IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

BONE CARE INTERNATIONAL, LLC and GENZYME CORPORATION,	)	
Plaintiffs,	)	Case No. 08-cv-1083
v.	)	Judge Robert M. Dow, Jr.
PENTECH PHARMACEUTICALS, INC., and COBREK PHARMACEUTICALS, INC.,	)	
Defendants.	)	

MEMORANDUM OPINION AND ORDER INCORPORATING FINDINGS OF FACT AND CONCLUSIONS OF LAW FOLLOWING BENCH TRIAL

This patent infringement case concerns Plaintiffs Bone Care International's and Genzyme Corporation's ("Plaintiffs") patented pharmaceutical drug, Hectorol®,[1] of which Defendants Pentech Pharmaceuticals, Inc., and Cobrek Pharmaceuticals, Inc., ("Defendants") seek to produce and sell a generic version. The Court presided over a lengthy bench trial in October and November 2010 on the issues of the validity and enforceability of Plaintiff's patent for Hectorol®. Having carefully considered the evidence presented at trial as well as the parties' lengthy post-trial submissions[2] and

[1] Bone Care owns the '116 patent. Genzyme – a subsidiary of Bone Care – bought Bone Care and its patent rights. (Bishop Trial Tr. 1616:9-10.) Genzyme also is the holder of the FDA-approved New Drug Application No. 021-027 for Hectorol® – brand name of injectable doxercalciferol. In this opinion, the Court occasionally refers specifically to the entities Bone Care and Genzyme, but otherwise collectively calls them Plaintiffs.

[2] The parties submitted more than 400 pages of post-trial briefing encompassing their proposed findings of fact and conclusions of law and respective objections thereto.

applied that evidence against the pertinent legal standards, the Court concludes that the patent is both valid and enforceable. Specifically, the Court holds as follows:

(1) As the parties stipulated prior to trial, Defendants have infringed claim 7 of the '116 patent (see Trial Tr. 16:4-17:18; 17:25-18:10);

(2) Notwithstanding the absence of any express finding by the patent examiner, Plaintiffs are entitled to a 1988 priority date because Example 4 of the '371 application satisfies the written description and enablement criteria;

(3) Even with the Perry article[3] and other recent publications, Defendants have not come forward with sufficiently strong evidence from which the Court could conclude that the invention claimed by Plaintiffs is inoperable;

(4) Although Plaintiffs' invention was a good candidate for further study as of 1988, Defendants have not shown that it was either obvious or obvious to try as of that date;

(5) Because Plaintiffs are entitled to the 1988 priority date, the references that Dr. Bishop allegedly failed to disclose to the PTO, all of which post-dated the priority date, are immaterial as a matter of law, and Bishop therefore did not engage in inequitable conduct.

In the opinion that follows, the Court sets out its findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a). In the interest of readability, the Court has integrated its findings of fact and conclusions of law into a single analysis section. The Court has endeavored to indicate with citations to the record the testimony and other

[3] K. Wesseling-Perry, *et al.*, *Calcitriol and Doxercalciferol are Equivalent in Controlling Bone Turnover, Suppressing Parathyroid Hormone, and Increasing Fibroblast Growth-Factor 23 in Secondary Hyperparathyroidism*, Kidney International 2010.

evidence on which it has relied in making findings of fact and has noted those instances in which its findings have been influenced by credibility determinations.[4]

I. Background

A. Factual Background

Hectorol® is an injectable drug indicated for the treatment of patients with hyperparathyroidism secondary to ("SHPT") end-stage renal disease ("ESRD"). [616, at ¶ 434.] Its active ingredient is a vitamin D_2 compound called doxercalciferol (also referred to by its chemical abbreviation, $1\alpha OHD_2$, or one-alpha-hydroxy-vitamin D_2).

Hectorol® is covered by claim 7 of the patent-in-suit, U.S. Patent 5,602,116 ("the '116 patent"), entitled "Method for Treating and Preventing Secondary Hyperparathyroidism." Claim 7 teaches a method of using an effective amount of doxercalciferol to lower and maintain lowered parathyroid hormone ("PTH") levels in human patients who suffer from hyperparathyroidism ("HPT" or "SHPT") secondary to end-stage renal disease ("ESRD"). The '116 patent issued on February 11, 1997, from the '488 application, which was filed on April 3, 1995. The '116 patent is related, through a chain of continuation and continuation-in-part patent applications, to the '371 application (also known as the "parent application"), which was filed on August 2, 1988. (Sofocleous Trial Tr. 1351:16-1352:12, citing DTX 1262.) The '116 patent was issued to inventors Joyce Knutson, Ph.D., Charles Bishop, Ph.D., and Richard Mazess, Ph.D., and was assigned to Bone Care. The '116 patent expires on February 11, 2014. [616, at ¶ 435.] On April 6, 2000, the U.S. Food and Drug Administration ("FDA") approved Plaintiff Genzyme's New Drug Application ("NDA") for doxercalciferol, and Plaintiffs

[4] To the extent that certain factual findings may be deemed to be conclusions of law, they should also be considered conclusions of law. Similarly, to the extent that conclusions of law may be deemed findings of fact, they should be considered findings of fact.

began producing and selling the drug under the brand name Hectorol®. [616, at ¶¶ 430-33.]

Defendants Pentech Pharmaceuticals, Inc., and Cobrek Pharmaceuticals, Inc. ("Defendants") filed an Abbreviated New Drug Application ("ANDA") with the U.S. Food and Drug Administration ("FDA") that sought the FDA's approval to manufacture, produce, and market a generic version of Hectorol®. Plaintiffs subsequently brought this lawsuit against Defendants under the Hatch-Waxman Act, 35 U.S.C. § 271(e)(2), alleging that, as a result of the filing of the ANDA, Defendants were liable for infringement of claim 7 of the '116 patent. Plaintiffs seek a declaratory judgment, injunctive relief, litigation costs, attorneys' fees, and – in the event that Defendants proceed with the manufacture, use, or sale of doxercalciferol prior to the 2014 expiration of the '116 patent – money damages. [197.] Defendants answered and counterclaimed that claim 7 of the '116 patent is invalid and unenforceable under various theories. [227.] Specifically, Defendants counterclaimed that (1) claim 7 was obvious in view of the prior art, (2) the '116 patent is not entitled to a priority date earlier than April 3, 1995, and thus, that any art prior to that date may be considered by the Court in its assessment of obviousness, and (3) the '116 patent is unenforceable because Plaintiffs' inventors and patent attorneys committed inequitable conduct in prosecuting the patent applications before the U.S. Patent and Trademark Office ("PTO") that ultimately led to issuance of the '116 patent. Defendants also contend that the '116 patent is inoperable. Defendants seek attorneys' fees based on the alleged inequitable conduct.

B. Plaintiffs' Motion to Dismiss Defendants' Counterclaims A, B, C, D, E, F, G, and IX

Plaintiffs moved to dismiss Defendants' inequitable conduct affirmative defenses and counterclaims A-G. [241]. The Court granted in part and denied in part Plaintiffs' motion, dismissing Defendants' affirmative defenses and counterclaims A, B, C, and E, but denying the motion as to affirmative defenses and counterclaims D, F, and G. [327]

Defendants alleged in affirmative defense and counterclaim D that Plaintiffs engaged in inequitable conduct in prosecuting the '488 application – a continuation-in-part application that eventually issued as the '116 patent – by intentionally failing to submit to the PTO material prior art references that had been disclosed during prosecution of the '488 application's ancestor applications. Defendants alleged in counterclaim and affirmative defense F that Plaintiffs engaged in inequitable conduct in filing the '488 application because they intentionally failed to disclose to the PTO abstracts and posters ("the Gallagher Abstracts") that were material to the '488 application and antedated its 1995 filing date. In counterclaim and affirmative defense G, Defendants alleged that claim 7 of the '116 is unenforceable because Plaintiffs engaged in inequitable conduct when they submitted to the PTO a 1994 article co-authored by one of the inventors of claim 7 despite knowing that the article obscured the existence of the Gallagher Abstracts.

C. Claim Construction

After holding a tutorial and claim construction hearing and considering the parties' claim construction briefs, the Court construed claim 7 as follows:

> A method for lowering elevated blood concentrations of parathyroid hormone ("PTH") or maintaining lowered blood concentrations of PTH in human patients having increased (*i.e.*, above normal) secretion of PTH by

> the parathyroid gland as a result of a disease wherein the patients' kidneys no longer function at a level necessary to sustain life and thus require chronic dialysis or kidney transplantation, comprising: administering 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.

[468.][5] In other words, claim 7 requires that at a dose that is equipotent to, or equivalently effective as,[6] calcitriol (1α,25-$(OH)_2$ vitamin D_3) and alfacalcidol (1α-OH vitamin D_3) – that is, a dose that produces the same level of PTH suppression as the other two compounds – doxercalciferol (1α-OH-vitamin D_2) would achieve a lower incidence of hypercalcemia.

D. Plaintiffs' Motions for Summary Judgment on Defendant's Counterclaims D, F, G, and IX

Plaintiffs moved for summary judgment on counterclaim and affirmative defense D. [332.] Plaintiffs argued that there were no genuine issues of material fact regarding whether Plaintiffs satisfied their duty to disclose the prior art references to the PTO during prosecution of the '488 application, as Plaintiffs had disclosed the relevant prior art references in the ancestor applications and bore no additional duty to re-submit the references. Plaintiffs argued that Defendants had not sufficiently rebutted the presumption that the PTO examiner had reviewed the ancestor applications during

[5] The Court issued its original claim construction opinion [363] on June 4, 2010; on July 30, 2010, the Court issued a revised claim construction opinion [468].

[6] Defendants interpret the Court's construction of claim 7 as requiring equipotent doses of doxercalciferol and calcitriol and alfacalcidol in terms of PTH-suppression; Plaintiffs state that the term "equipotent doses" is ambiguous and interpret the Court's construction instead as requiring "equivalent effectiveness" of those compounds. Although the Court might quibble with these interpretations, at the end of the day, the Court must and does read claim 7 as construed – that is, a method of administering doxercalciferol at a dose that "achieve[s] the same level of PTH suppression" as calcitriol and alfacalcidol – a construction for which the Court views both "equipotent doses" and "equivalent effectiveness" are roughly analogous, if not identical, terms.

prosecution of the '488 application in compliance with governing PTO guidance. The Court agreed, and granted Plaintiffs' motion for summary judgment motion on counterclaim D. [496, 528.]

Plaintiffs also moved for summary judgment on inequitable conduct counterclaims and affirmative defenses F and G, as well as counterclaim IX. [336.] In counterclaim IX, Defendants seek attorneys' fees pursuant to 35 U.S.C. § 285 on the ground that Plaintiffs engaged in litigation misconduct by arguing that claim 7 of the '116 patent is entitled to a 1988 priority filing date. The Court denied Plaintiff's motion for summary judgment with respect to affirmative defenses and counterclaims F, G, and counterclaim IX. [498.]

E. Trial

The Court held a bench trial in October and November 2010. At trial, Defendants challenged the '116 patent on three grounds. First, Defendants argued that claim 7 was invalid because it was entitled only to its 1995 priority date (the date on which the '116 patent issued) rather than the August 2, 1988 priority date of the '371 parent application. Specifically, Defendants contended that claim 7 did not meet the 35 U.S.C. § 120 priority date requirements of enablement and written description, as set forth in 35 U.S.C. § 112, ¶ 1. Second (and related to the first), Defendants argued that claim 7 was invalid because it was obvious from prior art, assuming that it was entitled only to the 1995 priority date, under 35 U.S.C. § 103. Third, Defendants argued that the '116 patent is unenforceable based on inequitable conduct. Defendants also seek attorneys' fees under 35 U.S.C. § 285.

1. Expert Testimony

a. Plaintiffs' Experts

Plaintiffs' expert Dr. Craig B. Langman is a nephrologist who treats ESRD patients, SHPT patients, and metabolic bone disease patients with doxercalciferol and calcitriol. (Langman Trial Tr. 1760:4-17, 1760:23-1761:2, 1761:3-11, 1762:18-22.) Dr. Langman has been an investigator in many clinical trials, including some relating to vitamin D studies in ESRD patients, and teaches a course on clinical trial design. (Langman Trial Tr. 1761:12-18, 1762:17-24.) Dr. Langman testified at trial about what the '116 patent's ancestor application – the '371 application – would have conveyed to a person of ordinary skill in the art ("POSA") at the time of its filing in 1988. (Langman Trial Tr. 1759:22-1761:11; Keana Trial Tr. 556:24-557:19; Segre Trial Tr. 658:10-17; Segre Deposition Tr. 39:2-7.)

Plaintiff's expert Dr. Anthony Norman has a Ph.D. in biochemistry and conducted his doctoral research in the laboratory of Dr. Hector DeLuca (the inventor of doxercalciferol), where he studied the synthesis of vitamins D_2 and D_3. (Norman Trial Tr. 2107:9-23.) Dr. Norman's subsequent research and publications have all focused on vitamin D research. (Norman Trial Tr. 2109:14-2110:18, 2113:6-2114:18.)

Plaintiffs' expert Mr. Richard A. Killworth is a patent attorney who has worked at the PTO, the U.S. Court of Customs and Patent Appeals, and in private patent law practice.

b. Defendants' Experts

Defendants' expert Dr. Leonard J. Deftos is a board-certified endocrinologist and internist who works in the field of bone and calcium metabolism. Dr. Deftos manages

the treatment of patients with SHPT, and manages and directs clinical and research laboratories assessing patients with calcium and bone disease by measuring PTH levels and vitamin D. Dr. Deftos has published extensively on vitamin D with respect to bone and calcium metabolism. Dr. Deftos also has J.D. and L.L.M. law degrees.

Defendant's expert Dr. John F. W. Keana is a Ph.D. and expert in synthetic and medicinal chemistry. Dr. Keana is the inventor or co-inventor of numerous patents in the area of medicinal chemistry, and has extensive experience prosecuting pharmaceutical patents and consulting for and managing pharmaceutical companies.

Defendants' expert Dr. Gino V. Segre is a medical doctor and board-certified internist. His work focuses on the diagnosis and treatment of patients with disordered calcium metabolism and bone-loss – especially parathyroid gland diseases and renal disease. Dr. Segre has published numerous papers on PTH metabolism, chronic kidney disease, and vitamin D.

Defendants' expert Mr. Michael Sofocleous is a patent lawyer with experience in private patent litigation and in the prosecution of patents within the PTO. He spent more than 30 years working as a PTO examiner, a patent interference examiner for the Board of Patent Interferences, and an administrative patent judge at the Board of Patent Appeals and Interferences.

2. Fact Witnesses

a. Plaintiffs' Fact Witnesses

Plaintiffs called as a fact witness Dr. Charles W. Bishop, Ph.D., one of the named inventors on and co-authors of the '116 patent and its ancestor applications. Dr. Hector DeLuca, the creator of doxercalciferol, appeared via video.

b. Defendants' Fact Witnesses

Defendants called as a fact witness Dr. Donald J. Sherrard, a medical doctor with clinical and research experience treating ESRD patients with vitamin D analogs.[7]

II. Analysis

Where, as here, the PTO has issued a patent, that patent is entitled to a presumption of validity and enforceability. 35 U.S.C. § 282. A party seeking to show that the patent is invalid or unenforceable must do so by clear and convincing evidence. *Research Corp. Techs. v. Microsoft Corp.*, 2010 WL 4971008, at *9 (Fed. Cir. 2010). Thus, for example, if a patent challenger seeks to show that a patent is invalid due to prior art, the challenger must provide clear and convincing evidence that the prior art is invalidating. *Id.*; *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327, 1329 (Fed. Cir. 2008). Here, Defendants' "burden to prove invalidity" – an "ultimate burden[] of persuasion" – never "shifts to the other party." *Tech. Licensing Corp.*, 545 F.3d at 1327. Rather, "the risk of decisional uncertainty stays on the proponent of the proposition." *Id*.

A. Person of Ordinary Skill in the Art

The trier of fact must determine whether a patent can claim priority under 35 U.S.C. § 120 (*i.e.*, is enabled and provides sufficient written description under 35 U.S.C. § 112, ¶ 1) or is obvious under 35 U.S.C. § 103 from the perspective of a person of ordinary skill in the art ("POSA") as of the claimed priority filing date. A POSA is a hypothetical person. (Langman Trial Tr. 1770:12-1771:2.) The parties contest how the Court should define a POSA for purposes of this case.

[7] Consistent with the Court's pre-trial rulings [see 525], Dr. Sherrard testified as both an expert and a fact witness.

Plaintiffs' experts testified that the POSA has *either* a medical degree and is board-certified in nephrology or endocrinology *or* a Ph.D. in biochemistry and at least two years of experience in the field of vitamin D drug discovery. (Langman Trial Tr. 1770:22-1771:2; Norman Trial Tr. 2121:23-2125:11.) Defendants' experts testified that the POSA has *both* a medical degree with a specialization in nephrology or endocrinology and clinical experience treating ESRD *and* "significant experience" in vitamin D and parathyroid research. (Deftos Trial Tr. 42:14-21; Segre Trial Tr. 672:11-19.) Defendants state that "significant experience" could be a Ph.D. in biochemistry or a related field *or* research experience equivalent to that of a Ph.D. Neither Defendants nor Plaintiffs presented as expert witnesses any individual who has both a medical degree and a Ph.D. or equivalent research experience in the relevant fields. Moreover, the inventors of the '116 patent were Ph.D.s, but none was a medical doctor.

The Court concludes that for purposes of this case, the POSA is an individual who has *either* a medical degree and is board-certified in nephrology or endocrinology *or* a Ph.D. in biochemistry and at least two years of vitamin D research experience. As indicated by the fact that both parties called as experts individuals who held one or the other (but not both) of these qualifications, the Court believes that either combination of educational and professional background is sufficient to qualify someone as a person with ordinary skill in the art of treating ESRD and SHPT patients with vitamin D drugs. For example, a board-certified nephrologist or endocrinologist physician would have ordinary skill in identifying, from a clinical perspective, which treatment among the range of known and available treatments would be most appropriate for this patient group; a Ph.D

doctorate would have ordinary skill in identifying, from a biochemical research perspective, the same from a laboratory environment.

B. Infringement

Prior to trial, Defendants stipulated to infringement of claim 7 of the '116 patent. Accordingly, the Court need not further discuss any issues relating to infringement.

C. Priority

Bone Care filed the '488 application – which eventually issued as the '116 patent-in-suit – on April 3, 1995, as a continuation-in-part application of the '371 application. Through claim 7 of the '116 patent, Plaintiffs claim priority to the August 2, 1988 filing date of the '371 application pursuant to 35 U.S.C. § 120. [616, at ¶ 213 (citing Sofocleous Trial Tr. 1356:3-1357:10).] Defendants have mounted a challenge to Plaintiffs' claim to the priority filing date of August 2, 1988, asserting that claim 7 is entitled only to the April 3, 1995 filing date of the '488 application. In sorting out the priority issue, the Court must navigate a fairly complex web of standards, burdens, and terminology – all of which is made more challenging by the absence of any express finding on priority by the patent examiner in this case.

1. The '371 Application

Plaintiffs filed the '371 application on August 2, 1988. [616, at ¶ 207 (citing Killworth Trial Tr. 2045:18-2045:20).] Dr. Bishop drafted the '371 application along with Carl Gulbrandsen, Bone Care's patent attorney. [616, at ¶ 243 (citing Bishop Trial Tr. 1564:15-18).] Dr. Bishop wrote all four examples in the '371 application. [610, at ¶ 245 (citing Bishop Trial Tr. 1565:18-21; 1566:15-16; 1566:24-1567:4; 1615:12-16).][8]

[8] The '371 application issued as U.S. Patent No. 5,106,864 ("the '864 patent"). [616, at ¶ 252 (citing Bishop Trial Tr. 1611:10-14; Sofocleous Trial T. 1351:21-1352:1).]

The '371 application contains four examples: Example 1 reports H-101, an actual human clinical trial of doxercalciferol in six post-menopausal osteoporotic women. [616, at ¶ 209 (citing Langman Trial Tr. 1775:11-1775:17).] Examples 2 and 3 are prophetic examples – that is, they describe clinical trials that had not yet been conducted at the time of filing – of clinical trials in which doxercalciferol was administered to treat osteoporosis in women. [616, at ¶ 210 (Langman Trial Tr. 1776:2-1776:6).] Bone Care's H-102 protocol, which it submitted to the FDA in May 1989, was written in accordance with example 2 of the '371 patent. [616, at ¶ 254 (citing Bishop Trial Tr. 1567:7-11, 1569:14-1570:9).] Bone Care's H-103 and H-104 protocols, which were submitted to the FDA in April 1991, were written in accordance with example 3. [616, at ¶ 255 (citing Bishop Trial Tr. 1567:7-14, 1570:10-1571:16).]

Like examples 2 and 3, example 4 of the '371 application is a prophetic example. [616, at ¶ 247 (citing Bishop Trial Tr. 1565:9-21, 1566:20-1567:9).] Example 4 describes a clinical trial in which doxercalciferol is administered as a treatment for patients with renal disease.[9] [616, at ¶ 211 (citing Langman Trial Tr. 1776:18-1776:22)].

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[9] The full text of Example 4 follows:

> 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 micrograms/day) and the other group receives a matching placebo Both treatment groups receive a maintenance dosage of Vitamin d3, 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.

Example 4 of the '371 application describes a randomized, double-blind placebo-controlled study of 30 men and women who have renal disease and are undergoing chronic hemodialysis. [616, at ¶ 216, 224 (citing Langman Trial Tr. 1778:13-16, 1782:21-1784:22).] Example 4 divides the 30 patients into two groups, one of which receives doxercalciferol (the treated group) while the other receives a placebo (the untreated group). [616, at ¶ 220 (citing Bishop Trial Tr. 1604:10-19; Langman Trial Tr. 1776:2-22; Keana Trial Tr. 376:3-21).] Both groups of patients undergo an eight-week control period during which the patients' prior renal disease therapy – including any vitamin D therapy – is stopped, so as not to influence the results of the trial. [616, at ¶ 221 (citing Langman Trial Tr. 1781:22-1782:15, Segre Trial Tr. 959:6-23, Keana Trial Tr. 376:3-21).] The primary endpoint for measuring results in Example 4 was a measurement of serum calcium. [610, at ¶ 69 (citing Keana Trial Tr. 372:7-374:14, 377:7-11, 377:22-378:10, 380:2-18, 390:9-12; Segre Trial Tr. 932:1-5, 936:22-937:5; Bishop Deposition Tr. 157:14-20).]

Example 4 reported results of the placebo group of patients showing frequent hypocalcemia as well as significant reductions in radial and spinal bone density.[10] [616,

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> 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 compounds how 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 treated group.

(JTX60 at FGALL 000945-946, '371 application at 13-14, PH000022-23).

[10] A decrease in bone mineral density in ESRD patients is known as hyperparathyroid bone disease and is the metabolic result of hypocalcemia and SHPT. (Langman Trial Tr. 1789:6-20.) The disease results from chronically elevated PTH in SHPT patients, which results in a continual

at ¶ 226 (citing Langman Trial Tr. 1785:8-11, Langman 1790:13-1792:6).] The example describes the treated group of patients as reporting results of normalized serum calcium levels and stable radial and spinal bone densities. [616, at ¶ 234 (Langman Trial Tr. 1797:1-10).] The treated patient group is reported to have an "insignificant" incidence of hypercalcemia. [616, at ¶ 238 (citing Langman Trial Tr. 1801:5-8).]

Bone Care submitted the H-106 protocol to the FDA in September 1994. The protocol was written in accordance with example 4 and sought the FDA's approval for using doxercalciferol to treat patients with ESRD and SHPT. [616, at ¶ 256 (citing Bishop Trial Tr. 1567:14-17, 1571:7-1573:3).] When the H-106 protocol was approved – after the '488 application was filed – Bone Care conducted the first human clinical trial of doxercalciferol on ESRD and SHPT patients. [610, at ¶ 8 (citing Bishop Trial Tr. 1571:10-1572:2).]

The '371 application states that the four examples included in the application "demonstrate that [doxercalciferol] is effective in preventing or restoring the loss of bone mineral content while being substantially less toxic than [alfacalcidol]." [616, at ¶ 240 (citing Langman Trial Tr. 1801:9-15).]

2. Claim 7 of the '116 Patent

Bone Care filed the '488 application – which ultimately issued as the '116 patent – on April 3, 1995. [616, at ¶ 267 (citing Sofocleous Trial Tr. 1351:16-1352:12; Bishop Trial Tr. 1612:2-11).] The '488 application was filed as a continuation-in-part application of earlier patent applications that ultimately led back to the '371 "parent" application. [615, at ¶ 267.] At the time of filing of the '488 application, doxercalciferol

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signal to the bones to release stored calcium, which in turn leads to a decrease in radial and spinal bone mineral density. (*Id.*)

had been administered to treat osteoporosis in women, but had not been administered as a treatment for men and women diagnosed with SHPT and ESRD. [610, at ¶ 8 (citing Bishop Trial Tr. 1571:10-1572:2).]

While the claims of the '371 application were directed in large part to the treatment of osteoporosis patients, the claims of the '488 application were directed to the treatment of ESRD and SHPT patients. [616, at ¶ 267 (citing Sofocleous Trial Tr. 1351:16-1352:12; Bishop 1612:2-11).] Specifically, claim 7 of the '116 patent teaches a method of administering doxercalciferol to ESRD and SHPT patients. [616, at ¶ 274 (citing Bishop Trial Tr. 1615:20-24).] The endpoint described in claim 7 is the measurement of PTH. [616, at ¶ 270.] As construed by the Court, claim 7 describes:

> A method for lowering elevated blood concentrations of parathyroid hormone ("PTH") or maintaining lowered blood concentrations of PTH in human patients having increased (*i.e.*, above normal) secretion of PTH by the parathyroid gland as a result of a disease wherein the patients' kidneys no longer function at a level necessary to sustain life and thus require chronic dialysis or kidney transplantation, comprising: administering 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.

[468.] As construed, claim 7 may be broken down into four "key elements":

1) human patients suffering from ESRD;
2) SHPT;
3) lowering and maintaining lowered PTH levels;
4) with a lower incidence of hypercalcemia.

[616, at ¶ 212.]

3. The PTO Examiner's Determination of Priority During Prosecution of the '116 Patent

Before turning to whether, in the Court's view, example 4 of the '371 application would reasonably have conveyed to a POSA as of 1988 the invention set forth in claim 7

of the '116 patent, the Court will address the parties' contentions concerning whether the PTO examiner expressed any view on that subject. For, if he did so explicitly, the examiner's views would require the Court to place a thumb on the scale in favor of Plaintiffs on the issue of priority. But if that is not so, then the Court must make an independent assessment, applying the standards set forth under controlling Federal Circuit law.

The PTO issued the '116 patent on February 11, 1997. The '116 patent issued from a chain of five patent applications:

> 1. Application no. 415,488 ("'488 application"), filed on April 3, 1995 and issued as the '116 patent on February 11, 1997;
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> 2. Application no. 119,895 ("'895 application"), filed on September 10, 1993 and issued as U.S. Patent No. 5,403,831 ("'831 patent") on April 4, 1995;
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> 3. Application no. 812,056 ("'056 application"), filed on December 17, 1991;
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> 4. Application no. 569,412 ("'412 application"), filed on August 17, 1990 and issued as U.S. Patent No. 5,104,864 ("'864 patent") on April 14, 1992; and
>
> 5. Application no. 227,371 ("'371 patent application"), filed on August 2, 1988.

[616, at ¶ 275 (Sofocleous Trial Tr. 1351:11-1352:12).]

When it was first filed, the '488 application did not specifically reference the '371 application in its relate-back clause. [616, at ¶ 277 (Killworth Trial Tr. 2047:8-2047:13).] The '488 application initially included 16 claims, which were directed to methods of treatment, compositions, pharmaceutical compositions, and an article of manufacture. [616, ¶ 278 (citing joint trial exhibits).] In a Preliminary Amendment dated April 29, 1996, Plaintiffs added four new claims: claims 17-20. [616, at ¶ 279.]

Claim 17 of the '488 application ultimately issued as claim 7 of the '116 patent. [616, at ¶ 280 (Killworth Trial Tr. 2046:13-2046:18, 2047:22-2048:7).]

PTO Examiner Criares ("the Examiner") held an interview with Plaintiffs' patent attorneys, Welch and Gulbrandsen, on June 26, 1996. [616, at ¶ 281.] The Examiner's notes from that meeting indicate that he and the attorneys discussed "all claims" of the application, prior art, and amendments that might overcome the prior art. [616, at ¶ 282.] Specifically, the Examiner, Welch, and Gulbrandsen discussed the claims of the '488 application in view of two extant patents – U.S. Patent No. 5,063,221 ("the Nishii patent"), which issued on November 5, 1991, had a filing date of March 29, 1990, and had a foreign priority date of April 5, 1989; and U.S. Patent No. 4,948,789 ("the Slatopolsky patent"), which issued on August 14, 1990, and had a filing date of March 28, 1989. Welch and Gulbrandsen had brought the Nishii patent to the Examiner's attention in an Information Disclosure Statement dated December 4, 1995. [616, at ¶ 284.] The applicants brought the Slatopolsky to the Examiner's attention at the June 26, 1996 interview. [616, at ¶ 284.] Following the interview, the Examiner rejected all claims of the application over the Nishii and Slatopolsky prior art. [616, at ¶ 283.]

In response to the Examiner's rejections of the claims, Welch amended the '488's application relate-back clause to include a claim for priority to the August 2, 1988 filing date of the '371 application. [616, at ¶ 287 (citing Killworth Trial Tr. 2046:23-2047:1; 2050:18; 2052:1-2052:8).] The relate-back clause drew the Examiner's attention to the fact that "applicants' priority date antedates the filing dates of the prior art discussed in the interview, namely Nishii * * * and Slatopolsky * * *." [616, at ¶ 288 (citing Keana Trial Tr. 2046:23-2047:1, 2050:10-20150:18, 2052:1-2052:8).] Welch also cancelled

claims 5, 6, 10-14, and 19-20, and amended claims 1, 2, 15, and 16. [610, at ¶ 106(f).] In addition, she narrowed claims 1 and 2 in order to distinguish them from the Nishii and Slatopolsky patents. [610, at ¶ 113.] Welch stated that the amendments to the application made the invention "distinguishable" from the Nishii and Slatopolsky prior art. [610, at ¶ 278 (citing Keana Trial Tr. 356:24-357:18).] Welch did not submit affidavits or other evidence showing conception of the invention of a method of administering doxercalciferol to lower serum PTH in SHPT and ESRD patients prior to the filing of the Nishii and Slatopolsky patents. [610, at ¶ 126 (citing Keana Trial Tr. 364:11-24).] Further, Welch did not submit a supplemental oath or declaration when she amended the relate-back clause, as required by the Manual of Patent Examining Procedure ("MPEP"), Sixth Edition, Jan. 1995 at § 1.67(c). [610, at ¶ 134 (citing Killworth Trial Tr. 2071:20-2072:18).]

Examiner Criares did not issue an Office Action on the merits in response to the applicants' amendments; instead, on July 12, 1996, he issued a Notice of Allowability that allowed claim 17 (among others). [610, at ¶ 131 (citing Sofocleous Trial Tr. 1356:22-1357:17, Killworth Trial Tr. 2054:1-5, 2060:19-20).] The Notice of Allowability did not include an explicit determination regarding priority of the '488 application at any time during the prosecution of that application. [610, at ¶ 136 (citing Sofocleous Trial Tr. 1357:4-21).]

Defendants argue that because (1) applicants' relate-back clause improperly failed to file a supplemental oath or declaration, (2) the Examiner did not have evidence that claim 17 was conceived of or reduced to practice in 1988, and (3) the Examiner did not make an explicit determination regarding priority during the prosecution of the '488

application, the '488 application – and the '116 patent that issued from it – should not be entitled to a 1988 priority filing date. [610, at 130-136.] Defendants further argue that, although the Examiner ultimately issued a Notice of Allowability despite his earlier rejections of all claims over the Nishii and Slatopolsky patents, the basis of allowance has nothing to do with a priority date determination, but rather shows that the Examiner believed that the invention of claim 17 was "distinguishable" from the prior art. [610, at ¶ 117 (citing Keana Trial Tr. 360:20-363:4).]

Plaintiffs contend that by drawing the Examiner's attention to their priority claim, the inventors set up the issue of priority for determination. [616, at ¶ 292.] Plaintiffs argue that the MPEP § 201.08 requires the examiner to make such a determination under these circumstances. [616, at ¶ 292 (citing Killworth Trial Tr. 2052:9-14).] Because the Examiner issued a Notice of Allowability for claim 17 (and other claims) after Welch submitted the amended claims, Plaintiffs argue that the Examiner necessarily had to have concluded that the prior art references were overcome by the claim to priority to August 2, 1988 filing of the '371 application. [616, at ¶¶ 294-296 (Killworth Trial Tr. 2054:1-9, 2054:15-24, 2058:17-2059:9, 2060:19-2060:20).] Otherwise, Plaintiffs assert, the Examiner could not have allowed claim 17 over the Nishii and Slatopolsky references. Plaintiffs further argue that the Examiner had sufficient time and familiarity with the subject matter of the '488 and '371 applications to substantively consider the claim to priority. [616, at ¶ 298 (citing Killworth Trial Tr. 2061:22-2062:6).]

In a prior opinion at the summary judgment stage [496, at 8-10], this Court set forth the principles that govern a court's assessment of the whether a PTO examiner has signed off on a priority determination. Without repeating the full analysis, the Court

reiterates the Federal Circuit's statement that "[t]he PTO's own procedures indicate that examiners do not make priority determinations except where necessary." *Power Oasis, Inc. LLC v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1305 (Fed. Cir. 2008). Of course, when the PTO does render a decision on priority, that decision is entitled to deference from the courts. See *id*. at 1304. But "[w]hen neither the PTO nor the Board [of Patent Appeals and Interferences] has previously considered priority, there is simply no reason to presume that claims in a CIP application are entitled to the effective filing date of an earlier filed application. Since the PTO did not make a determination regarding priority, there is no finding for the district court to defer to." *Id*. at 1305.

The Court noted in its earlier opinion – and reiterates here – that there was no express priority finding by Examiner Criares. The difficulty in this instance is that the Court has no way of determining with any degree of confidence, much less certainty, why no finding was made. Since the Examiner had before him multiple arguments for issuing the Notice of Allowance, some of which were consistent with an implicit finding of a 1988 priority date and others of which were not – for example, the argument that claim 17 is distinguishable from the prior art – there is no way of inferring a priority finding from the Examiner's silence on the issue. The upshot of the foregoing analysis is that the contested aspects of the priority determination under 35 U.S.C. § 112, ¶ 1 (written description and enablement[11]) must be assessed without according any deference to the Examiner's (unstated) views.

[11] The third requirement of § 112, ¶ 1, best mode, is not at issue here.

3. Written Description – Whether Example 4 of the '371 Application Would Reasonably Have Conveyed the Invention Set Forth in Claim 7 to a POSA in 1988

At trial, Plaintiffs presented evidence that they contend shows that claim 7 is entitled to August 2, 1988 filing date because the '371 application provides a written description the invention. Defendants countered with evidence purporting to show that that the invention described in claim 7 was not sufficiently described by the '371 application, thereby entitling claim 7 only to the 1995 filing date.

As a threshold matter, the Court will restate, and perhaps clarify [see 502, at 13 n.9], its understanding of the controlling law on the written description requirement. Where, as here, the Defendants have contended that a patent is invalid based on anticipating prior art, the Plaintiffs have "the burden of going forward with evidence * * * that * * * it is not prior art because the asserted claim is entitled to the benefit of a filing date prior to the alleged prior art." *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008). This requires the Plaintiffs "to show not only the existence of the earlier application, but why the written description in the earlier application supports the claim" – that is, the existence of "an ancestor" to the patent at issue with a prior filing date that "contains a written description that supports all the limitations" of the claim. *Id*. Once "the evidence and argument in support of the earlier filing date is * * * before the court, the burden of going forward again shifts to the proponent of the invalidity defense," and Defendants must *convince* the court that [Plaintiffs are] not entitled to the benefit of the earlier filing date." *Id*. at 1328 (emphasis added). As the Federal Circuit stressed, "'[c]onvince' is the operative word, because if the court is not persuaded by clear and convincing evidence that [Defendants are]

correct," the Defendants have failed to carry their ultimate burden of persuasion, and their defense of invalidity fails. *Id*. In short, the "ultimate burden" that is on the challenger to show by clear and convincing evidence that a patent is invalid "never shifts, however much the burden of going forward may jump from one party to another as the issues in the case are raised and developed." *Id*. at 1329.

Here, because "the evidence and argument in support of the earlier filing date is * * * before the court, the burden of going forward again shifts to the proponent of the invalidity defense," and Defendants must *convince* the court that [Plaintiffs are] not entitled to the benefit of the earlier filing date." *Tech. Licensing Corp.*, 545 F.3d at 1328; see also *Ralston Purina Co. v. Far-Mar-Co.*, 772 F.2d 1570, 1574 (Fed. Cir. 1985) ("A party asserting invalidity based on 35 U.S.C. § 112 bears no less a burden and no fewer responsibilities than any other patent challenger"). "It is elementary patent law that a patent application is entitled to the benefit of the filing date of an earlier filed application only if the disclosure of the earlier application provides support for the claims of the later application, as required by 35 U.S.C. § 112." *In re Chu*, 66 F.3d 292, 297 (Fed. Cir. 1995).

As the Court previously has explained [see 498, at 11-12], to satisfy the written description requirement, a patent application to which inventors later claim priority (*i.e.*, a parent application) must "contain a written description of the invention and process of making and using it * * *." 35 U.S.C. § 112, ¶ 1. The written description requirement is satisfied when "the disclosure of the [invention in the parent application] reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351

(Fed. Cir. 2010) (*en banc*) (citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)). The test 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 ("POSA"). Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." *Id*. The original application need not recite the claimed invention *in haec verba* – that is, in exactly the same terms as the later application does – but it must do more than merely render the invention obvious. *Id.* at 1352.

Although the specification "must *describe* the claimed invention with all its limitations" (*Tronzo v. Biomet*, 156 F.3d 1154, 1158 (Fed. Cir. 1998) (emphasis added)), a 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, LLC v. Advantage Dental Products, Inc.*, 309 F.3d 774 (Fed. Cir. 2002) (emphasis added). It is sufficient for purposes of the written description requirement that a POSA would find it "reasonably clear what the invention is and that the patent specification conveys that meaning." *Id.*; see also *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1997) ("a prior application itself must describe an invention, and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought"). In short, the written description must "actually or inherently disclose" each element claim. *PowerOasis*, 522 F.3d at 1307. Finally, "[c]ompliance with the written description requirement is a

question of fact, which, following a bench trial," is reviewed by the court of appeals for clear error. *Tech. Licensing Corp.*, 545 F.3d at 1332.

Defendants argue that example 4 of the '371 application would not reasonably have conveyed the invention set forth in construed claim 7 to a POSA in 1988, and thus that the '371 application does not sufficiently describe the invention so as to entitle claim 7 to the filing date of the '371 application. Specifically, Defendants presented evidence that the '371 application did not describe three of the four "key elements" of construed claim 7: administration of doxercalciferol to SHPT patients (element two) in a manner that lowered or maintained lower PTH levels (element three) with a lower incidence of hypercalcemia than calcitriol or alfacalcidol (element four).

Plaintiffs acknowledged that at the time the '371 application was filed, the inventors did not have clinical data on the use of doxercalciferol patients in ESRD patients [610, at ¶ 67 (citing Bishop Deposition Tr. 147:6-13, 148:1-14)]. However, Plaintiffs presented evidence purporting to show that example 4 of the '371 application provided the first written record of Plaintiffs' desire to evaluate doxercalciferol in patients with SHPT and ESRD [610, at ¶ 67 (citing Bishop Deposition Tr. 134:1-7)] and thus evidenced the conception and reduction to practice of the invention set forth in claim 7 [610, at ¶ 67 (citing Bishop Deposition Tr. 143:3-16, 145:19-147:5)].

a. ESRD

As stated above, example 4 of the '371 application describes a prophetic clinical trial in which doxercalciferol is administered to 30 men and women who have renal disease and are undergoing chronic hemodialysis. [616, at ¶ 216 (citing Langman Trial Tr. 1778:13-16).] Plaintiffs' and Defendants' experts agreed that a POSA in 1988 would

have understood that patients who have renal disease and are undergoing chronic hemodialysis have ESRD. [616, at ¶ 217 (citing Langman Trial Tr. 1778:10-25; Segre Trial Tr. 937:18-23; Keana Trial Tr. 376:6-8; 565:3-14); .610, at ¶ 80 (citing Segre Trial Tr. 770:24-771:25, 804:4-22, 937:18-938:1; Langman Trial Tr. 1778:2-1779:4).] The Court thus finds that example 4 sufficiently describes this element of claim 7.

b. SHPT

Plaintiffs' expert Dr. Langman testified that a POSA in 1988 would have understood that patients undergoing chronic hemodialysis (*i.e.*, who have ESRD) would have SHPT. [616, at ¶ 35 (citing Langman Trial Tr. 1779:13-1781:14).] Dr. Langman stated that in a randomized double-blind placebo trial like the one described in example 4 of the '371 application, the results of the placebo group provide the POSA with information regarding the disorder with which both patient groups present. [616, at ¶ 225 (citing Langman Trial Tr. 1776:10-15, 1783:10-14).] Here, example 4 explicitly states that the placebo group experienced (1) frequent hypocalcemia and (2) a loss of radial and spinal bone density [616, at ¶¶ 226, 229 (citing Langman Trial Tr. 1785:8-11, 1789:6-20).] Dr. Langman testified that these two conditions would have told a POSA in 1988 that the patients had SHPT. Specifically, Dr. Langman testified that a POSA would have interpreted the term hypocalcemia to be synonymous with SHPT in patients who have ESRD. [616, at ¶ 228 (citing Langman Trial Tr. 1788:16-1789:25).] In addition, Dr. Langman testified that a loss of bone density in ESRD patients would have been understood to be a symptom of metabolic bone disease that was caused by elevated PTH in untreated patients with SHPT.[12] [616, at ¶ 230 (citing Langman Trial Tr. 1789:6-20).]

[12] The parties' experts' contested whether the type of bone mineral density measurements commonly performed in 1988 would be understood by a POSA to be an endpoint for SHPT.

Dr. Langman noted that the FDA-approved label for calcitriol in 1988 stated that it was to be used "for the management of hypocalcemia and the resultant metabolic bone disease in patients undergoing chronic renal dialysis."[13] [616, at ¶ 231 (citing Langman Trial Tr. 1792:22-1793:11).][14] Plaintiffs also presented evidence that a POSA in 1988 would have concluded that the patients in example 4 were being treated for SHPT by virtue of the control period prescribed in the example. [616, at ¶¶ 221, 223 (Langman Trial Tr. 1782:16-20).] The control period required that both patient groups "receive a maintenance dose of vitamin D_3." Because vitamin D is used only in ESRD patients to treat SHPT, Dr. Langman testified that the control period would tell a POSA in 1988 that the patients had SHPT. [616, at ¶¶ 221, 223 (Langman Trial Tr. 1782:16-20).]

Defendants argued at trial that nothing in example 4 defines whether the patients have SHPT. [610, at ¶ 80.] First, Dr. Segre testified that, contrary to Dr. Langman's assertion, the term "hypocalcemia" and "SHPT" in ESRD patients are not synonymous: some ESRD patients would have normal serum PTH levels, and others might have a condition known as tertiary hyperparathyroidism (a condition that is unresponsive to vitamin D therapy). [610, at ¶¶ 89-90 (citing Segre Trial Tr. 761:6-11, 767:6-14, 772:10-13, 773:9-16, 810:5-19, 816:19-820:8, 834:2-17, 962:1-4, 1000:24-1001:5).] In either of those cases, the patients would not have SHPT. [*Id.*]

Ultimately, however, Dr. Segre testified that the bone loss, tested by radial bone mineral density, would be consistent with elevated PTH and SHPT. [See 635, at pp. 19-20.]

[13] Defendants counter that the Physician's Desk Reference entry for the commercially available form of calcitriol in 1988 does not discuss restoring the loss of bone mineral density to SHPT patients, but merely states that the drug "may reduce * * * the histological manifestations of osteitis fibrosa cystica and defective mineralization." [634, at ¶ 477.] Defendants explain that osteitis fibrosis cystica is caused by prolonged by SHPT. . [634, at ¶ 479.] If anything, Defendants explanation appears to support the inference that a POSA in 1988 would have understand that patients with bone loss density treated with vitamin D would be suffering from SHPT.

Second, Defendants argued that Dr. Langman's opinion that the control period supports an understanding that the patients have SHPT is an assumption not based on evidence, and is unwarranted. [634, at ¶ 473.] Dr. Segre testified that example 4 does not state whether the patients were receiving any medications before the control period began, and that it would not necessarily be clear to a POSA that the control period was mandated in order to wash out calcitriol, which would show that the patient group had SHPT. [610, at ¶ 99 (citing Segre Trial Tr. 2450:11-2451:22; Langman Trial Tr. 1782:5-20, 1784:6-9).] The Court finds Dr. Segre's testimony on this point unpersuasive. The control period mandates that all patients receive a maintenance dose of vitamin D_3. Vitamin D_3 was known in 1988 to be used in the treatment of SHPT but not in the treatment of patients who had normal serum PTH levels (who would have no need for vitamin D treatment) or who had tertiary hyperparathyroidism (for whom vitamin D_3 is contraindicated). Therefore, requiring a maintenance dosage of vitamin D_3 reasonably would convey to a POSA in 1988 that the ESRD patients described in example 4 would have SHPT.

Third, Dr. Segre testified that some ESRD patients experiencing hypocalcemia may suffer from a condition called osteomalacia, or "aluminum bone disease," rather than SHPT. [610, at ¶ 91 (citing Segre Trial Tr. 833:3-834:1, 943:21-944:9, 2438:7-9).] Dr. Segre also testified, however, that in 1988, osteomalacia in ESRD patients was "almost always the result of aluminum toxicity." [635, at p. 23 (citing Segre Trial Tr. 938:1-315).] Dr. Segre testified that patients with aluminum bone disease typically did not have hypocalcemia. [*Id.*] Plaintiffs argue that, by "logical extension," patients with osteomalacia in 1988 typically did not have hypocalcemia. [635, at p. 23.] Because the

patients described in example 4 are said to be hypocalcemic, the Court finds that a POSA in 1988 would have understood that the patients were suffering from SHPT and not aluminum bone disease or osteomalacia.

c. Lowering and Maintaining Lowered PTH Levels

Plaintiffs presented evidence purporting to show that example 4 describes and enables the element of claim 7 requiring lowering or maintaining lowered PTH levels. Dr. Langman testified that the goal of treating patients with ESRD and SHPT is to manage their hypocalcemia and prevent the loss of bone mineral density [616, at ¶ 233 (citing Langman Trial Tr. 1792:22-1793:11)], and that in 1988 a POSA would have understood this goal to be linked to lowering PTH levels. This is because hypocalcemia provokes increased PTH levels. [616, at ¶ 235 (citing Langman Trial Tr. 1798:7-1799:2; Segre Trial Tr. 946:18-946:24; Deftos Deposition Tr. 109:20-110:20).] Example 4 states that the treated patient group will have normalized serum calcium levels – *i.e.*, levels of serum calcium that are increased from sub-normal to normal levels – and stable radial and spinal bone densities. [616, at ¶ 234 (citing Langman Trial Tr. 1797:1-10).] Dr. Langman testified that a POSA in 1988 would have understood that normalized serum calcium levels and stable radial and spinal bone densities in the treated group are results consistent with lowering and maintaining lowered PTH levels in patients with SHPT. [616, at ¶¶ 236-237 (citing Langman Trial Tr. 1796:21-1800:6).] Dr. Langman testified that this understanding would have been shored up by the contrast of the treated group with the placebo group, which showed frequent hypocalcemia and loss of bone mineral density. [616, at ¶ 237 (citing Langman Trial Tr. 1796:21-1800:22).]

Defendants' expert Dr. Segre stated that the endpoints identified in example 4 of the '371 application – calcium levels and bone mineral density – do not correlate with serum PTH and would not have told a POSA in 1988 that serum PTH is being lowered and maintained at lower levels. [610, at ¶ 82 (citing Segre Trial Tr. 831:1-8, 834:18-835:8, 836:24-838:1, 850:7-851:18).] Defendants pointed out that the endpoint in the '116 patent are measurements of serum PTH levels, and argued that the different endpoints with respect to PTH levels are significant as they speak to what the patients described in the two applications were being treated for. [634, at ¶ 481.] Defendants contend that the bone mineral density measurements that were used as endpoints in example 4 are useful and appropriate analytical techniques for osteoporosis (the condition indicated by examples 2 and 3 of the '371 application). [610, at ¶ 79 (citing Segre Trial Tr. 697:18-20, 773:23-774:2).] Dr. Segre testified that bone mineral density measurements are not reliable predictors for diagnosing and treating SHPT. [610, at ¶¶ 83-87 (Segre Trial Tr. 686:6-692:14, 697:18-23, 777:9-778:4, 778:5-798:4, 972:8-973:14, 974:25-975:5, 979:6-24, 1001:10-1002:23, 2429:17-2430:19, 2507:6-2508:16.)[15] Rather, Dr. Segre testified, bone biopsy and serum PTH measurements were relied upon in the 1970s and 1980s to assess renal osteodystrophy in ESRD patients. [610, at 102 (citing Segre Trial Tr. 839:23854;12).] In sum, Defendants argued that the non-PTH endpoints

[15] Dr. Segre testified that this is because while certain types of bones lose density in SHPT patients, other types of bones in the same patients actually become denser. [610, at ¶ 83 (citing Segre Trial Tr. 676:14-677:7, 701:9-17, 702:13-17, 740:5-9, 835:14-836:10).] Defendants stated that it was known prior to 1988 that PTH was a better measurement of treatment of SHPT than bone mineral density. [610, at ¶ 84 (citing Segre Trial Tr. 686:3-16, 691:6-692:14, 697:18-23, 778:5-798:4, 972:8-973:14, 974:25-975:5, 979:6-24, 1001:10-1002:23).] Dr. Segre testified that Dr. Langman's reliance on an article ("the Chesney article") purporting to show that bone mineral density measurements were appropriate endpoints was misplaced, given that the study involved children rather than adults, and the bone growth and renewal processes differ in these groups. [610, at ¶ 86 (citing Segre Trial Tr. 674:11-19).]

described in example 4 of the '371 application are not a "reasonable conveyance" of lowered PTH or maintaining lowered PTH [634, at ¶¶ 482-491], and that a POSA would not believe that Dr. Bishop and the other authors were in possession of the invention set forth in claim 7 of the '116 patent when they drafted example 4. (Segre Trial Tr. 799:11-24.)

Plaintiffs presented evidence purporting to show that Defendants' concerns with respect to the endpoints identified in example 4 are misplaced. Plaintiffs argue that serum calcium, not serum PTH, measurements were the primary method of measuring PTH levels in 1988 [635, at 15 (citing Sherrard Trial Tr. 1094:21-1097:4, 1097:16-1098:4)] and that the FDA-approved labels for ESRD and SHPT drugs in 1988 said that they were approved for management of hypocalcemia and renal osteodystrophy in ESRD patients, *not* for "SHPT" or "PTH" [635, at 15 (citing Bishop Trial Tr. 1591:15-23, 1596:8-17).] Indeed, Plaintiffs note that Defendants' own expert, Dr. Segre, stated that normalizing serum calcium (the endpoint used in example 4) was a key component of the treatment of patients with ESRD and SHPT. [635, at 16 (citing Segre Trial Tr. 2479:2-13).] Further, Defendants' witness Dr. Sherrard testified that serum calcium was the primary endpoint for measuring the treatment of patients with ESRD and SHPT because, as of 1988, PTH assays were inconvenient.[16] [616, at ¶ 265-266 (citing Sherrard Trial Tr. 1094:21-1097:4, 1097:16-1098:4; Segre Trial Tr. 981:24-982:17).] Finally, Plaintiffs

[16] Defendants acknowledge that PTH assays were inconvenient in 1988, as the results were not quickly available; therefore, physicians in 1988 did not dose-adjust calcitriol based on PTH assays but rather dose-adjusted to correct for hypercalcemia. [634, at ¶ 488 (citing Sherrard Trial Tr. 1094:21-1097:4).] Defendants' experts testified that PTH assays were nevertheless used in the 1970s and the 1980s to monitor serum PTH levels in hemodialysis patients treated with calcitriol and alfacalcidol. [610, at ¶ 74 (citing Segre Trial Tr. 840:5-854:12).] Defendants stated that that in the 1980s, PTH assays demonstrated "good correlation" between PTH levels and bone formation rates in patients with renal osteodystrophy, despite some differences. [610, at ¶ 73 (citing Segre Trial Tr. 745:18-753:1, 754:21-757:24, 776:15-25, 927:7-931:21).]

argued that the bone biopsy endpoints that Dr. Segre deemed appropriate were not the only method for monitoring vitamin D treatment of ESRD and SHPT patients that were known to a POSA in 1988. [635, at 16.] Dr. Langman testified that, in 1988, a POSA would have believed bone densitometers to be useful in measuring the loss of bone mineral density in SHPT patients. [616, at ¶ 263 (citing Langman Trial Tr. 1802:3-9, 1802:16-1803:6, 1803:21-1804:16).] Plaintiffs thus contend that Dr. Segre's assertions with respect to bone biopsy endpoints should be given little weight. [635, at 16.]

Although Defendants' discussion of the endpoints in example 4 raises some challenging questions in regard to whether the written description is sufficient as to the third element of claim 7, the Court ultimately finds that Dr. Langman's and Dr. Sherrard's testimony, taken together, support the conclusion that example 4 reasonably conveys the concept of lowering and maintaining lowered PTH levels. In considering the endpoints argument, it is important to bear in mind that the focus of the patent application as a whole was primarily osteoporosis, and only secondarily, through example 4, patients with renal disease. As Dr. Langman's testimony makes clear, bone density was a useful measure for both sets of concerns. Moreover, Dr. Langman persuasively explained that a POSA in 1988 would have concluded from the "normalized" serum calcium levels *and* the stable bone densities in the treated group – contrasted with the frequent hypocalcemia and reduced bone densities of the placebo group – that example 4 described lowering and maintaining lowered PTH levels. Dr. Sherrard, who testified as both a fact witness and an expert and is (like Dr. Langman) a nephrologist, actually provided support for Dr. Langman's explanation by confirming that as of 1988, clinicians used measurements of serum calcium, not PTH, to assess treatment of SHPT. That testimony undercuts Dr.

Segre's opinion that the endpoints were inconsistent with the notion that the inventors adequately conveyed element three. Indeed, Drs. Langman and Sherrard appeared to be on the same page as to the use of serum calcium as a primary endpoint for both safety and efficacy as of 1988.

d. Lower Incidence of Hypercalcemia

Claim 7 requires "lower comparative hypercalcemia at equipotent doses." [634, at ¶ 492 (citing Langman Trial Tr. 1773:24-1774:10).] The parties dispute whether that element is described by example 4 of the '371 application.

At trial, Defendants first argued that the '371 application does not provide sufficient comparative data or otherwise demonstrate that doxercalciferol is "substantially less toxic" than calcitriol at equipotent doses so as to provide a sufficient written description of the invention set forth in claim 7. [634, at ¶ 498.] Defendants concede that the '371 application states that doxercalciferol has a lower incidence of hypercalcemia than calcitriol and/or alfacalcidol. [634, at ¶ 500.] However, Defendants point out that these statements are not substantiated by any comparative data regarding the relative incidence of hypercalcemia or comparative data regarding equipotent PTH-suppressive doses.[17] [610, at ¶¶ 60-61; 634, at ¶ 500.] Defendants' expert Dr. Segre testified that example 4's statement that the treated group experiences an "insignificant incidence" of

[17] Defendants point out that Dr. Langman's reliance upon example 1 in the '371 application to conclude that doxercalciferol has an insignificant incidence of hypercalcemia for the patient group in example 4 is unpersuasive, as example 1 concerns osteoporotic patients with normal kidney function, whereas example 4 concerns ESRD patients on hemodialysis who cannot clear and urinate any increasing amounts of serum calcium. [610, at ¶¶ 95-96 (citing Langman Trial Tr. 1795:7-1796:16, 1844:3-1846:7; Segre Trial Tr. 866:16-861:23; Sherrard Trial Tr. 1072:6-23). Dr. Langman also conceded that example 1 provides "no dosing information on how to dose these osteoporosis patients [in example 1] to achieve the same level of PTH suppression among these three drugs." [610, at ¶ 95 (citing Langman/1995:21-25).] The Court agrees that example 1 does not teach PTH suppression or dosing to achieve equipotency of PTH suppression among the three drugs in construed claim 7.

hypercalcemia would not tell a POSA that the group experienced less hypercalcemia than patients treated with calcitriol or alfacalcidol because "insignificant incidence" is not defined and because no comparative testing of the compounds in ESRD patients was available at that time. [610, at ¶ 93 (citing Segre Trial Tr. 864:19-866:1).] Similarly, Dr. Segre testified that example 4's statement that the placebo group – which was described as receiving a "normal" intake of dietary calcium – experienced "frequent hypocalcemia" is uninformative, since example 4 is silent as to the baseline levels of serum calcium in the placebo and treated groups and does not explain what is a "normal" intake of dietary calcium. [610, at ¶ 94 (citing Segre Trial Tr. 801:2-13, 860:22-25, 862:3-11).]

Even if Dr. Segre's criticisms concerning the lack of data in example 4 are well founded, the test under § 112 is not how much data a parent patent application provides to substantiate the invention set forth in a later patent application, but rather what a POSA would understand the parent application to reasonably convey. The Court thus examines whether, notwithstanding the lack of hard data, the '371 application would reasonably convey claim 7 of the '116 patent to a POSA in 1988.

Defendants' expert Dr. Sherrard testified that a POSA in 1988 did not understand the extent to which the dosing of calcitriol and alfacalcidol related to the incidence of hypercalcemia. [610, at ¶ 9 (citing Sherrard Trial Tr. 1092:3-1094:20, 1097:5-1098:16, 1099:16; Langman Trial Tr. 1987:9-23).] Defendants showed that scientists in 1988 thought it was necessary or desirable to administer a certain dosage of vitamin D in ESRD patients to reduce PTH levels to at or below twice the upper limit of normal PTH. (Sherrard Trial Tr. 1098:5-12; Langman Trial Tr. 1971:16-1972:12.) At those levels, however, scientists in 1988 did not realize that they were *over*suppressing PTH, which

led to adynamic bone disease and hypercalcemia.[18] (Sherrard Trial Tr. 111:7-1114:9; Langman Trial Tr. 1954:16-1955:19, 1987:23.) Dr. Sherrard testified that as doctors learned how to dose those drugs properly, the incidence of hypercalcemia was largely ameliorated. [610, at ¶ 9 (citing Sherrard Trial Tr. 1119:8-13).

Dr. Sherrard testified that in the early 1990s he published his conclusions from a trial ("the Toronto trial") that showed that calcitriol could be dosed to achieve a target range of PTH – 150 to 300 pg/mL – that avoided adynamic bone disease and resulted in a far lower incidence of hypercalcemia than previously associated with the drug. (Sherrard Trial Tr. 1118:5-1123:5.) Dr. Sherrard testified that he presented his conclusions to Dr. Jack Coburn in 1992 (Sherrard Trial Tr. 1121:7-1123:5), and that, in 1994, Coburn co-drafted with Dr. Bishop the treatment protocol for Bone Care's H-106 clinical trial of doxercalciferol in ESRD patients (Bishop Trial Tr. 1661:2-9, 1658:20-22.) Dr. Sherrard testified that Dr. Coburn used the same dosing protocol in the H-106 trial that Sherrard had used in the Toronto trial and presented to Coburn. (Bishop Trial Tr. 1659:24-1662:3; Sherrard Trial Tr. 1127:21-1129:15.)

Plaintiffs responded that much of Dr. Sherrard's testimony regarding the possible safe administration of calcitriol is inadmissible. Plaintiffs contended that Dr. Sherrard's testimony regarding his communications with Dr. Coburn is inadmissible as hearsay and that the Court should disregard it because Defendants did not provide any documentary corroboration of those communications. [635, at p. 5.] Plaintiffs also contended that Dr. Sherrard's testimony regarding oversuppression of PTH as a cause of adynamic bone

[18] Hypercalcemia is in part the result of the fact that the overworked parathyroid glands are less responsive to increases in serum calcium levels; for this reason, oversuppressing PTH in ESRD patients with vitamin D can result in hypercalcemia. (Sherrard Trial Tr. 1070:1-1072:23, 1073:16-1078:16; Langman Trial Tr. 1939:18-1941:17, 1945:6-22, 1949:17-21, 1966:6-11; Bishop Trial Tr. 1654:18-1655:9.)

disease or hypercalcemia is inadmissible because Dr. Sherrard did not discuss this subject in his expert report and it is improper opinion testimony from a fact witness. [635, at p. 2.] Plaintiffs further argued that even if Dr. Sherrard's testimony is admitted, it has no bearing on the issue at the heart of claim 7 – which is not whether calcitriol can be administered safely, but whether treatment with doxercalciferol results in a lower incidence of hypercalcemia than calcitriol. [635, at pp. 5-6.] Plaintiffs presented evidence that even if doxercalciferol *can* oversuppress PTH so as to cause adynamic bone disease, calcitriol more commonly leads to those results. [635, at 6 (citing Langman Trial Tr. 1942:4-19).] And, Plaintiffs argued, what matters ultimately is whether calcitriol or alfacalcidol more frequently induces hypercalcemia . [635, at p.6.][19]

Plaintiffs' expert Dr. Langman provided credible testimony that the '371 application conveyed the key element of lower incidence of hypercalcemia. First, Dr. Langman testified that, based on the prior art, calcitriol and alfacalcidol were known in 1988 to be associated with hypercalcemia at the dosages required to lower PTH in ESRD and SHPT patients. [616, at ¶ 239 (citing Langman Trial Tr. 1801:19-24).][20] In view of this understanding of calcitriol and alfacalcidol, Dr. Langman testified that a POSA in

[19] Plaintiffs also dispute the usefulness of Dr. Sherrard's testimony. Plaintiffs state that Dr. Sherrard's testimony does not support Defendants' assertion that adynamic bone disease is an inherent result of PTH oversuppression, but only supports the proposition that the oversuppression of PTH *can* lead to adynamic bone disease. [635, at p. 3.] Plaintiffs note that Dr. Sherrard dosed calcitriol based on measurements of serum calcium, and measured PTH only four times per year; he also targeted a 150-300 pg/ML range of PTH suppression (which is not at or below twice the upper limit of normal); finally, only 12% of the patients in Dr. Sherrard's Toronto study received calcitriol. [635, at pp. 3-4.] Dr. Sherrard's study concluded that "[t]he exact relationship of PTH to the bone lesions will need to be defined in a prospective study." [635, at p. 4, citing JTX 365 at 441.] Indeed, Plaintiffs argue that adynamic bone disease can result from numerous other conditions. [616, at ¶¶ 11-12; 635, at 4.]

[20] Plaintiffs presented evidence that a POSA in 1988 would have understood that the hypercalcemia associated with the vitamin D_3 compounds was exacerbated by the use of calcium-based phosphate binders, which were often used to control phosphate levels in SHPT patients. (Langman Trial Tr. 1816:19-1817:9.)

1988 would have understood that the "insignificant" incidence of hypercalcemia reported in example 4 signified an incidence of hypercalcemia that was lower than that associated with calcitriol and alfacalcidol at that time. [616, at ¶ 239 (citing Langman Trial Tr. 1801:19-24).] Dr. Langman stated that this understanding would be further buttressed by the '371 application's statement that doxercalciferol was "less toxic" than alfacalcidol, since a POSA in 1988 would have understood that the toxicity to which the application referred was hypercalcemia. [616, at ¶¶ 240-241 (citing Langman Trial Tr. 1801:9-18).] Dr. Langman thus concluded that the '371 application would have conveyed to a POSA in 1988 that doxercalciferol can be used to treat ESRD and SHPT patients by lowering and maintaining lowered PTH levels with a lower incidence of hypercalcemia than calcitriol and alfacalcidol. [616, at ¶ 242 (citing Langman Trial Tr. 1801:5-24).]

The Court finds that even if Dr. Sherrard's testimony were considered in its entirety and credibly shows that by the early 1990s it was known that calcitriol can be administered at doses that avoid hypercalcemia, Dr. Langman's testimony persuasively shows why Plaintiffs satisfied the fourth element as well in their written description. In particular, Dr. Langman demonstrated that as of 1988, a POSA would have known that (1) calcitriol and alfacalcidol were associated with a significant incidence of hypercalcemia and (2) example 4 conveyed that treating patients with ESRD and SHPT with doxercalciferol would be "effective in preventing or restoring the loss of bone mass or bone mineral content while being substantially less toxic" than the prior art.

e. Other Evidence Regarding When Plaintiffs First Possessed the Invention Set Forth in Claim 7

Three FDA-approved vitamin D drugs were used to treat ESRD and SHPT in 1988: Rocaltrol® (oral calcitriol), Calcijex® (intravenous calcitriol), and Calderol®

(oral 24-hydroxy-vitamin- D_3). [616, at ¶ 257 (Bishop Trial Tr. 1591:16-23; 1596:8-10).] These drugs worked to increase levels of serum calcium and lower levels of PTH in ESRD and SHPT patients. However, Dr. Bishop testified that none of the FDA-approved labels for all three drugs stated that they were indicated for "SHPT" or "lowering PTH." Rather, they were all indicated for the management of hypocalcemia or for the management of hypocalcemia *and* the resulting metabolic bone disease in patients undergoing chronic renal dialysis. [616, at ¶ 259 (citing Bishop Trial Tr. 1591:15-23, 1596:8-17).] Dr. Bishop testified that the labels showed that the FDA-approved endpoint for calcitriol in 1988 was serum calcium levels, not PTH levels. [616, at ¶¶ 261-262 (citing Bishop Trial Tr. 1604:2-9, 1611:1-3).]

By 1995, the FDA had approved a different endpoint – PTH levels themselves – in the treatment of ESRD and SHPT patients. [616, at ¶ 270 (citing Bishop Trial Tr. 1612:2-5).] Plaintiffs introduced a publication – the Tan article – to show that measuring PTH to monitor SHPT in ESRD patients was a new development as of the mid 1990s and could be done in lieu of measuring bone formation as a way to test the efficacy of vitamin D compounds in the patient population. [616, at ¶ 273 (citing Bishop Trial Tr. 1612:12-22, 1613:2-11).]

Dr. Bishop testified that he drafted example 4 with the FDA-approved indications for the vitamin D_3 drugs in mind, and for that reason he did not include the words "SHPT" or "PTH," but rather identified serum calcium levels and bone density as endpoints for the trial. [616, at ¶¶ 261-262 (citing Bishop Trial Tr. 1604:2-9, 1611:1-3).] Dr. Bishop testified that he drafted the '116 patent to include PTH levels as the endpoint

because the FDA had newly approved it as an endpoint.[21] [616, at ¶ 260-261, 268 (citing Bishop Trial Tr. 1591:15-20, 1603:24-1604:9, 1611:1-3.] In other words, Dr. Bishop testified that he altered the endpoint of the invention *not* because he conceived of the claim 7 invention only in 1994, but rather to reflect a change by the FDA between 1988 and 1995 in what the appropriate endpoint was for treating patients with ESRD and SHPT. [616, at ¶ 269-270 (Bishop Trial Tr. 1612:2-5.)

Defendants countered that Dr. Bishop's explanation regarding the FDA's lack of focus on serum PTH in 1988 as a measure for ESRD patients is not credible, as extant studies of clinical trials in 1988 expressly measured serum PTH levels, serum phosphorus, serum alkaline phosphatase, and bone biopsy results as endpoints. [634, at ¶ 486.] Defendants also presented the following evidence in support of their contention that Plaintiffs did not conceive of or diligently reduce to practice the invention of administering doxercalciferol to treat SHPT until 1994: (1) Bone Care recruited Dr. Chesney and Dr. Coburn as consultants in the spring of 1994; (2) Bone Care held a meeting with Dr. Chesney and Dr. Coburn in May 1994 to plan a clinical trial (the H-106 clinical trial) of doxercalciferol in renal disease patients; (3) Bone Care drafted the H-106 clinical trial protocol; (4) Bone Care submitted the H-106 protocol to the FDA on September 8, 1994; (5) Bone Care met with the FDA on November 2, 1994 seeking approval of the H-106 clinical trial; (6) the H-106 clinical trial began in December of 1994. [610, at ¶ 159 (Sofocleous Trial Tr. 1368:19-1372:1).]

[21] In their response to Plaintiffs' proposed findings of fact, Defendants contend that Dr. Bishop's assertion that he chose endpoints for example 4 that he believed the FDA would approve is not credible. [634, at ¶ 489.] However, Defendants do not point to evidence countering Dr. Bishop's assertion or otherwise explain why the Court should accord it little or no weight.

Defendants argued that this evidence shows that, although Plaintiffs used doxercalciferol as a treatment for osteoporosis since 1988, it was not until 1994 that they first began testing it as a treatment for SHPT patients. [610, at ¶ 161.] Dr. Keana and Dr. Bishop testified that around the time of the H-102 trial (1992 and 1993), the pharmaceutical companies Takeda and SmithKline abandoned their partnerships with Bone Care [610, at ¶ 147 (Keana Trial Tr. 404:117-405:16; Bishop Deposition Tr. 84:24-92:8); Dr. Bishop testified that the dissolution of the partnerships was attributable not to skepticism about the efficacy of doxercalciferol but to the development of a new class of drugs ("bisphosponates") that were thought to be more effective in treating osteoporosis than any vitamin D treatment [Bishop Trial Tr. 1575:10-17, 1578:6-10, 1578:21-1579:4, 1579:6-9, 1579:12-15, 1579:24-1580:3)]. Dr. Keana testified that Bone Care was unsuccessful in finding other partners for the development of doxercalciferol as a treatment for osteoporosis. [610, at ¶ 149 (citing Keana Trial Tr. 407:12-408:0).] Correspondence between Bone Care and the FDA in 1993 indicated that Bone Care was at that time still pursuing an IND for doxercalciferol of the treatment of osteoporosis, but did not mention any renal indications or SHPT. [610, at ¶ 149 (citing Keana Trial Tr. 408:11-25).] However, given the difficulties in securing a partner, Dr. Keana testified that Bone Care began looking for an alternate indication for doxercalciferol. [610, at ¶¶ 150 ((citing Keana Trial Tr. 409:7-25, 412:10-413:20; Bishop Deposition Tr. 88:17-90:1).] Dr. Keana surmised that it was Bone Care's efforts to seek a pharmaceutical partner that motivated it to explore doxercalciferol as a treatment for ESRD and SHPT patients, and that Bone Care did not switch its focus to renal indications until 1994. (Keana Trial Tr. 417:24-418:9.) Defendants presented numerous documents – including

press releases and letters to potential pharmaceutical sponsors – purporting to show that the evolution in Bone Care's use of doxercalciferol showed a date of conception of claim 7 sometime between the fall of 1993 and February 3, 1994. [610, at ¶¶ 137-162.]

Plaintiffs counter that Defendants' own patent expert, Mr. Sofocleous, admitted that a patent-holder's business development and licensing strategies are irrelevant to the question of priority. [635, at p. 27 (citing Sofocleous Trial Tr. 1448:2-22).] Plaintiffs also argue that Dr. Keana's testimony should be afforded little weight, as Plaintiffs claim that Keana lacks the expertise to opine on what example 4 would reasonably convey to a POSA in 1988. [635, at p. 27 (citing Keana Trial Tr. 564:14-23, 571:4-8).] The Court concludes that even if I were to place all of the weight on Mr. Sofocleous's and Dr. Keana's testimony that their testimony can bear, it merely would suggest that Bone Care accelerated its development of doxercalciferol more in the direction of treating renal patients rather than osteoporosis patients between 1988 and the early-to-mid 1990s. But that fact does not alter the relevant analysis, which focuses on (1) what Bone Care conveyed and (2) what the POSA understood, both as of 1988.

In sum, the Court concludes that all of the elements of claim 7 of the '116 patent are described by example 4 of the '371 application, and thus Plaintiffs satisfied the written description requirement.

4. Enablement

In regard to the other contested issue as to priority, the '371 application also must meet the enablement and utility requirements. A patent specification is enabling for purposes of Section 112 if it "teach[es] those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *ALZA Corp. v.*

Andrx Pharm., LLC, 603 F.3d 935, 940 (Fed. Cir. 2010). Here, one of the principal disputes as to enablement relates to the absence of clinical data concerning "equipotent doses." But that dispute is quickly resolved by the parties' agreement that a POSA readily could determine effective dosing as to both the prior art (calcitriol and 1aOHD3) and doxercalciferol. See [468, at 11] (citing Def.'s Claim Construction Brief [229] at 16 ("[d]etermination of the 'effective amount' for a given patient is within the skill of the POSA"); Pl.'s Response [433] at 8 n.8; *Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1383-84 (Fed. Cir. 2003) ("'effective amount' is a common and generally acceptable term for pharmaceutical claims and is not ambiguous or indefinite, provided that a person of ordinary skill in the art could determine the specific amounts without undue experimentation")).[22] The factual predicate for the utility aspect of enablement similarly need not detain the Court long, for the testimony of the experts in regard to (1) what was known to the POSA on the basis of the prior art as of 1988, (2) what was understood by the POSA from example 4, and (3) what has been learned since then through the Tan Manuscript and the widespread use of doxercalciferol in the marketplace establish its utility.

D. Operability

Defendants also contended at trial that example 4 of the '371 application *cannot* enable the invention claimed in claim 7 of the '116 patent because the invention is inoperable. A patent that is found to be inoperable (or inoperative) fails to satisfy the enablement requirement. *In re '318*, 583 F.3d 1317, 1324 (Fed. Cir. 2009). "Proof of inoperativeness or non-utility must be strong * * * [,] every reasonable doubt being

[22] A second, and more formidable and hotly contested challenge to enablement is Defendants' assertion that the invention at issue simply is inoperable altogether – a challenge that the Court takes up separately below.

resolved in favor of the patentee." *E.I. du Pont de Nemours & Co. v. Berkley & Co.*, 620 F.2d 1247, 1260 (8th Cir. 1980); see also *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762 (Fed. Cir. 1984); *Transco Prods., Inc. v. Performance Contracting, Inc.*, 1997 WL 459771, at *5 (Fed. Cir. 1997).

In particular, Defendants argued that recent publications (the "Dennis article," "KDIGO guidelines," and "Perry article,") show that doxercalciferol and the relevant vitamin D_3 drugs yield the same incidence of hypercalcemia when administered at equipotent PTH-suppressive doses. According to Defendants, the Dennis article constituted a "meta-analysis" of extant literature on doxercalciferol and the vitamin D_3 compounds and concluded that doxercalciferol did not demonstrate a lower incidence of hypercalcemia than calcitriol or alfacalcidol. Defendants stated that the Perry article was the first reported head-to-head randomized clinical trial between doxercalciferol and calcitriol and that it concluded that there was comparable hypercalcemic incidence between the two drugs. Finally, Defendants argued that the KDIGO guidelines establish criteria for scientifically adequate testing of vitamin D treatment of ESRD patients, and that the Perry article was consistent with those criteria. Taken together, Defendants concluded that the publications provide evidence that the invention set forth in claim 7 is inoperable because doxercalciferol has not been shown to cause less hypercalcemia than the vitamin D_3 compounds. In Defendants' estimation, because the Perry article and Dennis article prove that the invention is inoperable today, the invention was always inoperable, and could not have been enabled by any disclosure in 1988, in 1995, or at any time.

Plaintiffs did not contest the relevancy of the Perry article, Dennis article, and KDIGO guidelines notwithstanding the fact that the articles were published after the '488 application was filed.[23] However, Plaintiffs argued that the cited publications do not prove a consensus that doxercalciferol and the relevant vitamin D_3 drugs result in an equivalent incidence of hypercalcemia. Plaintiffs argued that the Dennis article is unreliable insofar as Defendants' own expert, Dr. Deftos, admitted that the Dennis article was not a "meta-analysis" and that it did not provide an independent analysis of existing data regarding the relevant drugs. Plaintiffs stated that the KDIGO guidelines confirm their view that doxercalciferol has shown "clear-cut" differences as compared with the vitamin D_3 compounds. And Plaintiffs contended that the Perry article does not establish equivalency of doxercalciferol and calcitriol with respect to incidence of hypercalcemia at equipotent PTH-suppressive doses, but in fact supports extant research that doxercalciferol is less hypercalcemic than calcitriol at the relevant dosages.

Plaintiffs initially noted that in its introductory section, the Perry article acknowledges that doxercalciferol has been shown to cause less hypercalcemia than calcitriol. Plaintiffs contended that the Perry article was not designed primarily to compare doxercalciferol and the vitamin D_3 compounds with respect to the incidence of hypercalcemia. Rather, Plaintiffs stated, the study considered hypercalcemia only as a secondary endpoint for a specific patient group (namely, children on peritoneal dialysis)

[23] Plaintiffs do have evidentiary objections to the articles themselves. Defendants contend that at least Perry and KDIGO fall within the "learned treatise" (FRE 803(18)) and "residual" (FRE 807) hearsay exceptions. The Court need not explore the evidentiary objections in great detail, however, because even assuming that the articles are admissible, they do not provide enough support for Defendants' position to carry the day. Certainly the testimony of the experts on both sides as to the opinions that they have formed based on the articles is admissible under FRE 702 and 703; the weight given to that testimony, of course, is affected by the persuasiveness of both the articles themselves and the analysis of them provided by the witnesses.

that was not covered by claim 7 (namely, men and women suffering from ESRD), and assert that the primary endpoint of the study was to examine differences in bone formation rate between patient groups. Indeed, Plaintiffs contended that the design of the study indicates that the studies' authors *expected* that calcitriol would cause excessive hypercalcemia, and for that reason took specific steps (*e.g.*, a higher PTH target range, a strict limitation on the level of serum calcium allowed, and use of certain dialysates) to minimize hypercalcemia to allow for better comparison of the two compounds to achieve the primary endpoint of the study, comparative bone formation rate.

Plaintiffs further argued that at various points in the study, PTH levels in the patient group treated with calcitriol were higher than those in the patient group treated with calcitriol, and that the requirement of equipotent PTH-suppressive doses required in construed claim 7 therefore was not met in the Perry study. Finally, Plaintiffs contended that, to the extent that the Perry article did assess relative hypercalcemia incidences between doxercalciferol and calcitriol, that assessment was not based on a statistical analysis because the commonly used statistical nomenclature and nomenclature that the author's article used as a matter of practice – "N/S" (no statistical analysis), – was not referenced. For these reasons, Plaintiffs read the Perry article as supporting a finding that doxercalciferol causes less incidence of hypercalcemia than calcitriol.

In addition to presenting evidence undermining Defendants' interpretation of the Dennis article, KDIGO guidelines, and Perry article, Plaintiffs presented affirmative evidence – in the form of Bone Care's clinical trials and treating physicians' anecdotal data – purporting to prove doxercalciferol's operability. Plaintiffs emphasized that the H-101 and H-106 clinical trials showed that doxercalciferol could be administered to treat

SHPT as effectively as calcitriol while resulting in a lower incidence of hypercalcemia. Plaintiffs noted that the same conclusion is reflected in the Hectorol® product label approved by the FDA. In addition, Plaintiffs' experts testified that treating nephrologists believe that doxercalciferol causes less hypercalcemia than the relevant vitamin D_3 compounds when administered to SHPT patients. Plaintiffs' experts testified that dialysis providers use doxercalciferol instead of the vitamin D_3 compounds, despite its higher cost, for precisely this reason. Indeed, Plaintiffs pointed out that Defendants' expert, Dr. Sherrard, testified that his hospital is switching to doxercalciferol from calcitriol to treat SHPT patients despite a financial disincentive to do so.

Defendants countered that Plaintiffs' anecdotal testimony is not as persuasive as a head-to-head randomized clinical trial, such as the Perry article, that complies with professional standards of clinical research, such as the KDIGO guidelines. The Court agrees that, in general, actual studies prove more substance to a trier of fact than anecdotes. However, after careful consideration of the expert testimony on the significance (or lack thereof) of the Dennis and Perry articles in light of the KDIGO guidelines, Defendants have not persuaded the Court that those materials are the "game changer" that Defendants deem them to be.

To be sure, the three publications collectively may cast *some* doubt on Plaintiffs' claims concerning the comparative incidence of hypercalcemia caused by doxercalciferol and the relevant vitamin D_3 drugs. At the same time, Plaintiffs pointed to numerous reasons why the Court should hesitate to draw the kinds of sweeping conclusions about inoperability that Plaintiffs posit. For example, Plaintiffs (and their experts) noted that the Perry study used different endpoints, tested four variables, and involved a different

patient population than that disclosed in the '116 patent or its ancestor applications. Defendants (and their experts) did not convincingly demonstrate why the Court should disregard Plaintiffs' experts' observations about the differences between the answers supplied by the studies' authors and the questions that a true head-to-head study would raise and seek to answer. Nor did Defendants' experts draw the kinds of links between the data supplied and the results reached by the studies' authors and the assertions of Defendants' lawyers that would establish the studies as the definitive word on the subject of relative incidences of hypercalcemia within the relevant population of ESRD patients with SHPT.

It may be that some day the Dennis and Perry studies will be viewed as the "game changer" that Defendants would like them to be. But science tends to proceed incrementally, and, as Judge Posner has written, "law lags science; it does not lead it." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996). Given the high bar imposed on parties seeking a ruling of inoperativeness or non-utility and the duty of the Court to resolve any reasonable doubts in favor of the patentee, the Court is unable to accept Defendants' contentions.

E. Obviousness

Defendants presented evidence at trial that the invention set forth in claim 7 was obvious as of (1) August 2, 1988 – the date to which Plaintiffs claim priority based on the filing date of the '116 patent's parent application, the '371 application – and (2) April 3, 1995 – the filing date of the '488 application from which the '116 patent issued directly. Accordingly, Defendants argued that claim 7 is invalid for obviousness under 35 U.S.C. § 103.

More specifically, Defendants contended that the prior art in 1988, considered as a whole, taught that the use of doxercalciferol as a treatment for renal osteodystrophy patients, many of whom have SHPT, would have had a reasonable expectation of success. [611, at ¶ 59.] Defendants further contended that the prior art taught that doxercalciferol increases intestinal calcium absorption, thereby raising serum calcium and correspondingly lowering PTH levels. [611, at ¶ 60.] Therefore, they contended, a POSA would have inferred that doxercalciferol would lower PTH. *Id.* A POSA also would have understood that both doxercalcferol and the vitamin D_3 compounds would inhibit the production of PTH in the parathyroid glands. *Id.* Defendants also argued that because in 1988 the vitamin D_3 compounds had been approved to lower PTH in SHPT and ESRD patients, a POSA would have inferred at that time that doxercalciferol could be used to the same effect. [611, at ¶ 61.] A POSA also would have inferred, they argued, that doxercalciferol would have been safe for human use based on what was known in 1988 about the metabolization process of the vitamin D_3 drugs. [611, at ¶ 62.] Indeed, Defendants argued that a POSA would have believed doxercalciferol to be safer than the vitamin D_3 compounds based on the 1985 Sjoden data, showing that doxercalciferol was significantly less toxic (*i.e.*, hypercalcemia-inducing) than alfacalcidol [611, at ¶ 75.].

Plaintiffs presented evidence that the invention set forth in claim 7, and described and enabled in the '371 application, was nonobvious as of the August 2, 1988 filing date of the '371 application. Plaintiffs argued that numerous other vitamin D compounds were known in 1988, and that Defendants did not present clear and convincing evidence explaining why a POSA would have picked doxercalciferol over the alternatives. [616, at

76-77.] Plaintiffs presented evidence that a POSA in 1988 would have selected the vitamin D_3 alternatives over doxercalciferol at that time. Moreover, Plaintiffs argued, even if doxercalciferol had been selected, it would not have been understood to have a reasonable expectation of success in lowering and maintaining lowered PTH levels in SHPT and ESRD patients without causing hypercalcemia. [616, at ¶81.] Plaintiffs argued that the Sjoden data would not have been understood to predict similar results in humans, given that the Sjoden studies were done on rats and administered doses of the drugs that were higher than would have been tolerated in humans. [616, at ¶¶ 84-92.] Indeed, Plaintiffs argued that, if anything, prior art taught away from, not toward, the claimed invention, and that the inventors themselves were surprised at the results they reached during the doxercalciferol trials. [616, at ¶¶96-105.]

A presumption of validity and non-obviousness attaches to an issued patent. 35 U.S.C. § 282. That presumption may be rebutted upon a showing, by clear and convincing evidence, that the invention claimed in the patent would have been obvious to a POSA at the time the underlying patent application as filed. See *Denniston Mfg. Co. v. Panduit Corp.*, 475 U.S. 809, 810 (1986). The Federal Circuit has held that "[o]bviousness is a question of law based on a series of factual determinations, including (1) the scope and content of the prior art, (2) the differences between the art and the claims at issue, (3) the level of ordinary skill in the art, and (4) any other objective evidence." *Intel Corp.*, 946 F.2d at 834 (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)). A court considering these factors will conclude that a claimed invention is obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). A court may find it necessary in this analysis to "look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a [POSA], all in order to determine whether there was an apparent reason" to create the claimed invention. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

In undertaking an obviousness inquiry, the Federal Circuit has cautioned district courts in two respects. First, the court has written that "[i]t is difficult but necessary that the decisionmaker forget what he or she has been taught at trial about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." *W.L. Gore & Assocs. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). Second, the court has stressed that "[t]he issue of obviousness is determined entirely with reference to a *hypothetical* 'person having ordinary skill in the art.'" *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) (emphasis in original). In regard to the second point, the court contrasted POSAs with inventors, noting that the former are persons "of *ordinary* skill," while the latter "possess something – call it what you will – which sets them apart from the workers of *ordinary* skill." *Id*. Taking these two concepts together, this Court must keep its focus on "one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights." *Id*.

1. Vitamin D Compounds and the Treatment of Hyperparathyroidism Secondary to End-Stage Renal Disease

Vitamin D compounds have long been used in the treatment of bone diseases and other diseases that are characterized by excess bone resorption,[24] reduced bone density, and bone fractures. One such disease is hyperparathyroidism secondary to ("SHPT") end-stage renal disease ("ESRD"). ESRD is fatal unless the patient obtains a kidney transplant or receives chronic dialysis. [616, at ¶ 22 (citing Langman Trial Tr. 1778:17-21; Sherrard Trial Tr. 1015:3-8).] ESRD causes SHPT [616, at ¶ 21 (citing Langman Trial Tr. 1772:1-11)]. SHPT is characterized by elevated levels of parathyroid hormones ("PTH") and sub-normal levels of serum (or blood levels of) calcium – a condition known as "hypocalcemia." [616, at ¶ 31 (citing Segre Trial Tr. 945:22-946:14; Langman Trial Tr. 1785:14-1786:4, 1786:23-1789:25; PTX 69).] In ESRD and SHPT patients, vitamin D compounds work to decrease levels of PTH in the blood and increase levels of serum calcium. [610, at ¶¶ 168-170 (Segre Trial Tr. 946:15-24; 2478:20-2479:13; Keana Trial Tr. 559:9-560:1; JTX 344A).]

A POSA in 1988 would have known that vitamin D had two principal forms: vitamin D_2 and vitamin D_3. [610, at ¶ 163 (citing Deftos 43:14-19); 616, at ¶ 2 (citing Norman Trial Tr. 2119:23-2120:2).] Healthy individuals metabolize vitamin D_3 absorbed from sunlight through the skin [616, at ¶¶ 56-57 (Deftos Trial Tr. 47:16-21; Norman Trial Tr. 2130:16-23; 2133:6-2134:23)] and ingest it in the diet [610, at ¶ 163 (citing Deftos Trial Tr. 45:7-11).] Vitamin D_3 is metabolized in the body to become an active hormone through a process known as hydroxylation, which takes place in the liver and kidneys.

[24] Bone resorption is the destruction or dissolution of bone tissue.

[610, at ¶ 166 (citing Deftos Trial Tr. 47:1-50:3).] Prior to metabolization, vitamin D_3 is inactive in the human body. [*Id.*]

Calcitriol (also known as "1,25$(OH)_2$-vitamin- D_3" or "1,25$(OH)_2$ D_3") and alfacalcidol (also known as "1α-OH-vitamin- D_3" or "1αOH D_3") are vitamin D_3 compounds or metabolites. Plaintiffs assert – and Defendants do not dispute – that a POSA would have known in 1988 that calcitriol is the hormonally active form of vitamin D_3. [616, at ¶¶ 51-52 (Segre Trial Tr. 1726:2-4; 1728:12-24; 1729:14-17; Langman Trial Tr. 1787:12-20)]. A POSA at that time also would have known that alfacalcidol is metabolized in the body to calcitriol, and that the two compounds therefore have essentially the same activity in the human body. [616, at ¶¶ 7, n.1, ¶ 51 (Deftos Trial Tr. 58:24-59:17, 120:6-16).]

Vitamin D_2 is not found naturally in humans (although it may be ingested through the diet). [616, at ¶ 3 (citing Norman Trial Tr. 2131:8-11; 2304:10-12); 634, at ¶ 433] Doxercalciferol (also known as "1-alpha-hydroxy-vitamin-D_2" or "1αOHD_2") is an analog of vitamin D_2. [616, at ¶ 3 (Norman Trial Tr. 2130:24-2131:15, 2140:11-2141:23; Segre Trial Tr. 1727:8-1728:22).] Doxercalciferol and other vitamin D_2 analogs are not metabolized in the body to calcitriol, but are activated in the body through a different metabolic process.[25] [616, at ¶ 3 (citing Norman Trial Tr. 2125:12-2127:6; 2130:9-2131:23; 2132:10-2135:7; 2159:15-2162:23); 635, at ¶ 434.] Doxercalciferol shares a

[25] Defendants and Plaintiffs dispute whether doxercalciferol is metabolized to 1,25$(OH)_2D_2$ or not. Defendants argued that vitamin D_2 is not metabolized to calcitriol, but it is metabolized to 1α25$(OH)_2D_2$ – a "naturally occurring hormone that is substitutable for 1α25$(OH)_2D_3$. [634, at ¶ 434.] Plaintiffs stated that before 1988, it was known or "strongly predicted" that doxercalciferol was metabolized to the active hormonal 1α,25$(OH)_2$D. [616, at ¶ 183 (citing Deftos Trial Tr. 64:23-68:12).] Plaintiffs also argued, however, that "Defendants offered no credible evidence that doxercalciferol was known in 1988 to be metabolized to 1,25$(OH)_2D_2$ in humans and that Defendants have offered no credible evidence to the contrary. [610, at ¶ 183; 635, at p. 48.]

similar chemical structure to calcitriol and alfacalcidol, but the structural deviations that do exist between the compounds alter their activity in the human body. [616, at ¶¶ 60-62.]

In 1988, a POSA would have understood that calcitriol – or, the hormonally active form of vitamin D_3 – assists in the absorption of calcium into the blood, thus increasing the level of serum calcium. [610, at ¶ 168 (Deftos Trial Tr. 51:13-55:23; Langman Trial Tr. 1787:13-16).] In 1988, a POSA also would have understood that one consequence of raising serum calcium was the lowering of serum levels of PTH in humans. [610, at ¶ 169 (Deftos Trial Tr. 54:13-55:23).] Further, it was known that calcitriol was supposed to lower serum PTH. [610, at ¶ 170 (citing Deftos Trial Tr. 52:14-16, 54:24-55:6, 55:21-23, 80:9-25).] This is because the human body naturally monitors serum calcium levels through the parathyroid gland. [616, at ¶ 25 (citing Langman Trial Tr. 1786:23-1787:7; Sherrard Trial Tr. 1031:18-1032:6; Segre Trial Tr. 946:12-14).] In a healthy human, if serum calcium levels fall below normal levels, the parathyroid glands increase their production and secretion of PTH. [616, at ¶ 25 (citing Langman Trial Tr. 1786:23-1787:7; Sherrard Trial Tr. 1031:18-132:6; Segre Trial Tr. 946:12-14).] Normally, PTH will restore serum calcium to proper levels in two ways. [616, at ¶ 26 (citing Langman Trial Tr. 1787:8-11).] First, PTH stimulates bone cells to resorb (*i.e.*, dissolve) bone tissue and release calcium from the bone into the bloodstream. [616, at ¶ 27 (citing Langman Trial Tr. 1791:4-10).] Second, PTH signals the kidneys to produce more calcitriol. [616, at ¶ 28 (citing Langman Trial Tr. 1787:8-11).]

Calcitriol regulates levels of calcium in the bloodstream through (1) "indirect action" – in which calcitriol stimulates the intestines to absorb calcium from the diet into

the bloodstream [616, at ¶ 29 (citing Norman Trial Tr. 2161:1-8; Langman Trial Tr. 1806:4-14; PTX 69)] – and (2) "direct effect" – in which calcitriol acts directly on the parathyroid glands, causing it to reduce PTH [616, at ¶ 29 (citing Langman Trial Tr. 1826:19-1828:13)]. The result of calcitriol's indirect action or direct effect is to return serum calcium levels to normal. [*Id.*] Once normal levels of serum calcium are achieved, the parathyroid glands respond by decreasing their secretion of PTH. [616, at ¶ 29 (Deftos Trial Tr. 2380:7-12; Langman Trial Tr. 1827:4-14); 610, at ¶¶ 189-193.]

In 1988, it was known that healthy, functional kidneys produce calcitriol. [616, at ¶ 29 (Langman Trial Tr. 1789:6-10; PTX 69).] However, in a person suffering from ESRD, the kidneys cannot produce calcitriol because the kidneys cannot synthesize adequate amounts of hormonally active vitamin D. [616, at ¶ 30 (Deftos Trial Tr. Trial Tr. 92:14-19; Sherrard Trial Tr. 1030:19-1031:3; Langman Trial Tr. 1788:24-1789:20; PTX 69); see also [610, at ¶¶ 171-172 (citing Deftos Trial Tr. 56:13-57:1, 90:18-91:24).] Because of the inability to produce calcitriol, ESRD patients cannot maintain normal levels of calcium in the blood and become hypocalcemic. [616, at ¶ 31 (Sherrard Trial Tr. 1030:19-1031:3; 1047:19-1048:5; Langman Trial Tr. 1788:24-1789:20; PTX 69); see also 610, at ¶ 171 (citing Deftos Trial Tr. 56:13-57:1).] As a result of the chronically low levels of calcium in the blood, the parathyroid glands continually secrete increased levels of PTH; however, there is no corresponding increase in calcium levels due to the malfunctioning kidneys. [616, at ¶ 32 (Langman Trial Tr. 1787:12-20); see also 610, at ¶ 171 (citing Deftos Trial Tr. 56:13-57:1).] This leads to a condition – called SHPT – wherein persistently low levels of serum calcium cause persistently elevated PTH levels,

which in turn persistently signals the bones to release stored calcium.[26] [616, at ¶ 33 (citing Langman Trial Tr. 1788:6-23, 1808:4-10), 610, at ¶ 174.] Because the bones are constantly releasing stored calcium, prolonged SHPT leads to decreases in bone density, known as "hyperparathyroid bone disease" or "renal osteodystrophy." [616, at ¶ 37 (Langman Trial Tr. 1791:18-1792:6); 610, at ¶¶ 172-173.] Low bone density renders the bones so fragile that they are easily or spontaneously fractured. [616, at ¶ 38 (Langman Trial Tr. 1791:11-17).]

In 1988, it was known that a substantial fraction of ESRD patients had SHPT. [610, at ¶ 174 (citing Deftos Trial Tr. 98:25-99:17).] It was also known at that time that renal osteodystrophy in ESRD patients was due at least in part to the failure in the human body to make hormonally active vitamin D. [610, at ¶ 173 (citing Deftos Trial Tr. 90:18-91:24, 92:4-94:15).] Therefore, before 1988, calcitriol and alfacalcidol (both vitamin D_3 compounds) were the main drugs administered to SHPT and ESRD patients to raise serum calcium levels [616, at ¶ 40 (citing Langman Trial Tr. 1797:18-25, 1805:12-1807:1, 1824:12-18; Deftos Trial Tr. 152:4-9)] and lower serum PTH in humans. [610, at ¶ 169 (citing Deftos Trial Tr. 54:13-55:23).] The parties agree that in 1988 a POSA would have known that when the vitamin D_3 drugs were administered at doses that effectively suppressed PTH in ESRD and SHPT patients, they were associated with a condition called "hypercalcemia" – that is, toxically *elevated* levels of calcium. [616, at ¶ 40 (citing Langman Trial Tr. 1797:18-25; 1805:12-1807:1; 1824:12-18; Deftos Trial Tr. 152:4-9), 610, at ¶ 9 (citing Langman Trial Tr. 1805:12-1813:10).] Indeed, the parties

[26] In addition, chronic hypocalcaemia causes changes in the parathyroid glands that make them less responsive to calcium, such that ever higher levels of serum calcium are needed to reduce PTH secretion. [616, at ¶ 33 (Langman Trial Tr. 1806:4-15; 1807:2-1809:3; JTX 366 at 2136; PTX 57 at 1100; PTX 71 at 93).]

agree that in 1988, a POSA would have believed calcitriol and alfacalcidol to be inherently hypercalcemic in SHPT and ESRD patients.[27] Hypercalcemia can result in cardiac arrhythmia, unwanted calcium deposits in heart, lungs, and other organs, and other harmful effects. [616, at ¶¶ 46-47 (Langman Trial Tr. 1813:13-1914:21; 1816:2-10; Deftos Trial Tr. 219:21-220:9).]

Plaintiffs argued at trial that, as of 1988, a POSA would not have expected doxercalciferol to cause less hypercalcemia than calcitriol and alfacalcidol when used to lower PTH in ESRD and SHPT patients. In other words, Plaintiffs argued that the invention set forth in claim 7 was not obvious to a POSA in 1988. Defendants contended that the (mis)perception of a POSA in 1988 that calcitriol and alfacalcidol were inherently hypercalcemic provided a motivation to seek alternative vitamin D sterols for treating ESRD. [634, at ¶ 496.] Defendants further contended that, based on what was known in 1988, it would have been obvious to a POSA (or obvious to try) to administer doxercalciferol to SHPT and ESRD patients to lower or maintain lowered PTH levels with a lower incidence of hypercalcemia than was associated at the time with calcitriol and alfacalcidol.

2. Pharmacological Development of Doxercalciferol [616, at ¶¶ 75-157]

In 1974, Dr. Hector DeLuca created doxercalciferol and published the first report of the drug. [616, at ¶ 94 (citing Norman Trial Tr. 2165:11-15, 2167:12-17; Keana Trial Tr. 559:9-560:1; JTX 344A).] Dr. DeLuca and others patented doxercalciferol and the

[27] Plaintiffs presented evidence that experts at that time had reported that treatment with calcitriol "necessarily" led to hypercalcemia, and that treatment with alfacalcidol caused "rampant" hypercalcemia. [616, at ¶¶ 44-45 (citing Langman Trial Tr. 1807:2-1809:5, 1810:7-1813:10; Sherrard Trial Tr. 1094:21-1096:15, 1187:8-1189:7, 1217:2-9).] Defendants concede that a POSA in 1988 would have understood the two compounds to be inherently hypercalcemic, but argued that this was in fact a misperception. [See 634, at ¶ 496.]

process by which it was prepared under U.S. Patent Number 3,907,843. [616, at ¶ 96 (citing Norman Trial Tr. 2275:9-14).] The patent was assigned to the Wisconsin Alumni Research Fund ("WARF") – a branch of the University of Wisconsin that is responsible for patenting and licensing discoveries made by faculty. [616, at ¶¶ 97-98 (citing Norman Trial Tr. 2275:9-14; Bishop Trial Tr. 1516:13-18).]

Meanwhile, Dr. Mazess – a medical physics professor at the University of Wisconsin – was developing a new machine with which to measure bone mineral density (known as a "bone densitometer") in patients with bone diseases. [616, at ¶¶ 80-81 (citing Mazess Deposition Tr. 20:13-25; 21:2-20, 47:23-25; 49:2-22, 56:12-18; Bishop Trial Tr. 1515:4-8).][28] Dr. Mazess launched the Lunar Radiation Corporation ("Lunar") in 1985 to manufacture and sell the bone densitometer that he eventually developed. [616, at ¶ 84 (Mazess Deposition Tr. 47:3-14; 49:5-22).] Dr. Mazess sought ways to expand the market for his bone densitometers, and believed that finding a safe and effective vitamin D treatment for osteoporosis would accomplish that goal. [616, at ¶¶ 86-87 (citing Mazess Deposition Tr. 49:20-50:5; Bishop Trial Tr. 1517:1-10).]

Dr. DeLuca promoted doxercalciferol as a possible treatment for osteoporosis. He recommended to Dr. Mazess that Mazess license one of the vitamin D compounds that DeLuca had synthesized. [616, at ¶ 92 (Mazess Deposition Tr. 58:12-59:4; Norman Trial Tr. 2169-25-2171:11)] Dr. Mazess subsequently licensed doxercalciferol [616, at ¶ 103 (Bishop Trial Tr. 1516:19-21; 1517:13-16)]. Dr. Mazess then began testing the drug through Bone Care – a subsidiary of Lunar that he founded in 1987. [616, at ¶¶ 106-107

[28] X-ray radiograph and quantitative histomorphology – two other techniques for looking at bone and measuring bone mineral density, were both known to have major drawbacks. [616, at ¶¶ 75-79 (citing Mazess Deposition Tr. 22:18-23:19, 24:6-25:4; Segre Trial Tr. 683:6-11, 964:18-965:25).]

(Mazess Deposition Tr. 47:6-14; 55:12-56:3; 59:2-12).] Dr. Mazess hired Dr. Bishop – a biochemist who specialized in vitamin D and had completed a post-doctorate in Dr. DeLuca's lab – as a Bone Care employee. [616, at ¶ 108 (citing Bishop Trial Tr. 1513:16-1514:4; 1514:18-1515:3).]

Dr. Bishop testified that he studied a Hoffman-La Roche (""Roche") clinical trial of calcitriol as a treatment for osteoporosis on which Dr. Mazess had advised. The Roche trial showed that calcitriol, when used at doses effective to treat SHPT, caused hypercalcemia. [616, at ¶¶ 111-115 (citing Bishop Trial Tr. 1528:2-1530:3, 1531:2-14, 1531:24-25, 1532:16-1533:4).] Dr. Bishop noted that at certain doses, calcitriol had a direct, positive effect on bone itself, and not simply the indirect effect of promoting dietary calcium absorption in the intestines, which is what most scientists focused on at the time. [616, at ¶¶ 119-124 (citing Bishop Trial Tr. 1528:8-1529:14, 1531:2-1531:12, 1532:16-1533:1; Langman Trial Tr. 1828:22-180:23, 1842:12-1843:11).] Dr. Bishop testified that he then set out to determine whether high doses of doxercalciferol could have a direct effect on peripheral tissues like bone and the parathyroid gland without causing hypercalcemia in osteoporotic patients. [616, at ¶¶ 126-127 (citing Bishop Trial Tr. 1521:7-17, 1530:2-7, 1532:23-1533:5, 1538:22-1539:2, 1540:4-1542:20, 1548:1-1549:5).]

Bone Care submitted an Investigational New Drug Application ("IND") to the FDA in March 1988 and received permission from the FDA to begin human clinical trials of doxercalciferol. [616, at ¶¶ 128, 142 (citing Bishop Trial Tr. 1537:17-21; 1543:2-1544:18).] The IND listed the sole indication for doxercalciferol as "Osteoporosis (abnormally low bone mass)." [(Keana Trial Tr. 404:4-15.) In correspondence between

DeLuca and the FDA in 1988, DeLuca expressly stated that the use of doxercalciferol was for age-related, post-menopausal osteoporosis. (Keana Trial Tr. 403:5-404:3.)

In 1988, Bone Care conducted the first human clinical trial of doxercalciferol, the H-101 trial. [616, at ¶ 129-131 (Bishop Trial Tr. 1537:24-1538:14, citing PTX 154A; 1589:4-19, citing JTX 25; Keana Trial Tr. 559:9-560:18).] The H-101 trial involved the administration of doxercalciferol to postmenopausal women suffering from osteoporosis. Dr. Bishop and Dr. Gallagher – a scientist at Creighton University who had significant experience with vitamin D compounds – prepared the H-101 protocol, for which Dr. Gallagher was the principal investigator. [616, at 132 (Bishop Trial Tr. 1545:6-1545:25).] They modeled the protocol after trials of calcitriol that Dr. Gallagher had previously conducted for Roche. [616, at ¶ 135 (citing Bishop Trial Tr. 1545:23-146:6).] The proposed doxercalciferol dosage range was 0.5 to 5 micrograms/day, with the dosage increasing depending on how well the drug was tolerated by the patient group. [616, at ¶¶ 137-139 (citing Bishop Trial Tr. 1546:18-1547:24, 1548:9-16).] Bone Care later sought and received approval from the FDA to increase the dosage to as high as 10 micrograms/day. [616, at ¶ 147 (Bishop Trial Tr. 1548:14-154914, 1549:25-1550:9; 1554:12-16, 1568:6-1568:21).] The H-101 trial showed that doxercalciferol could be used in postmenopausal osteoporotic women even at the highest dosage tested – 10 micrograms/day – without causing hypercalcemia. [152, at ¶ 152 (Bishop Trial Tr. 1548:2-19; 1549:25-1550:14; 1551:21-1552:6; 1552:23-1554:4; Langman Trial Tr. 1844:3-1845:21).] Dr. Bishop testified that he compared the results of the H-101 trial with the results of Roche's calcitriol trials and concluded that doxercalciferol, unlike calcitriol, could be administered at high enough doses to have a therapeutic effect on

target issues without resulting in hypercalcemia. [616, at ¶¶ 153, 155 (citing Bishop Trial Tr. 1548:21-1549:5, 1553:24-1554:4).]

In response to the H-101 trial, Plaintiffs filed U.S. Patent Application No. 227,371 ("the '371 application") on August 2, 1988. [616, at ¶ 12 (citing Bishop Trial Tr. 1559:13-21; 1560:7-11; JTX 60).] The preliminary results of the H-101 trial were set forth in example 1 of the '371 application. [616, at ¶ 14 (citing Bishop Trial Tr. 1564:15-1565:3).] Also in response to the H-101 trial, Bone Care sought partners to develop doxercalciferol for the osteoporosis market. [616, at ¶ 346 (citing Bishop Trial Tr. 1522:17-1523:11).] Dr. Bishop testified that he initially chose to pursue an osteoporosis indication because the osteoporosis market was larger than the renal market, and thus more appealing to potential development partners. [616, at ¶ 345 (citing Bishop Trial Tr. 1522:17-1523:11).] Bone Care entered into a partnership with two pharmaceutical companies, Takeda and SmithKline Beecham ("SmithKline") in that effort. [616, at ¶ 346 (citing (Bishop Trial Tr. 1574:15-1575:9).] Bone Care then designed and conducted the H-102 clinical trial of doxercalciferol for the treatment of osteoporosis. [616, at ¶ 349 (citing Bishop Trial Tr. 1567:7-17, 1569:17-1570:6, 1570:10-1571:6.) The H-102 trial results showed that doxercalciferol had a positive effect on bone. [616, at ¶ 350 (Bishop Trial Tr. 1578:21-1579:4).]

The H-106 trial – conducted in 1996 – was the first clinical trial that administered doxercalciferol to human patients with ESRD and SHPT.[29] [616, at ¶ 356-359 (citing Langman Trial Tr. 1851:24-1852-14; JTX 271 at 317; Chesnut Deposition Tr. 26:16-34:19; Bishop Trial Tr. 1567:14-17, 1571:7-1573:3).] The study showed that

[29] The H-106 trial was known as a "Phase III" study – that is, a study performed to obtain FDA approval for a drug. (Bishop Trial Tr. 1666:12-15, 1710:10-13; Langman Trial Tr. 1853:25-1854:3.)

doxercalciferol could be used to suppress PTH with a low incidence of hypercalcemia. [616, at ¶ 351 (citing Langman Trial Tr. 1851:24-1852-14; JTX 271 at 317; Chesnut Deposition Tr. 26:16-34:19).] The results of the H-106 trial were discussed in a 1997 article in Kidney International, the lead author of which was Dr. Tan, and co-authors of which included Dr. Mazess and Dr. Bishop ("the Tan article"). [616, at ¶ 360 (Langman Trial Tr. 1848:22-24.; Bishop Trial Tr. 1612:17-20, 1655:12-15).] The results of the H-106 trial were set forth in claim 7 of the '116 patent, which explicitly described a clinical trial in which doxercalciferol would be administered to ESRD and SHPT patients.

3. Whether Conventional Wisdom and/or Prior Art in 1988 Taught Away from Doxercalciferol to Treat SHPT and ESRD Patients

According to the testimony of Plaintiffs' expert Dr. Norman, conventional wisdom in 1988 favored working with and developing vitamin D_3 compounds rather than vitamin D_2 compounds. [616, at ¶ 55 (citing Norman Trial Tr. 2130:9-2131:11, 2139:12-2140:7, 2158:6-2159:5).] Dr. Norman testified that several facts supported this assertion. First, he stated that it was known at that time that the vitamin D_2 compounds were structurally related to vitamin D_3, which itself is produced naturally in humans. [616, at ¶ 55 (citing Norman Trial Tr. 2130:9-2131:11, 2139:12-2140:7, 2158:6-2159:5).] However, Dr. Norman testified that small structural deviations in the chemical make-up of vitamin D_2 and D_3 compounds were understood in 1988 to potentially dramatically alter a compound's activity. [616, at ¶¶ 60-62 (citing Norman Trial Tr. 2125:12-2127:6, 2132:0-2135:7, 2159:15-2162:23).]

Second, Dr. Norman testified that between 1974 (the year that doxercalciferol was first synthesized) and 1988, scientists were developing and testing hundreds of novel

vitamin D analogs to use as alternatives to calcitriol and alfacalcidol. [616, at ¶¶ 63-63 (citing Norman Trial Tr. 2123:12-2124:11, 2144:18-2145:14).] Of these hundreds, Dr. Norman testified that he had identified 45 that were 1α-hydroxylated vitamin D analogs – including doxercalciferol – that a POSA would take into account in the effort to develop a drug alternative to calcitriol and alfacalcidol. [610, at ¶ 218-219); 616, at ¶¶ 65-66 (citing Norman Trial Tr. 2146:2-2147:2, 2148:6-11, 2148:22-2149:5, 2150:3-9).] Dr. Norman testified that a significant majority of these 45 compounds were analogs of vitamin D_3, indicating that scientists were more interested in vitamin D_3 than vitamin D_2. [616, at ¶ 66 (citing Norman Trial Tr. 2119:21-2120:21, 2136:3-12, 2150:3-9).]

Third, Dr. Norman testified that of the more than 1,000 publications focused on vitamin D between 1960 and 1988, the vast majority related to vitamin D_3 rather than vitamin D_2 compounds; moreover, by 1988, more than 90 percent of relevant publications focused on D_3, indicating a move away from D_2 research. [616, at ¶ 67 (citing Norman Trial Tr. 2142:11-2144:7).] Fourth, as of 1988, the only studies of doxercalciferol in living animals were conducted in rats [616, at ¶ 71 (citing Deftos Trial Tr. 225:2-226:2)], and doxercalciferol had not been tested in a rat model for SHPT [616, at ¶ 72 (citing Deftos Trial Tr. 233:7-11)]. Dr. Norman concluded that POSA would not have been motivated to pursue its development. [616, at ¶ 74 (citing Norman Trial Tr. 2158:9-2159:5, 2219:14-2220:16).]

Defendants presented evidence disputing Dr. Norman's assertion. Defendants argued that it was known in 1988 that vitamin D_2 was not metabolized to calcitriol but instead to an active hormonal, hydroxylated form known as $1,25(OH)_2D_2$, a "naturally occurring" hormone. [634, at ¶¶ 434-435.] Because it was metabolized to a naturally

occurring vitamin D hormone, Defendants argued that a POSA would believe that doxercalciferol was safe, could increase intestinal calcium absorption, and could lower PTH. [634, at ¶¶ 434-435.] Defendants' expert Dr. Deftos testified that knowledge of vitamin D_2's metabolization would have motivated a POSA in 1988 to try doxercalciferol for the treatment of SHPT. [610, at ¶ 209 (citing Deftos Trial Tr. 45:1-15; Bishop Trial Tr. 1625:2-1626:13).]

However, Dr. Bishop persuasively testified that knowledge of vitamin D_2's metabolism did not provide information about the safety of doxercalciferol itself as a drug, and that, absent awareness of its safety profile, a POSA would not have been motivated to try doxercalciferol. [635, at ¶¶ 185-188 (citing Bishop Trial Tr. 1625:9-1626:1), ¶ 209.] Notably, calcitriol, which was metabolized to a naturally occurring hormone, was known by POSAs in 1988 to cause hypercalcemia. Therefore, the Court cannot conclude that the fact that doxercalciferol was metabolized to a naturally occurring hormone would indicate to a POSA that doxercalciferol was safer than calcitriol.

With respect to general familiarity with doxercalciferol in 1988, Defendants argued that Dr. Norman himself had published studies at that time showing that vitamin D_2 was an approved pharmaceutical, was widely used in livestock, and had similar intestinal calcium absorption activity as vitamin D_3. [634, at ¶ 432.] Defendants posited that the fact that doxercalciferol had not been used in humans in 1988, did not mean that prior art suggested that it should not be used in humans. [634, at ¶ 439.] Moreover, Defendants contended that Plaintiffs understated the available literature on and interest in vitamin D_2 analogs in 1988. [634, at ¶¶ 437-440.] Indeed, Defendants stated that Dr.

Norman's testimony ignored several publications ("Reeve 1978" and "Tjellesen 1985") that reported on the advantages of vitamin D_2 over D_3 in the treatment of renal osteodystrophy. [634, at ¶ 436] Defendants pointed to several other pre-1995 patents and articles that they argued show an interest in doxercalciferol in the scientific community at the time. [634, at ¶¶ 437, 440.])

Defendants also argued that Dr. Norman's comparative analysis of the 45 compounds failed to take into account numerous variables that a POSA would consider, such as biological testing, difficulty of synthesis, and licensing. [610, at ¶ 221-231.] Defendants contested the viability of specific compounds among the 45 on grounds that they may not have been reported before 1988, are metabolites instead of analogs or other types of compounds, were already patented, had different toxicity levels, were structurally dissimilar from calcitriol, or otherwise "were not good drug candidates." [see 635, at pp. 41-46.] Defendants' expert, Dr. Keana, testified that a POSA in 1988 *would* have selected doxercalciferol from among the 45 compounds given poor activity in biological testing, difficulty synthesizing, and difficulty licensing the other available compounds. [610, at ¶¶ 232-250.]

Plaintiffs countered that Defendants failed to present credible evidence that a POSA would have selected doxercalciferol over other similar vitamin D analogs for the treatment of ESRD and SHPT patients. [635, at p 46.] Preliminarily, Plaintiffs challenged the admissibility of Dr. Keana's testimony. Plaintiffs argued that Dr. Keana improperly discussed 30 prior art references for the first time in rebuttal, and that such evidence should be excluded as improper rebuttal evidence. [635, at p. 39.] In the alternative, Plaintiffs argued that even if Dr. Keana's testimony is admissible, it should be

given little weight because it was driven by hindsight and because Dr. Keana is not qualified to opine on the prior art as a whole. [635, at p.40.] Plaintiffs noted that Dr. Keana's research experience does not include a focus on vitamin D, its metabolites or analogs, clinical or clinical trial work, or treatment of SHPT patients. [635, at pp. 40-41.] Further, Plaintiffs stated that Dr. Keana's testimony was inconsistent in terms of the comparative standard he applied in evaluating the doxercalciferol syntheses that he cited and in evaluating the 45 compounds that Dr. Norman identified. [635, at p. 47.] Specifically, Plaintiffs faulted Dr. Keana's comparison for failing to consider the same factors (*e.g.*, lethality values, toxicity, biological data, licensing, and syntheses) across the board for all the chemical entities. [635, at p. 40, 42-43.] Importantly, Plaintiffs pointed out that Dr. Keana's analysis did not explain why calcitriol continued to be the only drug used in 1988 to treat ESRD and SHPT patients despite the other availability of other compounds. [635, at p. 48.]

At trial, the Court provisionally admitted Dr. Keana's testimony concerning the prior art references in its entirety, but stressed that its ruling would be subject to revision at any point, including after trial. Upon further reflection, the Court concludes that Dr. Keana's testimony should be excluded as to any references that he raised for the first time at trial. See *David v. Caterpillar, Inc.*, 324 F.3d 851, 857 (7th Cir. 2003); Fed. R. Civ. P. 26. Given the nature of the testimony – involving prior art from almost a quarter century ago – there was no justification for not including all of the references in an expert report (or reports) disclosed well in advance of trial. Springing the new references at trial was prejudicial, at least in the sense that it deprived Plaintiffs of an opportunity to

comprehensively challenge Dr. Keana's opinions in the calm light of the pre-trial day, rather than on the fly during trial.

In any event, even if the Court were to consider Dr. Keana's testimony as to all of the references as part of his expert testimony, those references do not carry the day for Defendants. Just as Dr. Keana opined that Dr. Norman's opinions were incomplete and thus less persuasive, so too did Dr. Keana's opinions overlook important considerations that might have assisted Defendants in carrying their burden of explaining why, as of 1988, a POSA considering conventional wisdom and the prior art would have selected doxercalciferol to raise serum calcium and lower PTH with less incidence of hypercalcemia than calcitriol or alfacalcidol. [See 635, at 40 (showing several ways in which Dr. Keana's analysis was incomplete).] This is not to say that Dr. Keana's testimony carried no weight at all. However, at best, Dr. Keana's opinions reinforced the Court's view of the testimony as a whole on the obviousness issue – namely, that as of 1988, doxercalciferol had been identified as a compound worthy of further study as a possible (and perhaps even promising) treatment for ESRD patients, but that it was neither obvious nor obvious to try as of that date because too little was known about how it would perform in the human body relative to other similar compounds.

The Court reaches a similar conclusion in regard to the large number of articles focusing on vitamin D that were published prior to 1988. [616, at ¶ 67 (Norman Trial Tr. 2142:11-2144:7).] The vast majority of these publications focused on vitamin D_3 [*Id.* (citing Norman Trial Tr. 2142:11-2144:7)], and many of these showed that calcitriol carried a risk of side effects of hypercalciuria (elevated levels of calcium in the urine), hypercalcemia, and calcium deposits in various tissues (Deftos Trial Tr. 131:24-133:16).

Between 1974 and 1988, seven publications included relevant data on doxercalciferol. Many of these articles were authored by Dr. Sjoden, who had worked in Dr. DeLuca's lab. [616, at ¶¶ 69-70, 164 (Norman Trial Tr. 2164:014-2166:18).]

Both parties presented evidence at trial on the issue of whether, based on the results reported in that prior art, a POSA in 1988 would have expected doxercalciferol to have a better safety profile in humans than calcitriol or alfacalcidol. (Bishop Trial Tr. 1629:8-16, 1639:7-20; Deftos Trial Tr. 133:20-22, 140:7-141:16-23, 142:9-155:15, 148:20-152:9.)) In other words, both parties presented evidence regarding whether a POSA in 1988, at the time the '371 application was filed, would have found that the invention set forth in claim 7 of the '116 patent was obvious or obvious to try.

The first article on doxercalciferol was published in 1974 and authored by Dr. DeLuca. [616, at ¶ 158 (citing Keana Trial Tr. 559:9-560:1; Norman Trial Tr. 2167:12-17).] Dr. DeLuca's 1974 article reported that doxercalciferol acted in a manner similar to alfacalcidol in rats, and had no clinical advantage over alfacalcidol. [616, at ¶ 159 (Norman Trial Tr. 2181:18-2182:19).] Four years later, Dr. DeLuca's laboratory published a second article on doxercalciferol, which reported a difference between doxercalciferol and alfacalcidol in terms of bone calcium mobilization. [616, at ¶¶ 160-161 (citing Norman Trial Tr. 2167:12-21, 2183:6-20, 2185:17-2186:15).]

A member of Dr. DeLuca's lab, Dr. Sjoden, published five papers ("Sjoden I-V") on doxercalciferol between 1984 and 1988; all five were incorporated into Dr. Sjoden's Ph.D dissertation ("Sjoden thesis"). [616, at ¶ 163, n.4 (citing Norman Trial Tr. 2165:20-2166:3).]. All of the Sjoden studies were conducted in rats. [616, at ¶ 163 (citing Norman Trial Tr. 2164:14-2165:7).] Sjoden I, published in 1984, compared

doxercalciferol and alfacalcidol, and reported comparable results in intestinal calcium absorption between the two. [616, at ¶ 164 (Norman Trial Tr. 2187:22-2191:6).] Sjoden II compared doxercalciferol, alfacalcidol, and calcitriol, and reported comparable results in intestinal calcium absorption and bone calcium mobilization; it also reported comparable results of doxercalciferol and alfacalcidol with respect to elevating levels of serum calcium. [616, at ¶ 165 (citing Norman Trial Tr. 2191:7-2195:10).] Significantly, Sjoden II reported that doxercalciferol was less toxic than alfacalcidol at lethal doses and less lethal at sub-acutely toxic doses. [616, at ¶ 172 (citing Norman Trial Tr. 2208:12-2210:10).] Specifically, Sjoden II reported that doxercalciferol is fifteen times less toxic than alfacalcidol at lethal doses and four to five times less lethal at sub-acute doses. (Norman Trial Tr. 2208:12-2210:10.) Sjoden III compared doxercalciferol and alfacalcidol, and reported that doxercalciferol was less effective than alfacalcidol in increasing intestinal calcium absorption but that the compounds were comparable in terms of elevating levels of serum calcium. [616, at ¶ 166 (citing Norman Trial Tr. 2195:11-2198:23).] Sjoden IV compared doxercalciferol and alfacalcidol, and reported that doxercalciferol was less active than alfacalcidol in elevating levels of serum calcium. [616, at ¶ 167 (citing Norman Trial Tr. 2198:24-2199:25).] Sjoden V compared doxercalciferol and alfacalcidol, and reported comparable results in bone calcium mobilization and elevation of serum calcium levels. [616, at ¶ 167 (citing Norman Trial Tr. 2200:1-2202:8).]

Plaintiffs and Defendants dispute the import of the art on doxercalciferol available to a POSA in 1988. Defendants argued at trial that, based on the Sjoden studies' showing that doxercalciferol was five to fifteen times less toxic (*i.e.*, less hypercalcemic) than

calcitriol but as potent in terms of stimulating the intestinal absorption of calcium (which in turn suppressed PTH), a POSA in 1988 reasonably would have expected doxercalciferol to be as effective but safer in the treatment of ESRD and SHPT patients. [610, at ¶¶ 196-199 (citing Deftos Trial Tr. 133:17-143:21).].

Plaintiffs' expert, Dr. Norman, testified that, based on the art available at the time, a POSA would not have an expectation that doxercalciferol would cause less hypercalcemia than calcitriol or alfacalcidol in humans. [616, at ¶ 169 (citing Norman Trial Tr. 2202:9-2202:13).] Plaintiffs acknowledged that Sjoden II reported that doxercalciferol was fifteen times less "toxic" than alfacalcidol at lethal doses and five times less toxic at sub-acutely toxic doses in rats. [616, at ¶ 172 (citing Norman Trial Tr. 2208:12-2210:10).] However, Plaintiffs' experts testified that the compounds would never be administered to humans at lethal or sub-acutely toxic doses, because the doses administered "are simply too high to be relevant to an inquiry regarding incidence of hypercalcemia" in humans and would not provide the POSA with information as to the potential incidence of hypercalcemia following the administration of a safe dosage of the drugs to SHPT and ESRD patients. [616, at ¶¶ 174-176 (citing Norman Trial Tr. 2210:11-2212:5; Keana Trial Tr. 612:13-17; Chesnut Deposition Tr. 225:2-23, 226:3-11, 12-15).] In sum, Plaintiffs argued that, even in view of the Sjoden studies, practicing physicians in 1988 "would have expected doxercalciferol to be associated with the same dose-limiting toxicity in humans as calcitriol and alfacalcidol." [616, at ¶ 201.]

Defendants argued that Plaintiffs misconstrue the Sjoden studies. Defendants' expert Dr. Deftos testified that the Sjoden studies would in fact have made doxercalciferol obvious to try in 1988 specifically because it taught that doxercalciferol

could be used to treat SHPT with reduced calcemic side effects. [610, at ¶¶ 200-202 (citing Deftos Trial Tr. 133:20-22, 140:7-141:16-23, 142:8-144:15, 147:20-152:9; Bishop Trial Tr. 1629:19-1630:16, 1639:7-20).] Defendants presented evidence that although lethality of alfacalcidol may disappear at comparatively lower doses, differences in the toxicity of alfacalcidol and doxercalciferol at lower doses would not necessarily have disappeared. [635, at ¶ 449.] Consistent with the discussion above, the Court concludes that although Sjoden II's finding as to the relative toxicity of doxercalciferol and alfacalcidol would have been interesting and potentially even useful to a POSA in 1988, that finding did not enable the POSA to draw any firm conclusions with respect to physiologically tolerable doses in humans given the lethal and sub-acutely toxic dosages at which the compounds were administered to rats in the Sjoden studies.

Defendants also argued that although Plaintiffs diminish the Sjoden findings in arguing non-obviousness, they cited the Sjoden studies enthusiastically in filing the 1988 IND in order to garner FDA support for doxercalciferol trials, as well as in their efforts to market doxercalciferol. [610, at ¶ 197; 634, at ¶¶ 458, 459.] Defendants argued that the FDA accepted Plaintiffs' reliance on the Sjoden data and assurance of "better human safety" of doxercalciferol. [610, at ¶ 198.] Plaintiffs retorted, however, that there is no evidence that the FDA accepted the statements about Sjoden as evidence of "better comparable human safety" – rather, the FDA merely accepted them as adequate support for a Phase I study. [635, at ¶ 187.]

As an initial matter, in the Court's view it is fair to say that both parties have engaged in selective quotation from time to time throughout the case. This appears to be a function of the facts that this case has been heavily contested from the outset and that

much of the prior art and academic literature in the field is indeterminate, and thus can be molded to suit both parties' points of view on many of the matters in dispute. In regard to Bishop's 1988 statement to the FDA, his representation cannot bear the weight that Defendants seek to place on it. Bishop was writing to seek approval for a Phase I investigation and attested that he believed the Sjoden studies to be "adequate" to support the investigation. Again, while this establishes that doxercalciferol was a good candidate for further study as of 1988, there was insufficient data or understanding, even in the mind of a POSA, to isolate doxercalciferol as one of a finite set of compounds as to which success could be anticipated at that time.

Plaintiffs' experts Dr. Langman and Dr. Norman testified that other references published in or before 1988 would not support an expectation that doxercalciferol would cause less hypercalcemia than calcitriol or alfacalcidol in humans. [616, at ¶ 169 (citing Norman Trial Tr. 2202:9-2202:13).][30] Plaintiffs' expert Dr. Norman testified that of the published comparisons of doxercalciferol and alfalacidol in or before 1988, the vast majority reported a comparable biological profile, and the remainder stated that

[30] A study by Dr. Slatopolsky in 1984 suggested that the incidence of hypercalcemia relative to PTH-suppression efficacy was lower when calcitriol was administered orally instead of intravenously (because intravenous administration caused direct effect of calcitriol on the parathyroid glands rather than indirect effect via intestinal absorption of calcium). [616, at ¶ 190 (citing Langman Trial Tr. 1830:24-1833:20).] In other words, Slatopolsky taught that the higher the peak concentration of calcitriol, the lower the incidence of hypercalcemia. [616, at ¶ 195 (citing Langman Trial Tr. 1833:5-18).] The Sjoden thesis suggested that doxercalciferol has relatively low peak concentrations compared with alfacalcidol. [616, at ¶ 196 (Langman Trial Tr. 1834:8-1837:3).] A publication by Horst showed that doxercalciferol is cleared from the body more quickly than calcitriol, further suggesting that doxercalciferol has relatively low peak concentrations. [616, at ¶ 197 (Langman Trial Tr. 1837:4-1838:11).] Dr. Deftos testified that Slatopolsky is irrelevant to the POSA's expectancy in 1988 regarding the clinical effectiveness of doxercalciferol, because (1) calcitriol's direct effect on PTH was well known in 1988, (2) the study did not compare doxercalciferol with calcitriol, and (3) even if a POSA would know that doxercalciferol had a lower peak concentration than calcitriol, it would have been reasonable to expect that it also had lower toxicity than calcitriol. [634, at ¶¶452-457.]

doxercalciferol was less active than alfacalcidol. [616, at ¶ 170 (citing Norman Trial Tr. 2193:8-17, 2202:16-2203:25).]

Defendants' expert Dr. Deftos testified that the prior art in 1988[31] showed that doxercalciferol, calcitriol, and alfacalcidol all shared a common therapeutic benefit of raising serum calcium while lowering PTH in ESRD and SHPT patient, and that doxercalciferol was "readily substitutable" for the latter two compounds but had a "better therapeutic margin" than the other two compounds. [610, at ¶ 204, 207 (citing Bishop Trial Tr. 155:15-157:7).][32] To the extent that certain articles referenced by Dr. Langman showed an increased risk of hypercalcemia attendant to the use of calcitriol and alfacalcidol, Defendants argued that those studies reported an *over*suppression of PTH (which in turn causes an increased incidence of hypercalcemia), and thus do not undermine Defendants' assertion that doxercalciferol was "readily substitutable" for those compounds. [610, at ¶¶ 212-213 (citing Langman Trial Tr. 1954:16-20).] Defendants argued that Dr. Bishop conceded that a POSA in 1988 would have known that doxercalciferol was readily substitutable for both calcitriol and alfacalcidol in ESRD and SHPT patients. [610, at ¶¶ 206-208 (citing Bishop Trial Tr. 1620:22-1623:16, 1627:9-24; Deftos Trial Tr. 107:4-23).] Indeed, Defendants argued that Dr. Bishop and

[31] Dr. Deftos testified that a 1978 publication by Reeve reported that doxercalciferol was as or more effective at stimulating intestinal absorption of calcium as or than calcitriol or alfacalcidol in nephrectomized rats (rats with non-functioning kidneys). [610, at ¶ 205 (citing Deftos Trial Tr. 106:1-107:4); 635, at ¶ 436.] Plaintiffs countered that the nephrectomized rats are not analogous to human patients with ESRD, and that Defendants ignored evidence that, when administered at physiologically tolerable doses, doxercalciferol, calcitriol, and alfacalcidol cause similar elevations in serum calcium. [635, at p. 34.]

[32] Plaintiffs vigorously dispute this assumption. [635, at p. 34]. Plaintiffs stated that in 1988 it had in fact *not* been shown that doxercalciferol, calcitriol, and alfacalcidol had a common benefit, as doxercalciferol had not at that point been administered to human SHPT patients or even to a rat model of SHPT. Plaintiffs argued that Defendants provide no record support for this assertion (or explain what they mean by "a better therapeutic margin").

Dr. DeLuca had stated prior to 1988 that doxercalciferol could be substituted for the vitamin D_3 compounds. [610, at ¶ 207 (citing Deftos Trial Tr. 107:4-14, 117:1-118:11, 153:15; see also JTX 87, Table I).] Dr. DeLuca testified that based on the published data in 1988, it would have been "obvious to try" doxercalciferol to treat SHPT and ESRD patients.[33] Defendants further argued that a POSA would have been motivated to try doxercalciferol as an alternative to the vitamin D_3 compounds because, in 1988, it was known that a hormonally active form of vitamin D_2 was naturally found in the human body. [610, at ¶ 209 (citing Deftos Trial Tr. 45:1-15; Bishop Trial Tr. 1625:2-1626:13).] In sum, Defendants argued that a POSA would not be led away from doxercalciferol by the prior art in 1988. [634, at ¶ 456.] Rather, Defendants argued that POSA in 1988 would have a reasonable expectation that doxercalciferol could be administered with a lower incidence of hypercalcemia than calcitriol or alfacalcidol while as effectively suppressing PTH. [634, at ¶ 457.]

The Court agrees in part and disagrees in part with both parties on the question of obviousness. The Court is not persuaded by Plaintiffs' argument that the prior art as of 1988 actually "taught away" from the possible use of doxercalciferol to treat SHPT in patients with ESRD. Enough work had been done with doxercalciferol by that time – including, most significantly, the Sjoden studies – to surmise that doxercalciferol might hold promise as a drug candidate to match the effectiveness of the existing treatments without the hypercalcemic side-effects. At the same time, however, the Court finds that

[33] Plaintiffs countered that, to the extent that Bishop described the compounds as readily substitutable for one another, he (1) did so in a statement in the '596 patent, which does not constitute an "admission," (2) did so in reference to the compounds being a possible substitute for the treatment of hypercalcemia in mammals experiencing bone loss, not in the treatment of ESRD and SHPT patients, and (3) noted in the '596 patent itself that the statement was speculative and unsubstantiated by clinical data. [635, at p. 35.]

the prior art, and correspondingly the knowledge of the POSA, had not, as of 1988, advanced to the point to which doxercalciferol was obvious or obvious to try for human treatment. As of 1988, no one had treated human patients with doxercalciferol. Nor had anyone predicted how to extrapolate the Sjoden rat data, involving doses far in excess of the physiologically tolerable doses in humans, to likely human outcomes. Given the state of the art, the Court finds that even if a POSA might have hoped for success following further experimentation with doxercalciferol, the POSA could not have anticipated success based on what was then known.[34] In the Court's view, to find obviousness on the record compiled in this case would countenance one of the "kinds of error" against which the Federal Circuit has warned – namely, that "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) ("this court and its predecessors have repeatedly emphasized that 'obvious to try' is not the standard under § 103"). And, consistent with the foregoing analysis, the Court finds that the circumstances here are not like *KSR Int'l, Inc. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007), in which the Supreme Court held that a product that was one of "a finite number of identified, predictable solutions" that led to "anticipated success" may have constituted an instance where the product simultaneously was obvious to try and obvious under § 103.

[34] Defendants argued that, even if the Court does not conclude that the claimed invention as obvious in 1988, it was at least obvious as of 1995. [611, at ¶ 80.] That contention finds support in the work of Slatopolsky, Gallagher, and the additional animal and human testing done between 1988 and 1995. But the Court need not – and thus does not – address the argument further because it has determined that claim 7 of the '116 patent is entitled to the 1988 priority filing date of the '371 application.

Finally, Defendants' reliance on statements by Dr. Bishop (and Bone Care) in a March 1988 IND submitted to the FDA and by Dr. DeLuca during his deposition in this lawsuit cannot be given much, if any weight, given the Federal Circuit's admonition (cited above) that obviousness must be determined from the perspective of the POSA, not the inventor. "The actual inventor's skill is irrelevant to the inquiry," because "according to the concepts underlying the Constitution and the statutes that have created the patent system," inventors "possess something * * * which sets them apart from the workers of *ordinary* skill," including POSAs. *Standard Oil*, 774 F.2d at 454. Moreover, even if the inventor's skills and views were relevant, they would be only marginally so in the context of Bone Care's 1988 IND, for that document was submitted in an effort to obtain approval to test doxercalciferol in humans. The fact that such testing remained to be done actually reinforces the Court's conclusion that as of 1988 the POSA lacked the information necessary to form "a reasonable expectation of success." *In re O'Farrell*, 853 F.2d at 904. Dr. DeLuca's comment that doxercalciferol was "obvious to try" falls into much the same category. As the inventor of doxercalciferol itself and the supervisor of the Sjoden thesis, DeLuca surely possessed that "something" that in the Federal Circuit's view separates extraordinary inventors from ordinary persons of skill in the art (see *Standard Oil*, 774 F.2d at 454), and thus his views lie outside the proper scope of this Court's obviousness inquiry.[35]

[35] The Court also notes that certain "real world facts" reinforce the non-obvious nature of the invention at issue here, including (most notably) that several generic drug companies seek to sell generic versions of Hectorol® instead of something from the prior art from which the development of Hectorol® was said to be obvious.

F. Inequitable Conduct

"To hold a patent unenforceable for inequitable conduct, a court must find, by clear and convincing evidence, that the applicant omitted or misrepresented material facts with the intention of misleading or deceiving the patent examiner." *Monsanto Co. v. Bayer Bioscience N.V.*, 363 F.3d 1235, 1239 (Fed. Cir. 2004). The parties devoted a great deal of attention to the inequitable conduct issue, both before, during, and after the trial. Before trial, the Court granted Plaintiffs' motion for summary judgment as to several of Defendants' inequitable conduct claims. [See 498]. Two inequitable conduct claims remained for trial concerning abstracts and posters published in 1989 and 1993 and an article published in 1994, all of which involved work in which Dr. Bishop was engaged with Dr. J. C. Gallagher.

However, as the Court previously noted [see 498, at 7], Defendants have not disputed that the so-called Gallagher abstracts and Gallagher article "post-date the 1988 filing date of the Parent Application" on August 2, 1988. And Defendants therefore "concede that, if Plaintiffs are correct in claiming that Claim 7 of the '116 Patent is entitled to the benefit of the 1988 priority filing date," then the affirmative defenses and counterclaims for inequitable conduct "must fail." *Id*. Defendants' concession appears to have been well founded based on controlling law. See, *e.g., Trading Techs. Int'l, Inc. v. eSpeed, Inc.*, 595 F.3d 1340, 1362 (Fed. Cir. 2010) ("The district court did not clearly err by finding that Brumfield's software was immaterial given that his use of the software after the priority date would not have changed the examiner's analysis of the patent"); *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 940 (Fed. Cir. 1990) ("Since the Viatron 21 device was not prior art, it was not material to patentability" and "[a]bsent

materiality, inequitable conduct for failure to disclose cannot lie"); see also *Mallinckrodt, Inc. v. Masimo Corp.*, 147 Fed. Appx. 158, 186 (Fed. Cir. Sept. 7, 2005) ("Because the activities described in the Yorkey declaration and attachment cannot pre-date Masimo's invention * * *, Masimo was not obligated to submit those documents to the PTO during prosecution of either the '222 patent or the '850 patent" and "the district court correctly found that the Yorkey declaration and attachment thereto were not material to patentability and thus the district court was not bound to consider whether Masimo intended to deceive the PTO in not disclosing those documents"); *Ormco Corp. v. Align Technology, Inc.*, 2009 WL 466070, at *8 (C.D. Cal. Feb. 23, 2009) (granting summary judgment where the allegedly undisclosed information was not material because it post-dated the priority date).

As explained above, the Court has determined that in fact Plaintiffs are entitled to the August 2, 1988 priority date. Accordingly, Plaintiffs are entitled to judgment on Defendants' inequitable conduct counterclaims and affirmative defenses.[36]

[36] Because the disposition as to priority date renders the inequitable conduct claims moot, the Court need not – and thus does not – delve deeply into whether Defendants could have satisfied the "tighten[ed]" standards for intent and materiality announced in *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1290 (Fed. Cir. 2011) (en banc).

III. Conclusion

For the foregoing reasons, the Court concludes that the '116 patent is valid and enforceable.

Dated: March 22, 2012

Robert M. Dow, Jr.
United States District Judge