met their burden to prove otherwise by clear and convincing evidence. *See Tech. Licensing Corp.*, 545 F.3d at 1328.

[66] Dr. Langman explained that the long placebo-controlled trials at Northwestern University did not involve patients with end-stage renal diseases, but instead dealt with trials for other diseases. Tr. at 968:6-18 (Langman).

Consequently, the court will evaluate the parties' obviousness arguments based on the relevant prior art date of August 2, 1988.

D. Obviousness

The defendants challenge the validity of claim 7 of the '116 Patent as obvious in light of the prior art. In asserting this argument, the defendants specifically contend that: (1) the asserted claim is entitled to a priority filing date of August 2, 1995—the filing date of the '488 application—and is obviousness based on the prior art at that time; and (2) alternatively, if, as the court has found, the asserted claim is entitled to a 1988 priority filing date, the claim is still obvious in light of the prior art at that time. The court concludes, for the reasons that follow, that the defendants have failed to establish by clear and convincing evidence that the asserted claim of the patent-in-suit is obvious.

1. The Legal Standard

35 U.S.C. § 103(a) provides that a patent may not be obtained 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 to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law that is predicated on several factual findings. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). Specifically, the trier of fact is directed to assess four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness,[67] such as commercial success, long felt but

[67] As a pretrial agreement, the parties agreed that the only secondary consideration the plaintiffs could present would be long-felt but unmet need. The plaintiffs did not introduce any secondary considerations of non-obviousness through witness testimony and do not reference any such considerations in their Proposed Findings of Fact and Conclusions of Law. Consequently, the court will not take these factors into account in its analysis.

unsolved need, failure of others, acquiescence of others in the industry that the patent is valid, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

A presumption of validity and non-obviousness attaches to an issued patent. *See* 35 U.S.C. § 282. A party seeking to challenge the validity of a patent based on obviousness must demonstrate by "clear and convincing evidence"[68] that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. Importantly, in determining what would have been obvious to one of ordinary skill in the art, the use of hindsight is not permitted. *See KSR Intern. Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon *ex post* reasoning" in determining obviousness). Moreover, "a person of ordinary skill in the art" should be viewed not as an inventor—one who "possess something . . . which sets them apart from workers of *ordinary* skill—but, instead, as a hypothetical person of "ordinary" skill in the art. *See W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

In *KSR*, the Supreme Court rejected the rigid application of the principle that there should be an explicit "teaching, suggestion, or motivation" in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art, in order to find obviousness. *See KSR*, 550 U.S. at 415. The *KSR* Court acknowledged, however, the importance of identifying "'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Takeda Chem. Indus. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (quoting *KRS*, 550 U.S. at 418).

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[68] "Clear and convincing evidence is evidence that places in the fact finder 'an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Alza Corp v. Andrx Pharms., LLC*, 607 F. Supp. 2d 614, 631 (D. Del. 2009) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

"Obviousness does not require absolute predictability of success," but, instead, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolado, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)). To this end, obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Moreover, while the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art" to the extent that results may be unexpected, it also recognizes that, per *KSR*, evidence of a "finite number of identified, predictable solutions" or alternatives "might support an inference of obviousness." *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). Further, the Federal Circuit has also clarified that, where a method claim merely confirms a result in humans based on what was observed and predicted from animal testing, the claim is obvious. *See Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1363-64 (Fed. Cir. 2007) ("Scientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable invention.").

2. The Level of Ordinary Skill in the Art

A person of ordinary skill in the art with respect to the patent-in-suit would be: (1) a medical doctor board-certified in nephrology or endocrinology, or a biochemist with a Ph.D. and at least two years of Vitamin D drug discovery experience[69]; or (2) a nephrologist or an

[69] *See* Tr. at 908:14-909:2 (Langman). In particular, Dr. Langman described a person of ordinary skill in the art as:

> a hypothetical person, having the characteristics of an ordinary practitioner in the Vitamin D field, who would be aware of the common general knowledge in the field and has access to all publicly available prior art, who is working in the field of kidney diseases, and, specifically, someone having a medical degree who was board certified in nephrology or endocrinology, or a Ph.D. in biochemistry and least two years of experience in the field of Vitamin D drug discovery.

endocrinologist, or has a Ph.D. with appropriate training (five to ten years) in the field of Vitamin D.[70] The court concludes that the parties' definitions of a person of ordinary skill in the art do not differ in a meaningful way.

3. The Scope and Content of the Prior Art and Differences Between the Claimed Subject Matter and the Prior Art[71]

As a threshold matter, it is important to understand what claim 7 of the patent-in-suit encompasses and what it does not. Claim 7 is a method claim directed to teaching a method of using doxercalciferol to lower and maintain lowered PTH levels in patients who suffer from SHPT secondary to ESRD, and to do so with a lower incidence of hypercalcemia than experienced with treatment via calcitriol or alfacalcidol at the same level of PTH suppression. *See generally* '116 Patent; *see also id.* at col. 14:6-50.

Both at trial and in their post-trial briefings, the plaintiffs focused their non-obviousness arguments on one specific aspect of the invention—the selection of doxercalciferol as the Vitamin D analog. (D.I. 219 at 31-38.) Specifically, the plaintiffs assert that, for the defendants to meet their burden of demonstrating, by clear and convincing evidence, that the '116 Patent is obvious, they must show that: a person of ordinary skill in the art would have been motivated to select doxercalciferol from all available Vitamin D analogs; and, further, that that skilled artisan would have a "reasonable expectation that doxercalciferol could lower and maintain lowered

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Id. The plaintiffs indicate in their Proposed Findings of Fact and Conclusions of Law that, in their assessment, the "obviousness inquiry does not turn on the definition of the [person of ordinary skill in the art]." (D.I. 219 at 31 n.27.)

[70] The defendants' definition of a person of ordinary skill in the art differs from the plaintiffs' definition, in that it describes this individual as having five to ten years of experience in the general Vitamin D field, rather than two years of experience. Tr. at 609:24-610:20 (Friedman). Like the plaintiffs, however, the defendants' expert, Dr. Friedman, concluded that the difference in years of experience proposed by each side "wouldn't make any difference" and would not impact the obviousness analysis. *Id.* at 610:7-20.

[71] The court notes that, in keeping with its priority date finding for claim 7 of the '116 Patent, it makes its obviousness conclusion based on the prior art as of 1988. The defendants also provided two additional prior art references—a 1991 reference and a 1992 reference—that the court does not consider in its assessment. Specifically, these 1995 prior art references are: F. Sata, Y. Ouchi, et al., *Effects of Vitamin D_2 Analogs on Calcium Metabolism in Vitamin D-Deficient Rats and in MC3T3-E1 Osteoblastic Cells*, RES. EXP. MED. 1991:235-242 (1991); and European Patent Application 92104293.3.

PTH levels in patients with ESRD and SHPT with a lower incidence of hypercalcemia than would result from using calcitriol or alfacalcidol to achieve the same level of PTH suppression." (*Id.* at 35.) The plaintiffs contend that the defendants cannot make this showing because doxercalciferol was one of hundreds of the Vitamin D analogs that could have been selected and the prior art did not disclose that it would prove safer, via lower incidence of hypercalcemia, than other Vitamin D analog choices. (*Id.*) Consequently, while the court concludes that the prior art renders every element of the asserted claim nonobvious,[72] it will focus its discussion on how doxercalciferol was viewed as a potential candidate for the treatment of ESRD and SHPT in 1988 based on prior art references available at the time.

As noted, calcitriol and alfacalcidol, both Vitamin D_3 analogs, were used for the treatment of ESRD and SHPT in 1988. Doxercalciferol, though first synthesized as a Vitamin D_2 analog in 1974, was not approved for the treatment of these conditions until 1997. The plaintiffs assert several arguments in support of their contention that a person of ordinary skill in the art would not have selected doxercalciferol for the treatment of ESRD and SHPT and would not have anticipated that this analog would result in a lower incidence of hypercalcemia than calcitriol and alfacalcidol at the same level of PTH suppression.

Conversely, the defendants argue that, by virtue of the following, they have proved by clear and convincing evidence that the asserted claim of the patent-in-suit is obvious: (1) the six prior art references, discussed below, disclosed that doxercalciferol would be activated in ESRD patients, effective in treating ESRD, and could be used to treat patients with SHPT (D.I. 218 at 30); (2) the above-mentioned references also disclosed that doxercalciferol has the same efficacy, based on its calcium absorption, as alfacalcidol but more favorable toxicity, such that it

[72] The court has examined each element of the asserted claim of the patent-in-suit and concludes that the defendants have failed to show, by clear and convincing evidence, that the asserted claim is obvious. The court is persuaded in its assessment by the testimony of Drs. Norman and Langman.

was the only Vitamin D analog of "interest" (*id.* at 30-31); (3) by 1988, it was known to a person of skill in the art that doxercalciferol would result in a lower incidence of hypercalcemia than calcitriol and alfacalcidol (*id.* at 32 (citing DTX-450; DTX-506; Tr. at 644:4-19 (Friedman))); and (4) a skilled artisan in 1988 would have been motivated to administer doxercalciferol to treat ESRD and SHPT because calcitriol and alfacalcidol's relatively high incidence of hypercalcemia was known and was problematic from a treatment perspective (*id.* (citing Tr. at 766:2-9 (Norman)).)

While the defendants are correct that, by 1988, there were prior art references discussing doxercalciferol, the court does not agree with their assertion that these references and conventional wisdom would have led a person of skill in the art to select doxercalciferol and anticipate that its use would result in a lower incidence of hypercalcemia than calcitriol or alfacalcidol at the same level of PTH suppression. Rather, the court finds, based on the evidence presented and testimony adduced at trial, that the defendants' characterization of the prior art reflects a hindsight-driven analysis and, therefore, that they have failed to meet their burden of showing obviousness by clear and convincing evidence. In stating the reasons for its finding on this issue, the court examines the available prior art references introduced at trial below.

a. Prior Art Addressing the Selection of Doxercalciferol to Treat ESRD and SPHT

As noted in the court's Findings of Fact, *supra*, a person of ordinary skill in the art in 1988 was aware that Vitamin D compounds were used to treat bone diseases such as ESRD and SPHT. These skilled artisans were also aware that, while calcitriol and alfacalcidol were the primary drugs available to treat these ailments, these treatments caused patients to experience hypercalcemia even when administered at low dosages. Tr. at 79:10-17, 82:16-22, 84:11-85:5,

101:10-102:21 (Langman); *id.* at 675:21-676:24 (Friedman). Both calcitriol and alfacalcidol are Vitamin D_3 analogs.

At trial, the defendants presented six prior art references that would have been known to a person of ordinary skill in the art in 1988. The defendants maintain that two of these references in particular demonstrate that the selection of the Vitamin D_2 analog doxercalciferol was obvious for treating ESRD and SHPT.[73] The first prior art reference is a 1974 article authored by H.Y. Peter Lam and H.K. Schnoes, and senior authored by H.F. DeLuca[74] ("the Lam article"). This article disclosed the chemical synthesis of doxercalciferol and projected that the use of doxercalciferol would not require a functional kidney for activity.[75] Specifically, the Lam article explained that, "[a]lthough we have as yet not tested doxercalciferol in anephric rats—that means rats with kidneys removed—it would appear almost certain that this analog, like $1\alpha D_3$, alfacalcidol, does not require a functional kidney (the site of 1-α-hydrolyzation) for activity."[76] The defendants' expert, Dr. Friedman, testified that the article's finding would convey to a person of skill in the art that the Lam authors, led by Dr. DeLuca, "made . . . a connection between [ESRD] and their results" because they demonstrated that doxercalciferol can be activated without functioning kidneys. Tr. at 622:1-18 (Friedman).

Dr. Friedman further testified that a skilled artisan would conclude from this finding that doxercalciferol could be used, like alfacalcidol, in humans without functioning kidneys and,

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[73] The defendants argue that the six prior art references, viewed together, would lead a person of skill in the art to select doxercalciferol for the treatment of ESRD and SHPT. Specifically, and as outlined in greater detail in this section, the defendants contend that a skilled artisan in 1988 would select this Vitamin D analog because it was known to treat ESRD and SHPT and, among other characteristics, had a better safety profile than calcitriol and alfacalcidol. Thus, the court notes that, while it addresses only two prior art references in this subsection in connection with the selection of doxercalciferol for the treatment of ESRD and SHPT, it considers the combined body of prior art together in assessing each element of the asserted claim.

[74] H.Y. Peter Lam, H.K. Schnoes, & H.F. DeLuca, *1αHydroxyvitamin D_2: A Potential Synthetic Analog of Vitamin D_2*, SCIENCE, 186:1038-40 (1974).

[75] *See id.* at 1039; *see also* Tr. at 623:16-24 (Friedman).

[76] *Id.*

therefore, could prove beneficial in the treatment of ESRD. *Id.* at 623:16-24. Dr. Friedman maintained that this conclusion and interest in doxercalciferol would not be undermined by the article's finding that "doxercalciferol[] appears to offer no advantages over the previously prepared Vitamin D_3 derivative, 1-α-D_3." *Id.* at 622:24-623:3. Thus, the defendants' assert, via Dr. Friedman's testimony, that the Lam article disclosed that doxercalciferol could be used to treat ESRD and that, although it did not predict advantages over alfacalcidol, it could be used in the same way and presented a Vitamin D_2 alternative for further biological study.[77] *Id.* at 622:1-623:3.

Another reference disclosing that doxercalciferol could be used to treat ESRD was a 1978 article authored by Drs. Reeve and Schnoes and lead authored by Dr. DeLuca[78] ("the Reeve article"). *See* DTX-481; Tr. at 628:15-629:4 (Friedman). Specifically, Dr. Friedman testified that the Reeve article disclosed that doxercalciferol: (1) could be used to treat ESRD in an anephric, or kidney-less, rat, which effectively mimics the human disease ESRD; (2) would be activated in patients without functioning kidneys, as the Lam article had predicted; and (3) could also be used to treat patients with SHPT. *See* DTX-481 at 166; Tr. at 628:15-629:4 (Friedman). The Reeve article reached these conclusions by testing doxercalciferol against a Vitamin D_3 compound in kidney-less rats. Tr. at 624:12-24 (Friedman). As a result, the authors' testing provided a model for treating ESRD in humans[79] and confirmed the findings predicted in the Lam article. *Id.* at 624:14-24, 628:6-629:4. Dr. Friedman testified that this article, coupled with the Lam findings, "shows that [researchers in the field] were making a connection between

[77] Specifically, Dr. Friedman testified that the Lam article, viewed as a whole, would lead a person of ordinary skill in the art to view doxercalciferol as "a very useful tool to probe some of the intricacies of Vitamin D biology." Tr. at 623:4-15 (Friedman).

[78] L.E. Reeve, H.K. Schnoes & H.F. DeLuca, *Biological Activity of 1 α-Hydroxyvitamin D_2 in Rat*, ARCH. BIOCHEM & BIOPHYS. 186(1):164-67 (1978).

[79] Dr. Friedman stated that the model employed in this study, though imperfect, can be "used carefully with careful study design and thoughtful interpretation of the results" and can "definitely provide useful information with applications to human patients." Tr. at 625:1-5 (Friedman).

doxercalciferol and end-stage renal disease" and that doxercalciferol could be used for this purpose. *Id.* at 625:14-22, 628:6-629:4. In view of the findings advanced in these articles, the defendants assert that skilled artisans in 1988 would have known to select doxercalciferol, rather than other possible Vitamin D analogs, for use in treating ESRD and SHPT and, therefore, that the selection was obvious.[80] (D.I. 218 at 29-31.)

In response to these references, the plaintiffs assert that neither the Lam nor Reeve articles taught that doxercalciferol should be selected out of all possible Vitamin D analogs available for further study. (D.I. 219 at 35-38.) Specifically, the plaintiffs note that, in contrast to Vitamin D_3 analogs—analogs which, as noted, are a natural form of Vitamin D made by humans—Vitamin D_2 analogs are synthetic. (*Id.* at 35 (citing Tr. at 759:19-760:16 (Norman)).) Dr. Norman, the plaintiffs' expert witness, testified that a person of skill in the art in 1988 would have known, based on conventional wisdom, that research should be focused on naturally produced, rather than synthetic, Vitamin D.[81] (*Id.* (citing Tr. at 753:19-754:10 (Norman)).) Dr. Norman further testified that this finding is confirmed by the fact that, by 1988, much more was known about Vitamin D_3 analogs than Vitamin D_2 analogs, demonstrating skilled artisans' interest. In particular, Dr. Norman noted that, between 1960 and 1988, over eighty-percent of all

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[80] In alleging that the selection of doxercalciferol to treat ESRD and SPHT was obvious, the defendants assert that the following two elements of claim 7 were obvious in light of the prior art: (1) the administering of an amount of doxercalciferol; and (2) to patients with ESRD and SPHT. (D.I. 218 at 31-32.)

[81] Dr. Norman testified that, with respect to whether skilled artisans in 1988 would prefer Vitamin D_3 analogs over Vitamin D_2 analogs:

> I do not believe that a [person of ordinary skill in the art] would have selected, logically, based on scientific journals, doxer[calciferol] as a drug candidate. And I have a number of reasons to support that argument. First of all, it is important to realize that Vitamin D_3, while it is referred to technically as being a vitamin, in point of fact, everybody in this room and all higher animals have the capability of producing Vitamin D_3 in their body without any dietary supplement, because of exposure of skin to sunlight and converting 7-D-hydrocholesterol into the compound Vitamin D_3. That, I think, more than anything is what attracted interest in the field, is it was an endogenous substance.
>
> Secondly, as a consequence of some of the experimental developments that I have referred to, there was a plethora of analogs that were available to study—not to study clinically—to profile, in terms of basic biological responses. So there would be analogs of Vitamin D_3.

Tr. at 753:19-754:16 (Norman).

relevant publications focused on Vitamin D_3[82] and over ninety-percent of the forty-five 1-α-hydroxy Vitamin D analogs synthesized and biologically tested in 1988[83] were Vitamin D_3 analogs (*Id.* (citing PDTX-282).) In addition, between 1974 and 1988 there were only seven original references on doxercalciferol and all were published by the same laboratory directed by Dr. DeLuca. (*Id.* (citing Tr. at 711:5-10, 772:4-23 (Norman)).) Dr. Norman testified that these publishing figures, coupled with the fact that doxercalciferol, though first synthesized in 1974, had not been administered to humans before Bone Care's clinical trials, make clear that skilled artisans in 1988 had minimal interest in Vitamin D_2 analogs in general, or doxercalciferol in particular, outside Dr. DeLuca's laboratory.[84] (*Id.*)

Finally, the plaintiffs also dispute that there was sufficient information available in the 1988 prior art to disclose that doxercalciferol would prove more effective and/or safer than calcitriol or alfacalcidol. While the court will address the parties' arguments related to doxercalciferol's safety profile in the subsection to follow, the court notes here that the plaintiffs also made this argument in advancing their position that the prior art did not direct skilled artisans to select doxercalciferol for the treatment of ESRD and SHPT. While the plaintiffs do not argue that prior art references—namely, the Lam and Reeve articles—identified doxercalciferol as a compound that could be used to treat ESRD and SHPT, they do contest the notion that a person of ordinary skill in the art would select doxercalciferol in 1988. Specifically, the plaintiffs note that the prior art did not reveal any advantages of doxercalciferol over calcitriol or alfacalcidol, such that a skilled artisan would have no reason to pursue further

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[82] The court notes that this statistic increased between 1984 and 1988, the four years before the filing of the '371 application, to ninety-percent of relevant publications focusing on Vitamin D_3 instead of Vitamin D_2. *Id.* at 763:20-764:1.

[83] *See* PDTX-282; *see also* Tr. at 757:4-759:21, 762:12-763:15, 7645:11-767:10 (Norman).

[84] The plaintiffs also note that, between 1975 and 1988, Dr. DeLuca's laboratory published 220 peer-reviewed articles, reporting on a variety of new vitamin D analogs, including fluorinated vitamin D_3 analogs that were suggested as potentially valuable therapeutic agents. (D.I. 219 at 36 (citing Tr. at 773:7-774:17 (Norman)).)

research and/or development of this compound. (*Id.* at 36-37.) The plaintiffs also note that the testimony of the defendants' expert Dr. Friedman confirmed this point when he stated that both doxercalciferol and alfacalcidol have "equal capacity" to raise serum calcium levels and, thus, would be equally effective. (*Id.* at 37 (citing Tr. at 631:10-16 (Friedman)).)

The court finds Dr. Norman's testimony credible and the plaintiffs' arguments persuasive. Specifically, and as will be addressed more fully in the subsections to follow, while the defendants have cited several prior art references addressing doxercalciferol and two disclosing its capacity to treat ESRD and SHPT, the court is not persuaded that a person of ordinary skill in the art in 1988 would have been motivated to select doxercalciferol over other Vitamin D_2 or Vitamin D_3 analogs available. The court grounds this conclusion in both the credibility of Dr. Norman's testimony and the limited number of prior art references available in 1988 that addressed doxercalciferol and/or distinguished its advantages as an ESRD and SHTP treatment. Importantly, the evidence adduced at trial indicates that only one laboratory was focusing on doxercalciferol as a Vitamin D analog worthy of further research as of 1988. While the defendants did elicit testimony from the plaintiffs' experts that Dr. DeLuca was well respected in the field of Vitamin D research and, therefore, that his laboratory's findings and articles would be well regarded,[85] the defendants have failed to prove by clear and convincing evidence that the prior art in 1988 taught one of ordinary skill in the art to select doxercalciferol over other available Vitamin D analogs. Consequently, the court concludes that the elements of claim 7 addressing the selection of doxercalciferol for the treatment of ESRD and SHPT was not obvious in light of the prior art.

b. Prior Art Addressing Whether Doxercalciferol Would Result in a Lower Incidence of Hypercalcemia Than

[85] *See* Tr. at 619:21-24 (Friedman); *id.* at 742:2-6 (Bishop); *id.* at 790:20-791:7 (Norman).

Calcitriol and Alfacalcidol & Could Be Used in the Treatment of Humans

The defendants further maintain that two other prior art references were available to persons of skill in the art in 1988 disclosing that doxercalciferol has a better "safety profile"—i.e., a lower incidence of hypercalcemia—than calcitriol and alfacalcidol and could be used to treat humans with ESRD and SHPT. (D.I. 218 at 29-31.) Specifically, the defendants first point to Dr. DeLuca's 1983 article, *Metabolism and Mechanism of Action of Vitamin D*,[86] which identified doxercalciferol as the "only other [Vitamin D] analog of considerable interest" and predicted that if doxercalciferol proved less toxic than calcitriol and alfacalcidol, doxercalciferol "may well provide increased therapeutic range for treatment of disease." *See* PDTX-257.

Second, the defendants cite the 1985 Sjoden thesis, which encompassed Dr. Sjoden's findings from a series of five articles published under the direction of Dr. DeLuca.[87] Regarding this thesis, the defendants argue that the Sjoden reference disclosed to those of ordinary skill in the art that: (1) doxercalciferol and alfacalcidol have the same efficiency based on each compound's capacity to "raise intestinal calcium absorption at the same level of PTH suppression" (D.I. 218 at 31 (citing DTX-495; Tr. at 630:16-23 (Friedman)); (2) doxercalciferol is ten to fifteen times less toxic than alfacalcidol (*id.* (citing DTX-495 at 3; Tr. at 631:4-632:25 (Friedman)); and (3) doxercalciferol has favorable toxicity data correlated with increased kidney calcification based on the comparison of doxercalciferol to alfacalcidol in rats (*id.* (citing Tr. at 958:23-959:12, 959:25 (Langman)). In light of these findings, the defendants contend that a

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[86] DeLuca, H.F., *Metabolism and Mechanisms of Action of Vitamin D—1982*, Bone and Mineral Research, Annual 1, Amsterdam: Excerpta Medica (1983).

[87] Sjoden, G., *Effects of Vitamin D*, ACTA ORTHOP. SCAND. SUPPL. 217 56:1-84 (1985); Sjoden, G., *The Effect of 1α-Hydroxyvitamin D_2 on Calcium Metabolismin Glucocorticoid-Treated Rats*, BONE 6:231-234 (1985); Sjoden, G. & U. Lindgren, *The Effect of Prednisolone on Kidney Calcification in Vitamin D-Treated Rats*, CALCIF. TISSUE INT. 37:613-16 (1985); G. Sjoden, C. Smith, J.U. Lindgren & H.F. DeLuca, *1α-Hydroxyvitamin D_2 is Less Toxic than 1α-Hydroxyvitamin D_3 in Rat*, PROC. SOC. EXP. BIO. MED. 178:432-36 (1985); Sjoden, G., J.U. Lindgren & H.F. DeLuca, *Antirachitic Activity of 1α-Hydropxyergocalciferol and 1α-Hydroxycholecalciferol in Rats*, J. NUTRITION 114:2043-46 (1984).

person of ordinary skill in the art in 1988 would understand that doxercalciferol results in a lower incidence of hypercalcemia than calcitriol and alfacalcidol at the same level of PTH suppression, rending that element of claim 7 obvious. (D.I. 218 at 31.)

The plaintiffs, however, dispute the validity of the defendants' arguments. Specifically, the plaintiffs assert that the defendants' contention the prior art disclosed that doxercalciferol is less toxic than calcitriol and alfacalcidol misrepresents the prior art and is based on clinically irrelevant data. (D.I. 219 at 36.) In support of this argument, the plaintiffs note that the defendants' expert on this issue, Dr. Friedman, did not rely on the data examined by the plaintiffs' expert, Dr. Norman, and instead based his conclusions on data selected with the benefit of hindsight. (*Id.*) For instance, the plaintiffs, via Dr. Langman, challenged Dr. Friedman's analysis that the Sjoden rat studies demonstrated that doxercalciferol was less toxic based on its LD_{50} values. In particular, the plaintiffs explain that these LD_{50} values—values referring to the dose at which fifty-percent of rat subjects are killed—represent very large dosages that "bear no resemblance to the doses of Vitamin D compounds administered to human patients" or "tolerable" to these patients. (*Id.* (citing Tr. at 929:18-20 (Langman); Tr. at 792:5-793:2 (Norman)).)

Moreover, the plaintiffs further assert that the clinical irrelevance of this data is confirmed by the fact that: (1) calcitriol and alfacalcidol have disparate LD_{50} values, but have equivalent effects on serum calcium and, thus, hypercalcemia (*id.* (citing Tr. at 792:5-793:2 (Norman)); and (2) Dr. Friedman, in reaching his conclusion on this element, ignored data indicating that the LD_{50} for calcitriol was higher than doxercalciferol, such that this data would

have suggested to a person of ordinary skill in the art that doxercalciferol is more toxic than calcitriol[88] (*id.* (citing Tr. at 930:13-931:3 (Langman); PDTX-133 at 1738; PDTX-259 at 433)).

The plaintiffs also challenge the Sjoden thesis' conclusion, with which Dr. Friedman agreed, that the efficiency of doxercalciferol and alfacalcidol are the same, but that doxercalciferol has lower toxicity.[89] Specifically, Dr. Langman opined that the Sjoden thesis is invalid because, in the rat studies conducted, doxercalciferol and alfacalcidol actually metabolized or activated at different rates, explaining their different toxicity profiles. Dr. Langman testified that these different activation rates demonstrate that doxercalciferol is metabolized more slowly than alfacalcidol, resulting in the appearance that it has lower toxicity. The plaintiffs also note that, while Dr. Sjoden indicates that his data does not support the

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[88] With respect to the toxicity of doxercalciferol as compared to calcitriol or alfacalcidol, Dr. Friedman quoted the Sjoden article's conclusion that the "[m]ortality rate was higher in rats intoxicated with 1-alpha-D_3, alfacalcidol, than for rats given 1-alpha-D_2, doxercalciferol. LD_{50} estimated to be five times to fifteen times higher for 1-alpha-OH Vitamin D_2, doxercalciferol." Tr. at 632:10-18 (Friedman). Dr. Friedman further explained that, in his view, a skilled artisan considering Sjoden's conclusions would believe it to disclose that "doxercalciferol is likely to be a safer drug to administer than alfacalcidol." *Id.* at 632:19-22.

In response, Dr. Langman critiqued Dr. Friedman's conclusions:

> Q: Do the L_{50} results tell the [person of ordinary skill in the art] anything about the relative incidence of hypercalcemia between doxercalciferol and alfacalcidol in treating patients with end-stage renal disease and secondary hyperparathyroidism?
>
> A: No, not at all. You can't equate LD_{50} data in rats into the likelihood of hypercalcemia in the human condition.
>
> Q: Was there any additional rat LD_{50} data available to the [person of ordinary skill in the art] in 1988 that Dr. Friedman did not mention?
>
> A: Yes . . . [t]he LD_{50} data were calcitriol, the other prior art compound. And I obtained this from the actual product label in 1988 for Rocaltrol, the synthetic product of calcitriol. That's PDTX-133. The product label. And in it, where he learned that even at 5 milligrams per kilogram calcitriol given to the rats, over half of them lived. And so the product label simply said, well, the LD_{50} must be greater than that, greater than 5 milligrams per kilogram. And, so certainly with calcitriol being greater than doxercalciferol, that would certainly lead the person of ordinary skill in the art away from choosing doxercalciferol as a safer compound, although as I said, the LD_{50}s don't mean anything. In addition, we also know in the human situation, calcitriol and alfacalcidol, when used to treat secondary hyperparathyroidism in end-stage renal disease patients gave similar frequent hypercalcemia. So, again, more evidence that the LD_{50} data has nothing to do with what happens to humans when related to hypercalcemia in treating secondary hyperparanthyroidism in end-stage renal disease.

Tr. at 930:13-931:13 (Langman).

[89] As Dr. Friedman explained, Sjoden relates "toxicity to renal calcification," "renal calcification to elevated serum levels," and concludes that the "efficacy of the two compounds is about the same despite the big difference in toxicity," such that both have "similar ability to raise serum, similar ability to suppress PTH," but lower toxicity. *Id.* at 643:13-644:3 (Friedman).

conclusion that the two Vitamin D analogs metabolized at different rates, he also states—and Dr. Friedman concurred—that this conclusion does not mean the activation rate explanation can be authoritatively dismissed. Tr. at 640:15-641:4 (Friedman).

Drs. Norman and Langman likewise challenged whether skilled artisans would have accepted Dr. Sjoden's toxicity conclusion in 1988. Specifically, these experts explained that persons of skill in the art in 1988 equated serum calcium levels with toxicity and would have questioned whether two compounds with equivalent serum calcium could have divergent toxicity. *Id.* at 930:13-931:15 (Langman). Dr. Langman, in particular, further challenged the clinical relevance of Dr. Freidman's data, upon which he relied to support the Sjoden thesis findings, through discussion of the "Duphar letter." This letter, a memorandum written by two employees of a potential licensee or business partner of Bone Care,[90] noted that:

> [i]f one believe[s] (as many do) that increased absorption of calcium is the primary task that Vitamin D should accomplish in order to increase bone density, then increased levels of calcium in blood and urine are just as much a part of efficacy as of toxicity. It would then be hard to image that one Vitamin D derivative could have a much better efficacy/toxicity ratio to show than another.

Tr. at 935:9-21 (Langman) (citing PDTX-268). According to Dr. Langman, this memorandum reflects what a person of ordinary skill in the art would have believed in 1988—namely, that "there is [an] intimate association between toxicity and efficacy because of the hypercalcemia." *Id.* at 935:22-24. Thus, based on this understanding, Dr. Langman argued that a person of skill in the art would question the viability of the Sjoden thesis' conclusion that alfacalcidol and doxercalciferol were equally efficient, but that doxercalciferol was less toxic.

In consideration of the foregoing and the relevant law, the court concludes that the element of claim 7 requiring that doxercalciferol result in a lower incidence of hypercalcemia

[90] While the defendants objected to the introduction of this document as not included in the prior art due to its 1991 composition date, the court allowed its introduction because, as the plaintiffs successfully argued at trial, the information contained in the internal memorandum addressed the prior art available in 1988. Tr. at 933:10-22.

than calcitriol and alfacalcidol at the same level of PTH suppression would not be obvious to a person of ordinary skill in the art in 1988. The court reaches this conclusion for the following reasons. First, the court agrees with and finds credible Drs. Langman and Norman's testimony that a skilled artisan in 1988 would question or, at the very least, would need to pursue further research to confirm: (1) the Sjoden thesis' conclusions that doxercalciferol is five to fifteen times less toxic than alfacalcidol and that LD_{50} data can support this conclusion; and (2) the Reeves and Sjoden prior art references' conclusions that doxercalciferol had lower toxicity than calcitriol and alfacalcidol and could be successfully tested in humans.

With regard to the former argument, the court finds Dr. Norman's testimony related to the questionable application of LD_{50} data persuasive and agrees that a skilled artisan in 1988 would have reason to doubt that this data did in fact demonstrate lower toxicity. Specifically, and as Drs. Langman and Norman explained, persons of skill in the art in 1988 equated serum calcium levels with toxicity, such that the Sjoden thesis' finding that doxercalciferol and alfacalcidol had equivalent effects on serum calcium but resulted in divergent toxicity levels, would give a skilled artisan pause. Tr. at 930:13-931:15 (Langman). In fact, even the defendants' expert, Dr. Friedman, conceded on cross examination that a person of skill in the art would not have understood, with any degree of certainty, the mechanism by which one Vitamin D analog could cause a lower incidence of hypercalcemia than another.[91] *Id.* at 681:5-21 (Friedman).

Moreover, the Sjoden thesis' conclusion and its reliance on LD_{50} data in evaluating toxicity would also be doubted due to the fact that calcitriol had a higher LD_{50} than

[91] The court notes that Dr. Friedman attributed the lower toxicity of doxercalciferol versus alfacalcidol to differences in their "cumulative effect . . . on serum calcium." Tr. at 637:14-638:10, 643:15-20 (Friedman). In light of Dr. Friedman's statement on cross examination, however, the court views his opinion as to the difference in toxicity between doxercalciferol and other Vitamin D_3 analogs through the lens of his admission that one of ordinary skill in the art would not have understood the mechanism by which one analog would have lower toxicity than another in 1988. *Id.* at 681:5-21.

doxercalciferol. Thus, notably, to the extent that LD_{50} data was thought to be clinically relevant, a person of skill in the art would anticipate that doxercalciferol was, in fact, more toxic than calcitriol. *Id.* Further, and as referenced above, Dr. Norman explained that the doses used in the Sjoden rat clinical trials were so large that they bore no resemblance to the doses of Vitamin D compounds that could be administered to humans. *Id.* at 792:5-793:2 (Norman). Consequently, Dr. Norman concluded that the Sjoden clinical trials and results did not readily suggest or teach that doxercalciferol could be used in humans despite the fact it suggested such use. *Id.* The court agrees. Thus, while the court finds that the Sjoden and Reeve references, the latter of which used a kidney-less rat clinical trial to mimic ESRD in humans, could lead interested skilled artisans to pursue greater research and experimentation with doxercalciferol, the court is unconvinced that these prior art references and others available in 1988 made the selection of doxercalciferol due to its lower toxicity obvious for the treatment of ESRD and SHPT in humans.[92]

Second, the court also finds persuasive Dr. Langman's testimony that the applicability of doxercalciferol to human treatment was uncertain in 1988 because skilled artisans did not know whether doxercalciferol operated through direct or indirect effect in the human body. Specifically, Dr. Langman explained that, as of 1988, the prior art taught that calcitriol could potentially reduce PTH secretion not only by increasing serum calcium ("the indirect effect"),

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[92] The court notes that even the defendants' expert, Dr. Friedman, seemingly agreed that LD_{50} data does not, in and of itself, predict whether one drug is safer than another:

> A: . . . I would be more likely to give the [Vitamin D analog] with less toxicity, if I wanted to give it. But you would want to know as much biology as you could but you can't do experiments in animals forever. At some point, it has to move to humans.
>
> Q: A person of ordinary skill in the art could not conclude the one drug will be safer than another in humans at therapeutic doses based on rat LD_{50} toxicity data?
>
> A: There would be no certainty of what you are describing, but if you had to guess, you would lean toward the one with the better profile in rats, and I think "lean toward" is probably too cautious. I would actually take into very serious consideration the rat data.

Tr. at 687:5-17 (Friedman).

but also by interacting directly with Vitamin D receptors on the parathyroid glands ("the direct effect"). *Id.* at 936:8-22 (Langman). However, as of 1988 the "direct effect" had only been observed in rats and had not been observed in humans because hypercalcemia prevented the administration of high enough doses of calcitriol. *Id.* at 938:17-20; *see also* PDTX-147 at 2142. Moreover, while Dr. Slatopolsky, the author of a 1984 paper, theorized that the direct effect could be achieved in humans via high peak concentrations of active forms of Vitamin D, Dr. Sjoden suggested that doxercalciferol administration actually resulted in a lower peak concentration than alfacalcidol. Tr. at 938:21-939:9, 940:13-941:5, 942:5-943:1 (Langman).

Dr. Friedman likewise agreed that, "as of 1988, it had not been established whether the administration of doxercalciferol would result in the production of an active Vitamin D compound to act directly on the parathyroid gland in humans." *Id.* at 688:16-23 (Friedman). Specifically, Dr. Friedman noted that "nothing" with respect to how doxercalciferol worked (i.e., direct or indirect effect) "had been established in humans" as of 1988 and, further, that skilled artisans were unaware of how doxercalciferol metabolized in humans, though it was clear that there were differences between the metabolism of Vitamin D_2 and Vitamin D_3. *Id.* at 688:18-23, 689:7-22. In light of these experts' testimonies, the court concludes that a person of ordinary skill in the art in 1988 would not have known whether doxercalciferol would have a direct effect in humans or how the rat study findings on doxercalciferol would be applied to humans. Thus, the court finds that the elements of claim 7 discussed in this section would not have been obvious in light of the prior art.

c. Prior Art Addressing PTH Levels

Finally, the defendants assert that the element of claim 7 measuring PTH levels was obvious based on the prior art.[93] In support of this argument, the defendants point to a 1974 article authored by Dr. Brickman[94] ("the Brickman article") and a 1978 article authored by Dr. Bordier[95] ("the Bordier article"). *See* DTX-450; DTX-506. With regard to the Brickman article, Dr. Friedman testified that this article disclosed: (1) the use of calcitriol to treat humans with SHPT; (2) that hypercalcemia is a potentially important side effect of administering Vitamin D analogs, including calcitriol and alfacalcidol; and (3) the authors preference for measuring PTH levels. (D.I. 218 at 30 (citing DTX-450; Tr. at 614:24-615:2, 615:3-20 (Friedman)).) The defendants also cite to the testimony of the plaintiffs' expert, Dr. Langman, who agreed that the Brickman article described treating patients with SHPT and that the authors measured PTH levels. (*Id.* (citing DTX-450; Tr. at 953:21-955:1 (Langman)).) Regarding the Bordier article, the defendants argue, via Dr. Friedman, that: (1) calcitriol and alfacalcidol are effective in treating bone disease and osteitis fibrosa, which are caused by SHPT; and (2) the authors measured PTH levels.[96] (*Id.* (citing DTX-506; Tr. at 615:21-619:11, 618:14-21 (Friedman)).) The defendants note that Dr. Langman also agreed with this assessment of the Bordier article. (*Id.* (citing Tr. at 955:2-957:10 (Langman)).)

The plaintiffs do not argue that the prior art disclosed measuring PTH levels or that the use of PTH levels for this purpose is unique to the claimed invention. (D.I. 219.) However, the

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[93] The court notes that it does not discuss the "lower and maintain lowered PTH levels" element of claim 7 in his subsection. As referenced in the foregoing discussion of the prior art, skilled artisans in 1988 equated toxicity, i.e., incidences of hypercalcemia, with PTH levels. Therefore, because lowering and maintaining lowered PTH levels is directly relevant to toxicity, the court's finding that this element of claim 7 is not obvious is encompassed in its "lower incidence of hypercalcemia than calcitriol and alfacalcidol" discussion above.

[94] Brickman, Arnold S. et al., *1,25-Dihydroxycholecalciferol: Effect on Skeletal Lesions and Plasma Parathyroid Hormone Levels in Uremic Osteodystrophy*, ARCH. INTERN. MED. 134:883-888 (1974).

[95] Bordier, Philippe, M.D., *The Effect of $1\alpha(OH)D_3$ and $1\alpha,25(OH)_2D_3$ on the Bone in Patients with Renal Osteodystrophy*, AM. J. OF MED., Vol. 64:101-107 (Jan. 1978).

[96] Dr. Friedman also testified, in connection with the Sjoden thesis, that in 1988 a "[person of ordinary skill in the art] can tell . . . that if serum calcium is raised to a similar extent, that PTH will be decreased to a similar extent." Tr. at 638:7-10 (Friedman).

court does not find this element of the claimed invention to be dispositive on the question of obviousness. Specifically, and as noted at the outset of this analysis, the parties' obviousness arguments centered on whether it was obvious to a person of skill in the art in 1988 to select doxercaliferol as a Vitamin D analog that would lower and maintain lowered PTH levels, resulting in a lower incidence of hypercalcemia than calcitriol and alfacalcidol at the same level of PTH suppression. The court agrees that the obviousness assessment turns on these questions and, therefore, its finding of non-obviousness is not undermined by the prior art disclosing this element.

d. Reasonable Expectation of Success

The defendants argue that a person of ordinary skill in the art in 1988 would have a reasonable expectation of success that doxercalciferol could be used to treat humans suffering from ESRD and SHPT and that it would result in a lower incidence of hypercalcemia than the Vitamin D_3 compounds calcitriol and alfacalcidol. (D.I. 218 at 32.) With regard to their contention that a skilled artisan in 1988 would have a reasonable expectation of success in selecting doxercalciferol for the treatment of humans with ESRD and SHPT, the defendants assert this statement, in the main, based on the fact that: (1) the Bordier, Brickman, and Lam articles disclosed rat study results indicating that doxercalciferol would metabolize and function in humans like known Vitamin D_3 compounds (*id.* (citing DTX-450; DTX-506)); (2) Dr. DeLuca predicted that doxercalciferol would be active in humans without a functioning kidney (*id.* (citing DTX-472)); and (3) the Reeves article confirmed Dr. DeLuca's prediction that doxercalciferol is activated by the liver and, therefore, could be used to effectively treat ESRD and SHPT. (*id.* (citing DTX-481).) The defendants also note that, with respect to the use of doxercalciferol in humans, Reeve developed his research model—specifically, testing rats with

removed kidneys—to mimic human ESRD disease.[97] (*Id.* (citing Tr. at 624:3-625:12).) According to the defendants, skilled artisans would have known the Reeve rat study to model human ESRD disease and would have applied his results in conjunction with the Sjoden article findings to develop a reasonable expectation of success that doxercalciferol could be used in humans to treat ESRD and SHPT.[98]

Moreover, and in support of their argument that persons of skill in the art in 1988 would have a reasonable expectation of success that use of doxercalciferol would result in a lower incidence of hypercalcemia than calcitriol and alfacalcidol at the same level of PTH suppression, the defendants note that: (1) the Reeve and Sjoden articles reported doxercalciferol to be as effective as alfacalcidol with lower toxicity; (2) Sjoden disclosed that doxercalciferol is five to fifteen times less toxic than alfacalcidol in a head-to-head study using rats (*id.* at 34 (citing Tr. at 634:13-644:3, 644:8-19, 649:17-22 (Friedman))); and (3) Sjoden explained that this lower toxicity relates to renal calcification and, further, that renal calcification relates to increased serum calcium levels, which cause hypercalcemia (*id.*).

The plaintiffs, however, dispute this characterization. Specifically, the plaintiffs maintain that the prior art actually taught away from the use of doxercalciferol. In support of this argument, the plaintiffs note that, as of 1988, relevant prior art references taught that calcitriol could potentially reduce PTH secretion "indirectly" by increasing serum calcium levels[99] or

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[97] The defendants also explain that rat studies were used in the Reeve and Sjoden articles because: (1) "rat calcium metabolism is similar to that of man"; (2) "rats have been used to study rickets since the early days of Vitamin D research"; and (3) "rats have been used in experimental models of clinically important conditions (e.g., osteoporosis)." (D.I. 218 at 33 (citing DTX-495; Tr. at 786:20-787:11 (Norman)).)

[98] The defendants maintain, with respect to the use of doxercalciferol to treat human patients with SHPT, that a person of ordinary skill in the art "would have been motivated to combine Reeve and Sjoden to practice the method of claim 7 because both references came from the DeLuca laboratory and taught the use of doxercalciferol in humans as the next logical step in finding a way to treatment SHPT with a lower incidence of hypercalcemia." (*Id.* at 34 (citing Tr. at 644:20-645:11, 608:5-19, 642:15-18 (Friedman)).)

[99] Dr. Langman explained the "indirect effect" as follows:

> [As] I am sure by now the Court knows absolutely that calcitriol, when administered, stimulates the intestine to absorb more calcium into the blood and raises the blood calcium that

"directly" by interacting with Vitamin D receptors on the parathyroid glands.[100] (D.I. 219 at 38 (citing Tr. at 936:8-22 (Langman); Tr. at 684:10-685:20 (Friedman)).) Although this "direct" effect had been observed in rats, it had not been observed in humans as of 1988 because hypercalcemia risk prevented high enough doses of calcitriol from being administered. (*Id.* (citing PDTX-147 at 2142; Tr. at 938:17-20 (Langman)).) Dr. Slatopolsky postulated, however, that a similar direct effect could be achieved in humans "via high peak concentrations of active forms of Vitamin D."[101] (*Id.* (citing PDTX-147 at 2142; Tr. at 938:21-939:9, 940:13-941:5 (Langman)).) Dr. Slatopolsky also noted "it would seem that in addition to this calcemic effect, calcitriol per se modifies the secretion of PTH." *Id.* The plaintiffs argue that these findings, coupled with Dr. Sjoden's conclusion that administration of doxercalciferol, at least to rats, resulted in a lower peak concentration of its active form than alfacalcidol, would lead a skilled artisan in 1988 to be taught away from the use of doxercalciferol.

As explained in the preceding subsections, the court is unconvinced that a person of ordinary skill in the art in 1988 would have a reasonable expectation of success that the use of doxercalciferol in the treatment of ESRD and SHPT would result in a lower incidence of hypercalcemia. The court notes that it is similarly unpersuaded, however, by the plaintiffs' argument that the prior art necessarily taught away from the claimed invention. Specifically, while the plaintiffs effectively highlight concerns the prior art presented with respect to success

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> way. This is called indirect, because calcitriol's action to increase the blood calcium and subsequently reduce the PTH in response is indirect, working through the intestinal absorption of calcium.

Tr. at 936:4-17 (Langman).

[100] Explaining the "direct effect," Dr. Langman noted that "[i]n this situation, calcitriol administered goes into the blood and goes directly to the parathyroid glands, and directly reduces PTH through its effect on the parathyroid glands." *Id.* at 936:18-22.

[101] In particular, Dr. Slatopolsky stated that "[t]he present studies demonstrate that calcitriol given intravenously has a greater suppressive effect on the release of PTH than the calcitriol given orally. The major effects of PTH release appeared to be due to an elevation in serum calcium." *See* PDTX-147; *see also* Tr. at 938:21-939:9 (Langman).

in treating ESRD and SHPT with a lower incidence of hypercalcemia—as reflected in the Sjoden and Slatopolsky findings regarding peak concentrations—the court disagrees with the assertion that the prior art taught away from the use of doxercalciferol for this purpose. For instance, while the Sjoden reference detailed lower toxicity findings in rats at doses that would prove intolerable to humans, the plaintiffs did not establish that such references taught away from further experimentation, even if the use of doxercalciferol was not obvious or obvious to try for purposes of the claimed invention in 1988.

Rather, some of the prior art references introduced at trial did in fact identify doxercalciferol for the treatment of ESRD and SHPT and may have been viewed by those of skill in the art as a compound worthy of further study. Thus, while the court concludes that the defendants have failed to prove by clear and convincing evidence that the claimed invention would be obvious to a person of ordinary skill in the art or that a skilled artisan would have a reasonable expectation of success in achieving the claimed invention, the court does not agree that the prior art references available necessarily taught away from further experimentation with doxercalciferol.

e. The Motivation to Develop a Doxercalciferol to Treat ESRD and SHPT

As noted, by 1988 persons of skill in the art were aware that calcitriol and alfacalcidol, even when administered at very low doses, resulted in hypercalcemia. (*Id.* at 32 (citing DTX-450; Tr. at 77:15-92:19 (Langman); Tr. at 615:3-20, 675:21-676:24 (Friedman)).) Because persistent hypercalcemia was known to have negative health effects, the defendants argue that there was a motivation to find a new Vitamin D analog that did not cause hypercalcemia or would, at least, cause a lower incidence of its occurrence in the treatment of ESRD and SHPT. (*Id.* (citing Tr. at 766:2-9 (Friedman)).) While the plaintiffs do not disagree with the defendants'

assessment that skilled artisans in 1988 were motivated to find a Vitamin D analog that caused a lower incidence of hypercalcemia, they dispute the defendants' contentions that a person of skill in the art would have: (1) selected doxercalciferol; (2) pursued doxercalciferol over other Vitamin D analogs based on the research and prior art references produced by Dr. DeLuca's laboratory; and (3) believed, from the prior art available, that doxercalciferol would result in a lower incidence of hypercalcemia or evidence different characteristics than calcitriol or alfacalcidol at the same level of PTH suppression. (*Id.* at 32-33; D.I. 219 at 36 (citing Tr. at 767:11-771:24, 775:1-8, 754:21-755:8 (Norman)).)

In view of the foregoing analysis, the court agrees with the plaintiffs. While it is clear that persons of skill in the art in 1988 were motivated to find a Vitamin D analog that would result in less hypercalcemia in the treatment of ESRD and SHPT, the defendants have not shown by clear and convincing evidence that the selection of doxercalciferol or its lower incidence of hypercalcemia would have been obvious. Specifically, and for the reasons stated more fully above, the court finds that the claimed invention would not have been obvious to a person of ordinary skill in the art in 1988 because: (1) aside from Dr. Sjoden's finding that doxercalciferol was less toxic than alfacalcidol and calcitriol, the prior art did not reliably demonstrate differences between doxercalciferol and these other Vitamin D compounds, such that skilled artisans in 1988 would select doxercalciferol from all other possible Vitamin D analogs available[102]; (2) Dr. Sjoden's finding that doxercalciferol is less toxic than calcitriol and alfacalcidol would likely have been questioned by a person of skill in the art in 1988 because

[102] *See Eisai Co. Ltd.*, 533 F.3d at 1359 (concluding that, where there are a "finite" and "identified predictable" number of solutions, an invention may be obvious). The court notes, as examined above, that there were a number of Vitamin D analogs from which the inventors could select a ESRD and SHPT treatment. In fact, even the defendants' expert, Dr. Friedman, noted that there was an "extensive catalog" of Vitamin D analogs. Tr. at 680:1-18 (Friedman). While Dr. Friedman and the defendants qualified this statement with the fact that several analogs were insignificant in quantity and that Dr. Norman did not consider which would be viable, nevertheless, it is clear to the court that there were multiple analogs and the number was not finite.

skilled artisans equated efficiency with toxicity, these artisans were unaware of how doxercalciferol metabolized in humans, and the doses of doxercalciferol administered in Dr. Sjoden's clinical trials would have been intolerable for humans; (3) doxercalciferol had not been tested in humans since it was first synthesized in 1974 and, as a result, evidence of how it affected humans was not available; and (4) although the measuring of PTH levels and doxercalciferol's potential as a treatment of ESRD and SHPT was known in 1988, the other elements of the claimed invention were not obvious and are central to the obviousness analysis.

This conclusion is further reinforced by the fact that writings on doxercalciferol specifically were limited primarily to Dr. DeLuca's laboratory in advance of the claimed invention and articles on Vitamin D_2 analogs represented less than ten-percent of all prior art references related to Vitamin D analogs in the four years preceding the '371 application. The court finds these facts persuasive in demonstrating that persons of "ordinary" skill in the art—as compared to an inventor, one who "possesses something" setting them apart from a person of "ordinary skill"—would not have viewed the prior art as teaching or suggesting the development of doxercalciferol in the invention claimed. *See W.L. Gore & Assoc.*, 721 F.2d at 1553. Consequently, the court concludes that the claim 7 of the '116 Patent is not obvious in light of the prior art.

IV. CONCLUSION

For the reasons stated above, the court concludes that: (1) the defendants' proposed products induce infringement of the asserted claim of the patent-in-suit and Sandoz's proposed products contributorily infringe the asserted claim; (2) the asserted claim of the patent-in-suit is not invalid as inoperative; (3) claim 7 of the '116 Patent is entitled to a 1988 priority filing date; (4) the asserted claim of the patent-in-suit is not invalid due to obviousness; and (5) the

plaintiffs' Rule 52(c) motion is granted and the defendants' Rule 52(c) motion is denied.[103] An appropriate order will follow.

Dated: June 11, 2012

CHIEF, UNITED STATES DISTRICT JUDGE

[103] As noted, the parties submitted Proposed Findings of Fact and Conclusions of Law, requesting that the court find in its favor on issues of infringement, utility, priority, and obviousness. For the reasons stated above and based on the court's findings, the plaintiffs' Rule 52(c) motion is granted and the defendants' Rule 52(c) motion is denied.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BONE CARE INTERNATIONAL, L.L.C. and GENZYME CORPORATION, Plaintiffs, v. ROXANE LABORATORIES, INC., SANDOZ, INC., and ANCHEN PHARMACEUTICALS, INC., Defendants.	)	C.A. No. 09-cv-285 (GMS) (Consolidated)

ORDER

At Wilmington this 14 day of June, 2012, IT IS HEREBY ORDERED THAT:

1. The defendants' proposed products induce infringement of the asserted claim of the patent-in-suit;

2. Defendant Sandoz's proposed products contributorily infringe the asserted claim of the patent-in-suit;

3. The asserted claim of the patent-in-suit is not invalid as inoperative;

4. The asserted claim of the patent-in-suit is entitled to a priority filing date of August 2, 1988;

5. The asserted claim of the patent-in-suit is not invalid as obvious;

6. The plaintiffs' Rule 52(c) motion is GRANTED and the defendants' Rule 52(c) motion is DENIED.

7. The Clerk of Court is directed to enter final judgment in favor of the plaintiffs and against the defendants.

CHIEF, UNITED STATES DISTRICT JUDGE