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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

WARNER CHILCOTT COMPANY, LLC, et al., Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Case No. 11-6936 (FSH) **FINDINGS OF FACT AND CONCLUSIONS OF LAW** March 4, 2015

HOCHBERG, District Judge:

This Opinion constitutes the Court's findings of facts and conclusions of law pursuant to Federal Rule of Civil Procedure 52.

I. INTRODUCTION

ATELVIA®—the osteoporosis drug covered by the challenged patents—purports to solve a problem experienced by patients who used earlier osteoporosis drugs: if the earlier drugs were taken with a meal, the active ingredient was captured by the calcium found in food molecules and was not absorbed into the body. [1] When the medicine failed to enter the bloodstream,

[1] Trial counsel for both parties, and the team of attorneys and staff supporting them, presented extraordinarily detailed chemistry with clarity and brevity. Each side presented only the most pertinent scientific points and condensed their arguments into a week-long presentation that the

patients' bones became susceptible to fractures. ATELVIA® addressed this "food effect" by combining the active ingredient risedronate with a calcium-blocking agent, EDTA, thus permitting patients to take the drug with a meal and still receive an effective dose.

It is uncontested that prior art disclosed combinations of the active ingredient and the calcium-blocking agent EDTA to increase absorption. The closest reference—the *Brazilian Application*—disclosed two mechanisms to increase absorption: (1) a process called chelation, where EDTA binds to calcium molecules in food and blocks them from capturing the active ingredient; and (2) permeability enhancement, where large doses of EDTA spread the pathways between intestinal cells, allowing more active ingredient to pass from the intestine into the bloodstream.

By binding to calcium ions in food, chelation increases absorption only when a patient has eaten a meal; absorption of the active ingredient is thus similar regardless of whether a patient has eaten or not. On the other hand, permeability enhancement amplifies overall absorption of any intestinal content. Increased intestinal permeability was viewed as harmful because other drugs or bacteria could also more easily pass into the bloodstream.

ATELVIA® employs only the first mechanism: it uses EDTA as a chelator to block the calcium in food, but not to enhance overall intestinal permeability. This achieves what the challenged patents call "pharmaceutically effective absorption," a limitation defined as similar absorption whether a patient has eaten or fasted. Fed exposure within about 50% of fasting

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Court was fully able to understand. They deserve a great deal of credit for their professionalism and judgment, conferring to narrow the areas of controversy so that judicial resources were expended only on resolving the heart of their dispute. The attorneys on both sides earned tremendous respect from all who watched, listened, and observed this trial.

exposure is expected to be "pharmaceutically effective absorption." Except for the "pharmaceutically effective absorption" limitation, the parties agree that the *Brazilian Application* contains "all of the elements of the asserted claim[s]." Thus, the main dispute is narrow: in light of the *Brazilian Application's* disclosure of EDTA's two mechanisms of absorption, whether it was obvious to modify the reference—using only the first disclosed mechanism of chelation and excluding the second disclosed mechanism of enhanced permeability—thus permitting a patient to take her osteoporosis medicine and receive a similar dose regardless of whether she has or has not eaten. In other words, was it obvious to use EDTA only as a calcium blocking agent to defeat the food effect, and would a skilled artisan have had a reasonable expectation of success in so doing?[2]

II. JURISDICTION

This Court has subject matter jurisdiction over this case pursuant to the patent laws of the United States and 28 U.S.C. §§ 1331, 1338, 1367, 2201 and 2202. Venue is proper in this District under 28 U.S.C. §§ 1391 and 1400(b). This Court has jurisdiction over the parties.

III. BACKGROUND

a. Procedural

Plaintiffs Warner Chilcott Co., LLC, and Warner Chilcott (US), LLC, (collectively "Plaintiffs" or "Warner") bring this patent infringement action against Teva Pharmaceuticals USA, Inc., ("Teva") under the Federal Food, Drug, and Cosmetics Act ("FFDCA"), and, more

[2] To answer this question, the Court also considers additional prior art, including the *Poiger Reference*, *WO '111*, the *Mahé Reference*, and the *Mitchell Reference*, and other relevant literature, including Lin, Janner, Ezra, Zakelj, Van Hoogdalem, Muranishi, and others.

specifically, the Hatch-Waxman Amendments to that law. Plaintiffs assert that two patents protect ATELVIA® from generic competition: U.S. Patent No. 7,645,459 (the "'459 patent") and U.S. Patent No. 7,645,460 (the "'460 patent"). Both patents describe a delayed-release formulation of the active ingredient risedronate in combination with ethylene diamine tetraacetic acid ("EDTA"). Warner acquired these patents when it purchased The Proctor & Gamble Company's pharmaceutical division in August 2009. (Joint Stipulation of Facts ¶ 3, Dkt. No. 270). Plaintiffs hold an approved New Drug Application ("NDA"), No. 22-560, under § 505(a) of the FFDCA, 21 U.S.C. § 355(a), for a delayed-release risedronate tablet formulation containing 35 mg of risedronate sodium and 100 mg of disodium EDTA, and marketed as ATELVIA®. (Joint Stipulation of Facts ¶¶ 5, 70, 71). These tablets were approved by the Federal Food and Drug Administration ("FDA") on October 8, 2010, and are promoted for the treatment of osteoporosis. (Joint Stipulation of Facts ¶ 69). Warner listed the '459, '460 patents and U.S. Patent No. 8,246,989 in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), in connection with ATELVIA®. (Joint Stipulation of Facts ¶ 77).

As required by 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Defendant Teva provided Plaintiffs with a "paragraph IV certification," notifying Plaintiffs that they had submitted an Abbreviated New Drug Application ("ANDA"), No. 20-3217, to FDA seeking approval to manufacture and market generic versions of ATELVIA® before the expiration of the '460 and '459 patents. Warner brought this patent infringement action against Teva within the forty-five day statutory period, filing a Complaint against the Defendant. Teva asserted counterclaims, seeking a finding that the challenged patents are invalid. Warner also filed patent infringement actions against the

pharmaceutical companies Watson Laboratories, Ranbaxy, and Impax Laboratories, asserting these same patents. The Watson, Ranbaxy, and Impax actions were each resolved by settlement.

In its case against Teva, Warner has dropped all asserted claims of U.S. Patent No. 8,246,989, and all asserted claims of the '459 and '460 patents except for claim 16 of the '459 patent and claim 20 of the '460 patent. Teva has stipulated to infringement of these claims. (Joint Stipulation of Facts ¶ 40). A bench trial was held regarding the validity of claim 16 of the '459 patent and claim 20 of the '460 patent.

b. Technology At Issue

The challenged patents claim an active ingredient called risedronate sodium. This drug is a member of a class called bisphosphonates, which have been used for decades to treat osteoporosis. This active ingredient is combined with an inactive ingredient called disodium EDTA, which chelates—or binds—metal ions in food, blocking them from capturing the active ingredient when a patient has eaten.

1. Bisphosphonates

Bisphosphonates have been used since the 1980s to treat osteoporosis and Paget's disease. (Trial Tr. 1A.100:16-25).[3] These diseases are characterized by a weakening of the bone. In a healthy human body, bone tissue is continually regenerated in an equilibrium of bone growth and bone disintegration. (Tr. 1A.103:14-104:9). Osteoblasts, a type of cell that builds new bone,

[3] Where the court reporter numbered the trial transcript with volume numbers, those volume numbers are used herein. Where the alternate court reporter dated, but did not number the trial transcript, the Court refers to the unnumbered trial transcript volumes as follows: July 14, 2014 P.M. Trial Tr. (hereinafter "Tr. 1B"); July 15, 2014 A.M. Trial Tr. (hereinafter "Tr. 2A"); and July 16, 2014 A.M. Trial Tr. (hereinafter "Tr. 3A").

are balanced by osteoclasts, a type of cell that destroys bone in a process called resorption. (*Id.*; Joint Stipulation of Facts ¶¶ 84, 85). In patients with osteoporosis, this normal balance is disrupted and bone resorption exceeds bone growth, leading to lower bone mass and a higher chance of fracture. (Tr. 1A.104:1-6).

Bisphosphonates have a strong affinity for the calcium crystals in bone, binding tightly to bone surfaces. (Tr. 1A.104:10-17). When a bone-destroying osteoclast engulfs a bone particle that is attached to a molecule of bisphosphonate, the osteoclast cell becomes less active or is destroyed. (*Id.*; PTX 135, at 176).[4] Consequently, bisphosphonates inhibit bone resorption. (DTX 167, at 280). Over time, the administration of bisphosphonates results in less active bone-destroying osteoclasts, less resorption, and more bone tissue. (Tr. 1A.104:15-24). Many pharmaceutical companies have developed species of bisphosphonate for the treatment of osteoporosis. For instance, Warner marketed a 35 mg delayed-release risedronate tablet, called ACTONEL®, which is the predecessor drug to the ATELVIA® drug at issue. Warner held patents covering risedronate and Warner's ACTONEL® product, which expired on December 10, 2013. Merck developed an alendronate product, marketed as FOSAMAX®; and Hoffmann-La Roche developed an ibandronate product, marketed as BONIVA®. (Joint Stipulation of Facts ¶¶ 42, 44, 57).

2. The "Food Effect"

Drugs that are administered by mouth travel from the mouth to the stomach, and then through the pylorus to the lower gastrointestinal tract—which includes the small and large

[4] Where available, the Court uses an exhibit's internal pagination.

intestine. (Joint Stipulation of Facts ¶¶ 88, 89). Bisphosphonate absorption occurs, to the largest extent, in the small intestine. (PTX 135, at 179). The small intestine consists of the duodenum, jejunum, and ileum. (DTX 234, at 589; Tr. 1A.106:3-6). There, the bisphosphonate passes from the intestines into the bloodstream.

There are two routes of transportation for molecules to pass from the intestine into the bloodstream: passing through the intestinal membrane cells themselves or passing through the spaces between the cells, called the tight junctions. (PTX 90, at 1744; Tr. 1A.107:1-8). Bisphosphonates do not pass through the membrane cells. Instead, they travel between the cells, through the tight junctions. (DTX 273, at 231; PTX 135, at 178-79; Tr. 1A.107:9-18). Once in the bloodstream, the bisphosphonate circulates; some is excreted and some is delivered to the bones, the site of the drug's action. (DTX 208, at 289; Tr. 1A.107:14-18).

Bisphosphonates are not absorbed, and do not pass into the bloodstream, when taken with a meal. This class of drug not only binds to the calcium in bone, it also binds to any stray calcium ions and other metals[5] it encounters in the stomach and intestines after a meal. (PTX 135, at 178; PTX 90, at 1745; Tr. 1A.108:23-109:4). In the gastrointestinal tract, calcium captures bisphosphonate, forming a combined calcium-bisphosphonate complex that is insoluble and is too big to pass through the intestinal tight junctions and into the bloodstream. (DTX 167, at 280, 283). Thus, when an osteoporosis patient simultaneously eats and takes her

[5] Divalent cations, including calcium, magnesium, and iron, interfere with bisphosphonate absorption. (Tr. 1A.109:10-16). The Court uses the term "calcium" in a general sense to refer to this group of metals.

bisphosphonate, she does not receive the benefit of the medicine because it never reaches the bone. (Tr. 1A.110:21-111:1). This phenomenon is known as the "food effect."

Because bisphosphonates interact with food, Warner's predecessor drug ACTONEL® had to be taken when the patient had fasted, specifically, after an overnight fast and at least 30 minutes before eating or drinking. (Joint Stipulation of Facts ¶ 53).

3. Chelating Agents

The compound disodium EDTA[6] binds to calcium and other divalent cations. This process is called chelation and EDTA is one of the most widely used and strongest chelators of calcium. (Tr. 1A.117:1-8). It tightly sequesters divalent ions, after which the ions cannot interact with other molecules. (Tr. 2A.26:9-27:5).

The bisphosphonate literature had shown that administering EDTA with bisphosphonate increased bisphosphonate absorption. Two mechanisms account for the increase in absorption: (1) chelation, in that EDTA acted as a calcium blocker; and (2) permeability enhancement, in that EDTA directly increased the permeability of the intestines. (*See* DTX 167, at 283; PTX 90, at 1745).

The first mechanism, calcium chelation, operates by blocking calcium from capturing the bisphosphonate active ingredient via competitive inhibition. (*See* DTX 167, at 283; PTX 90, at 1745). The active ingredient and the chelating agent both compete for the same pool of stray calcium. By introducing enough chelating agent, stray calcium is more likely to capture the

[6] There are different types of EDTA with different properties. Unless otherwise noted in this opinion, the Court uses "EDTA" to refer to disodium EDTA. Likewise, there are different versions of risedronate. The Court uses "risedronate" to refer to risedronate sodium.

chelating agent than the active ingredient. (Tr. 2B.40:1-2). Like a decoy, chelating agents block calcium ions from capturing the bisphosphonate, while the bisphosphonate remains free to enter the bloodstream without interference.

The second mechanism, increasing intestinal permeability, works by widening the pathway between the tight junctions of intestinal cells—by which bisphosphonate travels from the intestine into the bloodstream—permitting more bisphosphonate to be absorbed. (DTX 273, at 232; DTX 167, at 283; PTX 90, at 1745). The tight junctions between cells have molecules of calcium embedded in the channels. EDTA binds to these molecules, making the spaces between cells wider, and increasing permeability for many particles. (DTX 167, at 283). Thus, larger molecules like bisphosphonates pass more easily into the bloodstream. (PTX 90, at 1745; PTX 135, at 179). But spreading the tight junctions creates a risk that bacterial fragments and increased levels of coadministered drugs will pass through these wider pathways to the bloodstream. (PTX 175, at 1249). Consequently, unduly spreading the tight junctions was viewed as undesirable. (DTX 167, at 280; PTX 90, at 1745; PTX 135, at 185).

c. The Challenged Patents

Both the ’459 and ’460 patents share a provisional application filed on May 24, 2004. The utility application that issued as the ’459 patent was filed on April 15, 2005. The utility application that issued as the ’460 patent was filed on November 23, 2005 and is a continuation-in-part of the application that issued as the ’459 patent. The ’459 patent, entitled “Dosage Forms of Bisphosphonates,” and the ’460 patent, entitled “Dosage Forms of Risedronate,” both issued on January 12, 2010. The patentee disclaimed the terminal part of the ’460 patent beyond the

expiration of the ’459 patent, and both are scheduled to expire on January 9, 2028. (Joint Stipulation of Facts ¶¶ 34, 38). The inventors are listed as Richard Dansereau and David Burgio.

Claim 16 of the ’459 patent, like claim 20 of the ’460 patent, comprises one independent claim and several additional dependent claims. Claim 16 of the ’459 patent is reproduced below:

8. An oral dosage form having pharmaceutically effective absorption comprising:

(a) from about 1 mg to about 500 mg of risedronate sodium;

(b) from about 75 mg to about 250 mg of disodium EDTA; and

(c) an enteric coating which provides for release of the risedronate sodium and the disodium EDTA in the lower gastrointestinal tract of a mammal.

13. The oral dosage form of claim **8** comprising from about 10 mg to about 50 mg of risedronate sodium.

14. The oral dosage form of claim **13** comprising about 100 mg of the disodium EDTA.

15. The oral dosage form of claim **14** comprising about 35 mg of risedronate sodium.

16. The oral dosage form of claim **15** wherein the enteric coating is a methacrylic acid copolymer.

(DTX 2, ’459 patent, col. 38, ll. 50-57, col. 39, ll. 5-13). Claim 20 of the ’460 patent is reproduced below:

8. An oral dosage form having pharmaceutically effective absorption comprising:

(a) from about 1 mg to about 250 mg risedronate sodium;

(b) from about 25 mg to about 500 mg of disodium EDTA; and

(c) an enteric coating which provides for immediate release of the risedronate sodium and the disodium EDTA in the small intestine of a mammal.

15. The oral dosage form of claim **8** comprising from about 15 mg to about 55 mg of the risedronate sodium.

16. The oral dosage form of claim **15** comprising from about 75 mg to about 250 mg of the disodium EDTA.

17. The oral dosage form of claim **16** comprising about 35 mg of the risedronate sodium.

19. The oral dosage form of claim **17** comprising about 100 mg of the disodium EDTA.

20. The oral dosage form of claim **19** wherein the enteric coating is a methacrylic acid copolymer.

(DTX 3, '460 patent, col. 24, ll. 47-55, col. 25, ll. 8-20).

As shown above, claim 16 of the '459 patent and claim 20 of the '460 patent are both limited to an oral dosage form with 35 mg of risedronate sodium, 100 mg of disodium EDTA, and a methacrylic acid copolymer enteric coating. Claim 16 of the '459 patent differs from claim 20 of the '460 patent in the location of release of the formulation: claim 16 requires "release . . . in the lower gastrointestinal tract," whereas claim 20 requires "release . . . in the small intestine." The small intestine is part of the lower gastrointestinal tract. (Joint Stipulation of Fact ¶ 89). Claim 20 of the '460 patent also adds the limitation "immediate release," which means "dissolution of the core tablet in less than 60 minutes, when measured by standard USP definitions." (DTX 3, '460 patent, col. 4, ll. 13-16).

One feature of the claimed invention is the addition of the limitation in both claims called "pharmaceutically effective absorption," which is defined in both the '459 and '460 patents as:

> an amount of a chelating compound high enough to significantly bind the metal ions and minerals in food but low enough not to significantly alter absorption of the bisphosphonate[7] as compared to absorption in the fasted state. That is, absorption is similar with or without food. Given the high variability of bisphosphonate absorption, fed exposure within about 50% of fasting exposure is expected to be "pharmaceutically effective absorption."
>
> (DTX 2, '459 patent, col. 4, ll. 59-67; DTX 3, '460 patent, col. 4, ll. 64-col. 5, ll. 5).

The patent applications that issued as the '459 and '460 patents originally did not contain the term "pharmaceutically effective absorption." (PTX 3, at 1138). After the PTO examiner rejected the claims as unpatentable—because earlier references disclosed bisphosphonates combined with EDTA to increase absorption—the patentee amended every claim to add the limitation "pharmaceutically effective absorption." (PTX 3, at 636-38, 1138; PTX 5, at 542-544, 648). The examiner allowed the claims after that amendment. The concept is to permit the patient to take the drug either with or without food; however, FDA has approved ATELVIA® only to be taken with food.

IV. THE TRIAL

At trial, the evidence centered upon whether the asserted claims of the '459 and '460 patents are invalid due to anticipation or obviousness.

a. Anticipation

"A patent is invalid for anticipation under 35 U.S.C. § 102 if a single prior art reference discloses each and every limitation of the claimed invention." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014). In order to anticipate, the prior art reference must contain "each

[7] In the '460 patent, this word, "bisphosphonate," is replaced with the word "risedronate."

of the limitations of the claim." *Scaltech, Inc. v. Retec/Tetra, LLC*, 178 F.3d 1378, 1383 (Fed. Cir. 1999). "Claimed subject matter is 'anticipated' when it is not new; that is, when it was previously known. Invalidation on this ground requires that every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention." *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008). "[T]he dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from a prior art reference that every claim element is disclosed in that reference." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1055 (Fed. Cir. 2010) (quoting *In re Baxter Travenol Labs*., 952 F.2d 388, 390 (Fed. Cir. 1991)) (internal quotations and alterations omitted). "[T]he party asserting invalidity due to anticipation must prove anticipation, a question of fact, by clear and convincing evidence." *Orion IP, LLC v. Hyundai Motor Am.*, 605 F.3d 967, 975 (Fed. Cir. 2010).

"[A] single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference." *Allergan, Inc. v. Apotex Inc*., 754 F.3d 952, 958 (Fed. Cir. 2014). "[I]nherency operates to anticipate entire inventions as well as single limitations within an invention." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003). Recognition of an inherent limitation in the prior art by a person of ordinary skill in the art is not required to establish inherent anticipation. *Id.* at 1377. An inherent limitation is one that is necessarily present and not one that may be established by "probabilities or possibilities." *See Continental Can Co. v. Monsanto Co*., 948 F.2d 1264, 1268-69 (Fed. Cir. 1991). That is, "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id*.

1. The Brazilian Application

Teva introduced evidence that Brazilian Patent Application, No. BR2001-06601 (DTX 205), anticipated the claimed invention. The *Brazilian Application* was published on September 9, 2003. No patent has issued. It is prior art under 35 U.S.C. § 103(a) and (b) for both the '459 and the '460 patents. (Joint Stipulation of Facts ¶ 90). The *Brazilian Application* claimed: "at least one core containing one or more bisphosphonates, at least one core or core coating containing a chelating agent, said core or cores being coated individually or together by a gastroresistant and enterosoluble layer." (DTX 205, at 9). With respect to bisphosphonates, the *Brazilian Application* lists risedronate as well as thirteen additional bisphosphonates and their pharmaceutically acceptable salts and hydrates. (*Id*. at 5-6). Regarding chelating agents, it lists four acceptable chelating agents, including EDTA in either monosodium or disodium form. (*Id.* at 5). Finally, it disclosed a "gastroresistant and enterosoluble coating" to deliver the chelating agent "only into the small intestine," (*id.* at 3); the application requires bypassing the stomach so that there is no loss of chelating agent in the stomach, (*id.* at 4). Acceptable coatings include "copolymers of methyl methacrylate – methacrylic acid." (*Id.* at 6). The coating "preferably dissolve[s] rapidly in a neutral environment." (*Id.*). The bisphosphonate, chelating agent, and delayed release mechanism are combined to "increase[] the absorption of bisphosphonates by the action of chelating agents" using two mechanisms: "a) reduction of the formation/solubilization of insoluble complexes of bivalent [calcium and magnesium] ions with bisphosphonates, and b) increase in permeability of the intestinal mucosa." (*Id.* at 3).

The parties agree that "somewhere in [the *Brazilian Application*] are all of the elements of the asserted claim" except "pharmaceutically effective absorption," (Tr. 4A.51:16-23). They

dispute whether the *Brazilian Application* disclosed the particular claimed amount of 35 mg risedronate sodium combined with the particular claimed amount of 100 mg disodium EDTA.

2. Amount of Risedronate Disclosed

As in the asserted claims, the *Brazilian Application* used a subset of bisphosphonates for the purpose of "inhibiting osteoclast-mediated bone resorption." (DTX 205, at 2). The *Brazilian Application* did not instruct the use of a particular amount of risedronate sodium. Rather, it called for an "effective quantity" of any bisphosphonate, including risedronate sodium, where the "intervals (for example, daily or weekly) . . . , the effective quantity, and the rate of release depending on the pathology to be treated, as known to a person skilled in the art."

It is undisputed that risedronate sodium was "well-known as of 2005 . . . [as a] commercially available salt of risedronate." (Tr. 1A.126:4-7). Defendant's formulation scientist Dr. John Yates—the executive director of clinical research at Merck during development of FOSAMAX®—testified that a person of ordinary skill at the relevant time would understand the term "effective quantity" of risedronate to be a 35 mg once-weekly dose of risedronate sodium. (Tr. 1A.126:21-25). The 2002 ACTONEL® label listed the only approved doses of risedronate as the 35 mg weekly dose of risedronate sodium for osteoporosis, the 5 mg daily dose for osteoporosis, and the 30 mg formulation of risedronate sodium for Paget's disease. (DTX 185, at 5; Tr. 1B.26:4-9). The 35 mg once-weekly dose was the most commonly prescribed regimen of risedronate for osteoporosis. (Tr. 1B.25:23-25).

On the other hand, Dr. Stanley Davis—a professor of pharmaceutical science—testified that the *Brazilian Application* disclosed the use of substantially less than 35 mg risedronate based on the specification's statement that, "with this invention we obtain an effective treatment with a

small quantity of bisphosphonate compared to the current treatment." (DTX 205, at 4). Although it acknowledged that small quantities may be useful, the *Brazilian Application* explicitly suggested selecting an "effective quantity" of any bisphosphonate as "known to a person skilled in the art," which would include the 5 mg daily and 35 mg weekly dose. Unlike the amount of EDTA, for which it recommended "lower than the known quantities," the *Brazilian Application* did not suggest using less than the known "effective quantity" of the bisphosphonate. Consequently, a person of ordinary skill in the art would read the *Brazilian Application* to disclose as an acceptable choice for a bisphosphonate a weekly dose of 35 mg risedronate sodium.

3. Amount of EDTA Disclosed

It is undisputed that the *Brazilian Application* did not disclose solely 100 mg EDTA for use in a formulation. Rather, it disclosed a ten-fold range of EDTA to be paired with a bisphosphonate based on relative molarity. (Tr. 1A.128:18-24). Dr. Yates opined that the reference taught a person of skill in the art using risedronate to choose between 20 mg and 175 mg disodium EDTA.[8] (Tr. 1A.128:18-24). The claimed amount, 100 mg disodium EDTA, is within the *Brazilian Application's* disclosed preferred range for disodium EDTA.

"[I]f the prior art . . . discloses only a range of values, and the new claim recites an overlapping but different range, we have said that the prior-art reference must describe the

[8] Dr. Yates calculated this range based on the *Brazilian Application's* preferred upper limit for EDTA, that it is "preferable but not exclusively preferable for the daily intake of chelating agent, particularly EDTA, not to exceed about 175 mg"; and its preferred lower limit, that the agent should be "greater than 10% mol/mol [as compared to the bisphosphonate], particularly higher than 50% mol/mol." (DTX 205, at 6). He testified that, for a 35 mg risedronate dose, the preferred lower limit was about 20 mg EDTA. (Tr. 1A.128:18-24). This calculation was not disputed.

claimed range with sufficient specificity to anticipate the limitation of the claim—a broad prior-art disclosure that encompasses a narrower claimed range is sometimes not enough for anticipation." *In re Haase*, 542 F. App'x 962, 965-66 (Fed. Cir. 2013) (internal quotation marks and alterations omitted). Particularly where there is "considerable difference between the claimed . . . range and the range in the prior art," there is no anticipation. But a prior art range anticipates a claimed value if "a trial . . . reveal[s] a minimal difference between the [prior art] range . . . and the [claimed value], or that one of ordinary skill would interpret [the prior art range] as clearly disclosing [the claimed value] as an acceptable choice within that range . . . ." *OSRAM Sylvania, Inc. v. Am. Induction Tech.*, 701 F.3d 698, 706 (Fed. Cir. 2012). Evidence that the claimed value is not "critical" or that "the claimed method [does not] work[] differently at different points within the prior art range" indicates that a person of ordinary skill would have envisioned that the claimed value was an acceptable choice within the prior art. *See ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed. Cir. 2012) (finding prior art variable range of "150 ppm or less" anticipated claimed value of 50 ppm where there was no "evidence that different portions of the broad range would work differently [and] no allegation of criticality or any evidence demonstrating any difference across the range.").

It is uncontested that, for the bisphosphonate-EDTA formulation to work effectively, the amount of EDTA must be within a certain range: too low a dose of EDTA is insufficient to block calcium from capturing the active ingredient in the fed state, resulting in negligible absorption; too much EDTA will unduly spread the tight junctions in the fasted state, resulting in too much absorption and other undesirable effects. The question is whether the patentee's selection of a 100 mg EDTA dose from the *Brazilian Application's* disclosed range of 20 to 175 mg EDTA was critical to the invention's effectiveness. Formulation scientist Dr. Yates testified about

literature that taught that substantially all of the calcium in a calcium-rich meal would be competitively chelated by 75 to 150 mg EDTA in the small intestine, (Tr. 1B.60:21-61:4; Tr. 1B.62:14-17; *see also* Tr. 4B.24:16-23). Both Dr. Yates and Dr. John Dillberger—a former director of toxicology at several pharmaceutical companies—opined that far more than 175 mg EDTA would be required to increase absorption via altering the tight junctions in the fasted state. (Tr. 2A.49:3-12; Tr. 4B.89:18-90:13). Consequently, these experts' reasoning supports an inference that, at the very least, between 75 and 175 mg of disodium EDTA will work effectively.

On the other hand, the patentee Burgio testified that the invention required more precision than simply choosing a dose from the prior art range. He opined that success required balancing interdependent variables such that a formulation would not work unless "the doses of both bisphosphonate and the chelator . . . [were] titrated just properly." (Tr. 4A.72:11-14). He claimed that the particular dose of EDTA must vary with: the amount of the bisphosphonate; the type of bisphosphonate; and the location of release.

The weight of the evidence at trial, however, established otherwise; to wit, that the proportion of bisphosphonate to EDTA does not affect absorption because the two ingredients work independently of each other and are not interdependent. Defendant's formulation scientist Dr. Yates, Plaintiffs' toxicologist Dr. Joseph Rodricks—a former FDA Deputy Associate Commissioner—and Defendant's toxicologist Dr. Dillberger all agreed that an increase in the bisphosphonate dose does not require a corresponding increase or decrease in EDTA. (*See* Tr. 2B.41:8-20 ("THE COURT: So the amount of EDTA is not necessarily dependent in any way or connected to the amount of risedronate . . . it works independently? DR. DILLBERGER:

Independent. DR. RODRICKS: Independent. THE COURT: And I see both sides nodding yes to that.")).

The challenged patents confirm this reasoning. The specification asserts that a formulation will be pharmaceutically effective if: (1) a "weekly oral dosage form contains from about 10 to about 50 mg risedronate," (DTX 2,'459 patent, col. 7, ll. 21-23); (2) "[w]hen the chelating agent is disodium EDTA, the preferred range is from about 55 mg to about 500 mg, preferably from about 75 mg to about 250 mg per unit dose," (DTX 2,'460 patent, col. 9, ll. 37-41); and (3) it is delivered to the "lower gastrointestinal tract."[9] The patents encompass a number of "examples [that] illustrate the formulations . . . of the present invention," (DTX 2, '459 patent, col. 19, ll. 18-19), which include embodiments with double the amount of risedronate as EDTA, (DTX 2, at Example II, '459 patent col. 20, ll. 35-65 (150 mg risedronate sodium and 75 mg disodium EDTA)); far less risedronate than EDTA, (*id*., at Example IV, col. 22, ll. 60-65 (5 mg risedronate sodium and 75 mg disodium EDTA)); and levels of EDTA that vary independently of risedronate, (*id.*, at Example VIII, col. 27, ll. 55-65 (35 mg risedronate sodium and 150 mg disodium EDTA)). Despite the fact that the ratio of EDTA to bisphosphonate varies greatly, all embodiments are stated in the specification as exhibiting "pharmaceutically effective absorption."

Nor did the evidence at trial indicate that a particular level of EDTA was necessary for a particular type of bisphosphonate. Again, every testifying toxicologist agreed that combining bisphosphonates and chelating agents was "not like a recipe between the two. Because they're

[9] The '460 patent states a similar preference for between 15 and 55 mg risedronate, col. 6, ll. 22-25, for between 75 and 250 mg disodium EDTA, col. 8, ll. 14-17, and with release in the "small intestine."

not interacting with each other." (Tr. 2B.39:1-41:25). Even Plaintiffs' formulation scientist, Dr. Davis, knew of no evidence that bisphosphonates and EDTA were interdependent. (Tr. 4A.45:7-47:2). The record evidence is clear that EDTA does not interact with the bisphosphonate at the relevant doses. Its role is separate: to block calcium ions in food from capturing the active ingredient. (Tr. 2B.39:1-40:25).

Moreover, the '459 and '460 patents encompass pharmaceutically effective formulations containing a range of 75 mg to 250 mg disodium EDTA, but every claimed formulation requires "risedronate sodium" and not any other bisphosphonate. Thus, the patents assert that the disclosed range of 75 mg to 250 mg EDTA will work effectively with risedronate sodium. It does not indicate that any particular level of EDTA is critical for each type of bisphosphonate.

Similarly, the '460 patent asserts that EDTA between 75 mg and 250 mg will produce "pharmaceutically effective absorption." Every claim of that patent requires release in the "small intestine." Thus, a range of EDTA is intended to be effective in the small intestine, rather than any particular level of EDTA.

The evidence at trial, including the expert testimony and the patents' specification, revealed that a wide range of EDTA between 75 and 175 mg will allow the formulation to work as claimed. The formulation does not require specifically calculating the level of EDTA based on the type of bisphosphonate, amount of bisphosphonate, or location of release within the small intestine. Nor was evidence introduced showing that levels lower than 75 mg EDTA would be ineffective.[10] In sum, the evidence showed that the claimed amount of 100 mg was not critical

[10] Although some significantly lower doses were tested by Teva and did not achieve "pharmaceutically effective absorption," the record is silent as to the reason these formulations did not meet the limitation.

compared to the prior art's disclosure of between 20 and 175 mg EDTA. The clear and convincing evidence at trial "reveal[ed] a minimal difference between the [prior art] range . . . and the [claimed value]." *OSRAM*, 701 F.3d at 706. "[O]ne of ordinary skill would interpret [prior art range] as clearly disclosing [the claimed value] as an acceptable choice within that range . . . ." *Id.*

4. Whether a List of Ingredients Anticipates a Combination

The *Brazilian Application* disclosed the combination of one of approximately fourteen bisphosphonates (or their salts), with one of about four chelating agents (or their salts), and one of about six delayed-release mechanisms. Included in the *Brazilian Application's* disclosure were the claimed ingredients, including "risedronate . . . and the pharmaceutically acceptable salts and hydrates thereof"; used in combination with a subset of chelating agents, including "EDTA . . . in monosodium or disodium form"; and a delayed release mechanism, including "copolymers of methyl methacrylate – methacrylic acid."

When prior art discloses a list of acceptable ingredients combined with another list of acceptable ingredients for a particular purpose, "[t]he question for purposes of anticipation is therefore whether the number of categories and components in [the prior art] was so large that the combination . . . would not be immediately apparent to one of ordinary skill in the art." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1362 (Fed. Cir. 2012). If the amount of combinations of explicitly named ingredients is a "defined and limited class" and the amounts of the ingredients are within the prior art range, the result will be anticipated. *Id.* at 1361-62; *see also Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1377 (Fed. Cir. 2005)

("[S]pecific disclosure, even in a list, makes this case different from cases involving disclosure of a broad genus without reference to the potentially anticipating species.").

The prior art *Brazilian Application* disclosed a specific and limited number of bisphosphonates by name combined with a specific and limited number of chelating agents and delayed release mechanisms. The particular ingredients and amounts claimed by Plaintiffs were identified as acceptable within the prior art's disclosed categories and ranges. The number of possible combinations in the *Brazilian Application* was not "so large that the combination . . . would not be immediately apparent to one of ordinary skill in the art." Nor was evidence adduced that other combinations disclosed would not have been successful for the claimed purpose.

The *Brazilian Application* disclosed the claimed elements in the same combination, for substantially the same function: an active ingredient to prevent osteoporosis; a chelating agent to chelate calcium ions in the small intestine, and a delayed release mechanism to bypass the stomach. Thus, it does not require combining different disclosures or random selection from unrelated elements in the prior art, rather it "combine[s] [the elements] in the same way as recited in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008).

5. Whether "Pharmaceutically Effective Absorption" is Disclosed

The *Brazilian Application* did not use the term "pharmaceutically effective absorption." Distinguishing the prior art to overcome the Patent Office's initial rejection of the patents, the patentee stated that "pharmaceutically effective absorption" requires EDTA be used only to "address the food effect" via chelation, not to increase intestinal permeability because increased permeability would "result in vastly different bisphosphonate absorption and therefore exposure

depending on whether the patient is in the fasted state . . . or fed state." (PTX 3, at 1151). Thus, the definition of "pharmaceutically effective absorption" requires: (1) choosing an amount of EDTA sufficient to "significantly bind the metal ions and minerals in food" after a meal; (2) but which is "low enough not to significantly alter absorption" by increasing intestinal permeability; (3) with the result that "absorption is similar with or without food . . . [F]ed exposure within about 50% of fasting exposure is expected to be 'pharmaceutically effective absorption.'"

A. "Significantly Bind the Metal Ions in Food"

The concept of using sufficient EDTA to bind to the metal ions in food is found within the *Brazilian Application.* It instructed that delivering the formulation of bisphosphonate and chelating agent to the small intestine "eliminate[s] the interaction of [bisphosphonate] with the contents of the stomach," including the calcium and magnesium ions found in food that bind to bisphosphonate and prohibit the drug from entering the bloodstream. (DTX 205, at 3). The *Brazilian Application* proposed a solution to reduce the interaction of bisphosphonate with calcium and magnesium ions: using a chelating agent to "capture[] the bivalent ions in preference to the bisphosphonate, permitting the bisphosphonate to remain free for absorption by the body." (*Id.* at 4). Both parties' experts agreed that a person of ordinary skill in the art would have understood that the chelation mechanism disclosed in the *Brazilian Application* was intended to significantly bind metal ions from food in the small intestine so that the bisphosphonate remains free to be absorbed. (Tr. 1A.129:3-17 (Dr. Yates); Tr. 1A.133:9-11; Tr. 4B.87:22-25 (Plaintiffs' formulation scientist Dr. Davis stating that "the first part of [the *Brazilian Application*] is to avoid the interaction of the bisphosphonate with calcium and magnesium. And that would be something say in -- well, in the fed state.")). Although the *Brazilian Application* did not explicitly discuss the food effect, the clear purpose of the chelation

mechanism is to neutralize the metal ions in food that result in decreased absorption of bisphosphonate in the fed state. (Tr. 4B.86:4-25).

B. "Low Enough not to Significantly Alter Absorption"

The *Brazilian Application* did not teach this limitation, rather it suggests using EDTA to "increase permeability of the intestinal mucosa." Although the reference intended to alter absorption, some evidence at trial indicated that the *Brazilian Application's* preferred upper limit for disodium EDTA of 175 mg was, in fact, insufficient to alter intestinal permeability, and that the disclosed range was inherently low enough not to "significantly alter absorption."

EDTA alters absorption of bisphosphonate when there is sufficient unchelated EDTA to bind to the ions in the tight junctions, widening the pathways between cells. This does not occur when there is sufficient dietary calcium, as in the fed state. (Tr. 2B.68:25-69:3; Tr. 2B.63:18-22). Even in the fasted state, there is a calcium buffer which protects the cell walls from unchelated EDTA. (Tr. 2A.59:13-19). But where the amount of disodium EDTA exceeds both dietary calcium and the cellular calcium buffer, EDTA will harmfully alter intestinal permeability. Dr. Yates and Dr. Dillberger both opined that far more than 175 mg of disodium EDTA on an empty stomach would be required before there would be a substantial increase in intestinal permeability or increase in absorption. (Tr. 2A.49:3-12; Tr. 4B.89:18-90:13). Although Dr. Rodricks contested whether a person of ordinary skill would have known so at the time, he did not dispute that 175 mg would be insufficient to modify the tight junctions. Thus, all of the record evidence indicates that amounts of disodium EDTA less than 175 mg do not substantially alter absorption by increasing intestinal permeability.

C. "Similar Absorption"

As stated above, a skilled artisan using a formulation containing 35 mg risedronate and between 75 and 175 mg EDTA would not significantly alter absorption but would significantly bind to the metal ions in food. However, it is undisputed that even the claimed amount of 35 mg risedronate and 100 mg EDTA does not always produce "similar absorption" in the fed and fasted state. After the patents were filed, Plaintiffs discovered that they could achieve "similar absorption" using the claimed formulation in the small intestine, but not in the ascending colon. (PTX 352, at s3). Although some of the disclosed embodiments in the *Brazilian Application may* result in similar absorption in the fed and fasted state, there is insufficient evidence to clearly and convincingly find that any embodiment would *necessarily* produce the claimed element. *See Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268-69 (Fed. Cir. 1991). Thus, while it is a close question, the evidence does not reach the clear and convincing level that one practicing any disclosed embodiment of the *Brazilian Application* would inherently produce the claimed element of "pharmaceutically effective absorption." If the burden of persuasion were different, the outcome might well be different. Here, the *Brazilian Application* did not anticipate the asserted claims. *See Allergan*, 754 F.3d at 960-61.

b. Obviousness[11]

"A patent may not issue '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

[11] Although 35 U.S.C. § 103 was modified by the Leahy-Smith America Invents Act (AIA), Pub. L. No. 112-29, § 6 (2011), the Court applies the pre-AIA statute because the patentee filed its application before the effective date of the amendments. *Q.I. Press Controls, B.V. v. Lee*, 752 F.3d 1371, 1377 n.3 (Fed. Cir. 2014).

the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1068 (Fed. Cir. 2012) (quoting 35 U.S.C. § 103(a)).

Obviousness is a question of law based on underlying factual findings regarding: the scope and content of the prior art; the differences between the claims and the prior art; the level of ordinary skill in the art; and objective considerations of nonobviousness. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (citing *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17 (1966)); *see also Cyclobenzaprine*, 676 F.3d at 1068. Obviousness is analyzed from the viewpoint of a person of ordinary skill in the art, who has "ordinary creativity." *See KSR*, 550 U.S. at 421. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at 418. "A court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 417.

1. Level of Ordinary Skill in the Art as of April 2005[12]

The parties agree that the level of ordinary skill in the art is an individual with a Ph.D. or M.D. in pharmaceutical sciences with substantial practical experience developing and testing pharmaceutical formulations in humans, and who has access to other professionals in the formulation sciences, gastroenterology, and the treatment of osteoporosis.[13] (Tr. 1A.122:7-14). The Court agrees with and adopts this level of skill in the art and the concomitant description of a skilled artisan.

2. Scope And Content of the Prior Art

A. Skilled Artisan's Knowledge of the Bisphosphonate Food Effect Problem

It was well-known by the April 2005 effective filing date of the challenged patents that bisphosphonate absorption decreased when taken with a meal because of its interaction with the calcium in food. (Tr. 1A.109:8-16; PTX 90, at 1743, Table 2 (1994 publication on oral absorption of bisphosphonates showing about a five-fold decrease when administered with food as compared to the fasted state); PTX 135, at 178 (2000 publication stating that "oral absorption of [bisphosphonates] is diminished when the drug is given with meals, especially in the presence of calcium and iron."); DTX 185, at 17). For this reason, patients taking any member of the class of bisphosphonates were instructed to fast overnight before administration, and to wait 30 minutes after administration before eating breakfast. (Tr. 1A.112:21-113:2; Joint Stipulation of Facts ¶¶ 48, 50 (FOSAMAX® 2000); ¶¶ 57, 61 (BONIVA® 2003)).

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[12] The parties have stipulated that the effective filing date of the invention is no earlier than April 15, 2005. (Joint Stipulation of Fact ¶ 81).

[13] The parties agreed that there were no "meaningful" differences between their positions on this issue. (Tr. 1A.61:14-62:9).

Some patients found these dosing instructions inconvenient. (Tr. 1A.113:3-15). Other patients did not follow the dosing instructions and, as a result, did not receive an effective dose. (PTX 118, at 491, Figure 2 (1998 comparative research study finding that over 50% of patients administered bisphosphonate incorrectly and in a manner that reduced absorption)). As one inventor testified, "[i]t was well understood . . . in the industry . . . that indeed this was a problem." (Tr. 4A.70:24-25).

A skilled artisan[14] would have understood the cause of the food effect. Well before 2005, it was known that "cations [like calcium] will interfere with the absorption of ACTONEL." (DTX 185, at 17; DTX 208, at 295 (1995 publication stating that "the bioavailability of bisphosphonates is low, presumably a result of their highly charged structure and their tendency to form insoluble salts with polyvalent cations."); DTX 167, at 280, 283). As Warner Chilcott acknowledged, by 2004, "the current science told us" that the food effect was caused by "divalent cations in food, such as calcium, . . . bind[ing] to risedronate in the GI tract making the complex unavailable for absorption." (Tr. 2B.121:2-10 (Warner's Fed. R. Civ. P. 30(b)(6) designee Dr. Gary Galletta); Tr. 4A.69:20-23). It was also known that reducing calcium-bisphosphonate interaction was necessary to solve the problem. (Tr. 1B.124:22-25 (patentee Richard Dansereau stating he was interested in calcium concentrations because "it was a known fact that chemically risedronate does chelate calcium"); DTX 185, at 16 (predecessor drug ACTONEL® label prohibiting patients taking calcium supplements with their dose)).[15] Moreover,

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[14] The Court uses the term "skilled artisan" as interchangeable with "a person of ordinary skill in the art as of April 2005."

[15] Before trial, Warner argued that the causes of "the food effect are complex and, as of 2005, were poorly understood." But at trial Plaintiffs did not present evidence to support this

the magnitude of the problem was understood: the 1992 *Mahé Reference* measured the particular concentration of calcium within different locations in the gastrointestinal tract after a meal. (DTX 133, at 413 (comparing ions of calcium and magnesium in the ileum versus the jejunum after a meal)).[16]

The Court finds that, at the time the challenged patents were filed, a person of ordinary skill in the art would have recognized: (1) the problem—that bisphosphonates were ineffective when taken with food; (2) the cause and magnitude of the problem—that a particular amount of calcium from a meal captured the active ingredient risedronate and prevented it from being absorbed; and (3) the goal—to defeat the food effect by reducing the formation of calcium-risedronate complexes.

The skilled artisan would have known of one solution—the use of a calcium chelator to block calcium ions from forming calcium-bisphosphonate complexes—because that solution had been well explored in the literature.

B. EDTA's Use as a Chelator of Calcium

Long before 2005, many studies had shown how EDTA operated to increase bisphosphonate absorption. The 1991 Janner study (DTX 167, at 283) tested an oral formulation

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argument. Nor did they preserve the factual issue in their final proposed findings of facts. "This court need not reach issues [Plaintiffs] did not raise properly in proposed post-trial findings." *In re Omeprazole Patent Litig*., 483 F.3d 1364, 1375 (Fed. Cir. 2007).

[16] Risedronate is absorbed over a 30 minute period. The bisphosphonate literature taught that risedronate could be released anywhere along the lower gastrointestinal tract without statistically significant differences in the rate or extent of absorption. (DTX 273, at 230). Based on *Mahé,* a skilled artisan would expect the distal ileum to be exposed to about 0.3 millimolar concentration of calcium over a 30 minute period. (Tr. 1B.29:14-30:3).

containing a bisphosphonate and "a calcium chelator, EDTA," in rats and found increased intestinal absorption of the bisphosphonate. He noted that "bisphosphonates form polynuclear complexes with calcium [which] are precipitated as calcium-bisphosphonates" and posited that EDTA, as a chelation agent, would "reduce the formation of insoluble calcium-bisphosphonate and polynuclear complexes and hence, contribute to a better absorption of the bisphosphonates." (*Id.* at 280, 283). He also noted an alternative mechanism whereby EDTA bound to the calcium in the intercellular channels of the rat intestine, "directly enhancing intestinal permeability." *Id.* The 1994 Lin study expanded on the concept of the chelation property: "EDTA, by sequestration of calcium (or other metals), prevented the formation of a metal-alendronate complex which is poorly absorbed from the gastrointestinal tract." (DTX 168, at 1745). He also explained the permeability enhancing property: "chelating agents might alter the integrity of the intercellular tight junctions at high doses resulting in an increase in absorption" because "the tight junctions are formed by specific proteins and divalent cations, such as Ca^{2+} and Mg^{2+}." (*Id.*).

AstraZeneca's International Patent Publication WO 00/61111 connected EDTA's chelating properties as a possible solution to the "diminished [absorption] when [bisphosphonate is] given with meals, especially in the presence of calcium." (DTX 206, at col. 1, ll. 23-24). It suggested using chelating agents like EDTA, as well as various other agents, in combination with bisphosphonates to achieve "enhanced and/or less variable absorption [of] bisphosphonates," (*id.* at col. 4, ll. 4-7), and "allow the patient to take the medicament more conveniently, e.g. together with food intake," (*id.* at col. 2, ll. 15-18).

EDTA's use as a chelator of calcium was not limited to bisphosphonates. The 1978 *Poiger Reference* used disodium EDTA as a chelating agent to eliminate the food effect in humans observed with a drug called tetracycline. Like bisphosphonate, absorption of tetracycline

is greatly reduced in the presence of "the dietary content of metal ions" like calcium because "[t]etracycline forms chelates with calcium . . . which impairs permeation of the drug." (DTX 162, at 131). Using a formulation with an amount of EDTA that is "equivalent as a molar ratio to the amount of calcium" expected in the stomach, Poiger found that absorption of the active ingredient after ingesting calcium-rich milk was "almost equivalent" to absorption when the subjects had fasted. (DTX 162, at 129-30; *see also* Tr. 1B.11:2-12). Using this equimolar ratio, "the bioavailability of the drug remained constant irrespective of the diet." (DTX 162, at 131, Table 1 (experiment nos. 2 & 4 showing that tetracycline administered with EDTA showed fed absorption better than 50% of fasting absorption)). Moreover, disodium EDTA administered in the fasted state did not "significantly change absorption of the drug." (*Id.* at 129). In other words, even with 250 mg disodium EDTA, there was no enhanced absorption in the fasted state. (*Id.*, Table 1 (experiment nos. 1 & 2 showing no statistically significant increase in absorption of tetracycline administered in the fasted state without EDTA compared to tetracycline administered in the fasted state with EDTA)). This "obviate[d] special directions about diet during therapeutic use of [tetracycline]." A skilled artisan would recognize that Poiger disclosed a formula—an equimolar ratio of EDTA to expected calcium, (Tr. 1B.30:13-14)—for a formulation that would significantly bind to metal ions in food without significantly altering absorption, leading to similar bioavailability irrespective of diet.[17] (Tr. 1B.12:6-13:14).

[17] In their post-trial proposed fact findings, Plaintiffs assert that, unlike bisphosphonate, "Tetracycline absorption in the fasted state . . . is not enhanced by EDTA," therefore, "a POSA would not find [bisphosphonates] and tetracycline comparable in terms of absorption." (Pls.' Proposed Findings ¶ 57). Plaintiffs cite no testimony, expert or otherwise, to support this proposed finding of fact. Here, the strong weight of the factual evidence is to the contrary: "the mechanism by which bisphosphonate absorption is reduced with calcium is actually the same mechanism by which tetracycline absorption is reduced, which is the formation of insoluble calcium complexes." (Tr. 1B.13:11-14).

The Court also notes and restates its findings on the *Brazilian Application* above regarding the well-known use of EDTA as a calcium chelator to enhance bisphosphonate absorption. *See* § IV(a), *supra*. Additionally, both parties' experts agreed that a person of ordinary skill in the art would have understood that the calcium chelation mechanism disclosed in the *Brazilian Application* was intended to significantly bind metal ions from food in the small intestine after a meal so that the bisphosphonate remains free to be absorbed. (Tr. 1A.129:3-17 (Dr. Yates); Tr. 1A.133:9-11; Tr. 4B.87:22-25 (Davis)).

3. Objective Considerations

A. Teaching Away

Toxicology literature in the early 1990s indicated that the amount of EDTA required to be useful in the stomach was too high for safe administration to human patients. Before the *Brazilian Application* was published, the literature taught that the minimum effective oral dose of EDTA that enhanced absorption of bisphosphonate as a chelator of calcium was about 700 mg, scaled to human weight. (Tr. 1B.21:19-22). The literature, including Ezra, Lin, and Janner, also concluded that these high oral doses of EDTA were not clinically useful. (DTX 167, at 283; PTX 90, at 1745; PTX 135, at 185). However, in 2003 the *Brazilian Application* published and distinguished Lin and Janner's delivery to the *stomach* using "extremely high [doses] (more than 100 mg/kg of body weight)," from its proposed delivery "only into the *small intestine*" using "chelating agents in quantities lower than the known quantities." (DTX at 3, 6). This prior art proposed a limit of 175 mg EDTA. The *Brazilian Application* explained that delivery in the small intestine "eliminate[s] the interaction of these [chelating] agents with the contents of the stomach," where an abundance of calcium ions would otherwise "consume" the chelating agent

before it reaches the small intestine. (*Id.* at 3). "[R]elease of the chelating agents only into the small intestine permits a reduction in the dosage administered for the desired result, which is increased absorption of the bisphosphonates." (*Id.*).

Dr. Yates confirmed that a skilled artisan in 2005 would have known that delivery in the small intestine, rather than the stomach, would require far less chelating agent because the stomach has a higher concentration of calcium after a meal than the small intestine. (Tr. 1A.131:18-132:2). No expert witness testified to the contrary. Dr. Yates concluded that a skilled artisan would have known that 75 to 150 mg EDTA delivered to the small intestine would be sufficient to effectively chelate dietary calcium. (Tr. 1B.60:21-61:4).

"[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR Int'l, Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. A reference does not teach away, however, if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013). "The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). "Where the prior art contains apparently conflicting teachings . . . each reference must be considered for its power to suggest solutions to an artisan of ordinary skill considering the degree to which one reference might accurately discredit another. . . [T]he

prior art must be considered *as a whole* for what it teaches. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165-66 (Fed. Cir. 2006) (internal alterations and quotation marks omitted).

Compared to the broad conclusions drawn by Lin and Janner based on delivery of very high doses of EDTA to the stomach, the *Brazilian Application* made specific distinctions between safe and unsafe levels of EDTA delivered to the small intestine.[18] A person of ordinary skill in the art in 2005 would have understood that significantly lower doses than those used by Janner would be useful for the claimed purpose. Placed in context, Lin and Janner teach only that EDTA "alter[s] the integrity of the intercellular tight junctions at high doses," (DTX 168, at 1743 (Lin)), and that doses higher than 700 mg EDTA are "unsuitable," (PTX 82, at 283 (Janner)). But the literature does not discourage the use of the far lower doses known to be effective in the small intestine. Nor does it suggest that 100 mg EDTA will be unproductive if released in a location other than the stomach, like the small intestine. Reading the literature as a whole, Lin and Janner do not teach away from the claimed amount of EDTA. *See Hoffmann-La Roche Inc. v. Apotex Inc*., 748 F.3d 1326, 1331 (Fed. Cir. 2014); *see Medichem*, 437 F.3d at 1165-66 (finding that, where some references broadly suggested claimed compound would not work and others suggested it would work in low concentrations, prior art did not teach away).

Additionally, some of the literature noted the danger of using any amount of EDTA for certain purposes, while other references indicated that EDTA was generally safe. Attempting to

[18] The Ezra publication, a literature review, quotes Janner and Lin for the proposition that EDTA's use in pharmaceuticals is "impossible." (PTX 135, at 185). It did not conduct additional research or explore administration in the small intestine rather than stomach. Taken together, these publications advise against using EDTA at doses above 700 mg in the stomach, but do not discredit—or even note—the more recent research on the delivery of lower doses of EDTA to the small intestine.

reconcile these seemingly contrary conclusions, the Court heard expert testimony from two toxicologists: Dr. Rodricks for the Plaintiffs and Dr. Dillberger for the Defendant. Both experts agreed that none of this research directly tested the safety of the claimed dose delivered in the claimed manner. Although they differed in their ultimate conclusion about whether a skilled artisan would have believed that the claimed amount of EDTA was safe, when the Court posed its own questions to them, they were largely in agreement about what the literature taught in 2005. They agreed that there would be little concern if a dose of EDTA were administered with sufficient food. (Tr. 2B.68:25-69:3). Even without dietary calcium—as in the fasted state—both experts agreed that a skilled artisan would have known that there would always be calcium ions in the digestive tract. (Tr. 2B.69:4-10; Tr. 2B.57:16-58:7; Tr. 2B.78:17-19).

Dr. Dillberger testified that this calcium buffer—in the intestinal cells, the fluid surrounding the cells, and the blood supply to those cells—protects cellular tight junctions from EDTA; it must be depleted before there would be a concern that the tight junctions would be damaged. (Tr. 2A.59:13-19). He opined that a person of ordinary skill as of 2005 would know that these reserves of cations were available for EDTA to chelate, (Tr. 2A.49:3-12), and that merely fasting for a day would not clear the intestinal tract of this reserve of calcium, (Tr. 2B.57:22-58:7). Dr. Rodricks did not dispute that residual calcium in the cells would act as a buffer to protect the tight junctions. (Tr. 2B.69:4-10). Both experts agreed that extremely high doses like 700 mg, 7,000 mg and 35,000 mg, scaled to human weight, depleted the calcium buffer and caused separation of the tight junctions, (Tr. 1B.21:19-22), and that very low doses like 5 mg were recognized as so safe in pharmaceutical products that they were listed in the

Inactive Ingredient Guide, indicating that FDA required no additional safety research for such levels.[19] (Tr. 2A.64:17-22; Tr. 2B.12:5-9; Tr. 2B.14:22-15:11).

The factual dispute between the toxicologists was narrowed to whether a skilled artisan would have been deterred from delivering 100 mg disodium EDTA to the small intestine because of a concern that it would deplete the calcium buffer in the fasted state and harm the small intestines. The available literature was only tangentially related to this inquiry.

Before turning to this inquiry, the Court addresses the proffered references. The World Health Organization's Joint Expert Committee on Food Additives reported that 2.5 mg/kg per day of disodium EDTA was safe, (DTX 95, at 35); and disodium EDTA had achieved Generally Regarded as Safe ("GRAS") status, (DTX 134; Tr. 1B.129:17-20; DTX 87, at 3-4). But this safe daily-intake level assumed that EDTA was administered with food containing calcium. There was little safety concern when EDTA is administered with sufficient food or calcium. (Tr. 2B.68:25-69:3 (Dr. Rodricks)). Thus, the food additive literature does not bear in a persuasive way on the issue of potential concern.

Similarly, certain literature claimed that EDTA had "damaging effects on mucosal integrity," (PTX 74, at 427-28 (Van Hoogdalem)); was impractical because it has "been shown to be harmful to the epithelial cells of the intestine," (PTX 80, at 2 (Muranishi)); and that "EDTA in any kind of clinical study on humans would be inappropriate." (PTX 135, at 1252 (Zakelj)).

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[19] It is irrelevant that the claimed amount of 100 mg EDTA was twenty times the previous commercial embodiment—in the Inactive Ingredient Guide—of 5 mg, because the literature had already indicated that up to 175 mg EDTA could be used safely. "Nothing in the statute or our case law requires [defendant] to prove obviousness by starting with a prior art commercial embodiment and then providing motivation to alter that commercial embodiment." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737 (Fed. Cir. 2013).

However, a person of ordinary skill in the art would understand that EDTA can be used in at least two ways: as a chelator of calcium and as a permeability enhancer. These publications only discussed EDTA's use in high doses as an "Absorption Enhancer" to spread the tight junctions. Van Hoogdalem tested rat tissue for intestinal separation after cleansing the tissue of calcium. (Tr. 2A.56:22-57:25). Muranishi addressed only "permeation enhancers" that "promote the intestinal absorption of impermeable drugs." (PTX 80, at 2). Zakelj sought to test methods of "increas[ing] paracellular permeability . . . [by] depletion of extracellular [calcium]." (PTX 175, at 1252). He stated that the lowest dose found to cause statistically significant separation of the tight junctions was 2 millimoles. (*Id.* at 1251). The claimed amount of 100 mg is equivalent to 0.3 millimoles. (Tr. 1B.30:14-17). In fact, Plaintiffs even cited Zakelj to FDA as evidence that its formulation containing 0.3 millimoles was safe, arguing that "EDTA is known to enhance paracellular transport at concentrations much greater than two millimolar in vitro."[20] (DTX 97, at 306, 311; Tr. 4A.129:3-10).

In sum, these references did not opine on, or even discuss, the claimed use of EDTA as a chelator of stray calcium. Rather, they came to the uncontroversial conclusion that using high doses of EDTA to spread the paracellular tight junctions is undesirable. Reading these references so broadly as to suggest that all uses of EDTA are "damaging" or "inappropriate" is inconsistent with the weight of the literature. (*See, e.g.*, Tr. 2A.64:17-22). No expert witness adopted such a broad reading. Placed in context, these references suggest to the skilled artisan that EDTA is not

[20] In their post-trial proposed findings, Plaintiffs claim that the Zakelj reference "noted increased permeability and harm to cellular viability at low concentrations." (Pls.' Proposed Findings ¶ 44). Plaintiffs point to no expert testimony, nor any trial testimony, to support this assertion and it is unfounded. Zakelj said nothing of the kind.

suitable when used at doses so large that they spread paracellular tight junctions and enhance permeability. They do not suggest to the skilled artisan that EDTA in much lower doses used as a chelator of calcium will be unproductive.

Regarding the relevant concern for a person of ordinary skill in the art in 2005—whether 100 mg disodium EDTA delivered to the small intestine would be expected to deplete the calcium buffer in the fasted state, thus harming the small intestine—Plaintiffs' toxicologist Dr. Rodricks opined that the literature did not provide sufficient information to enable a person of ordinary skill to estimate the amount of residual calcium in any one location or loop of the intestines and ensure safety. (Tr. 2B.69:4-10; Tr. 2B.56:23-25). Consequently, he believed that "there would be a significant unknown about the effects" that would caution a person of skill against using EDTA. (*Id.*).

By contrast, Defendant's toxicologist Dr. Dillberger opined that, although the state of the art did not indicate exactly what dose of EDTA would have depleted calcium reserves, a skilled artisan would have known that it would have been at "much higher doses" than 100 mg. (Tr. 2A.16:10-17; Tr. 2B.56:17-19). He responded to Dr. Rodricks's concern—that a skilled artisan would be unable to estimate the concentration of residual calcium in any particular loop—by noting that a dose of EDTA would travel through the intestines at several inches per minute, such that no particular loop in the small intestine would be exposed to high levels of EDTA for a significant amount of time. (Tr. 2A.59:23-60:8). He also noted animal studies and human studies, like the *Poiger Reference*, which showed no harm to the intestines using doses of EDTA far higher than 100 mg. (Tr. 2A.17:17-25; Tr. 2A.51:6-15).

The prior art *Poiger Reference* documented the result of administering 250 mg of disodium EDTA[21] to human patients in the fasted state—the only state where there was a safety concern that EDTA would damage the tight junctions. In a patient who has fasted, the EDTA would have reached the intestines substantially in the unchelated state, like the claimed dose. (Tr. 2A.30:16-19 ("[M]ore than 95 percent of [disodium EDTA] swallowed gets down in the intestinal tract . . . .")). Yet when patients took 250 mg disodium EDTA in the fasted state, Poiger recorded neither intestinal harm nor a statistically significant increase in active ingredient absorption over administration without EDTA. This would suggest to a skilled artisan that 250 mg EDTA in the fasted state would not harmfully widen the tight junctions. It persuasively supports an inference to the skilled artisan that a far lower dose of disodium EDTA—such as the claimed dose—could be administered directly to the small intestine without harm. Accordingly, Dr. Dillberger aptly concluded that a person of ordinary skill in the art would have considered 100 mg disodium EDTA to be safe for human pharmaceutical use and that the literature did not discourage its use. (Tr. 2A.13:24-14:3).

This is also how Plaintiffs understood the literature in 2003 when they began giving EDTA to human subjects to support their new drug application to FDA. Before conducting any clinical safety evaluation on the EDTA-risedronate formulation in the fasted state, one of Plaintiffs' internal toxicologists told an Institutional Review Board—comprised of independent scientists and physicians charged with assessing the safety of early versions of ATELVIA®—that "the [100 mg] amount of EDTA selected . . . is designed to scavage any remaining divalent

[21] Poiger administered 500 mg EDTA samples. Although they were not pure disodium EDTA—they contained equal parts disodium EDTA and tetrasodium EDTA—each had at least 250 mg of unchelated disodium EDTA.

cations in the colon. This amount of EDTA is considered safe." (DTX 10, at Bates No. 487 (Clinical Protocol describing basis for conducting clinical trial in humans)). Based on the literature, Plaintiffs' primary nonclinical bisphosphonate toxicologist could not "recall ever believing that [100 mg EDTA] either was not safe or that we could not demonstrate that it was safe" as a chelator of calcium. (Tr. 2B.107:1-3). In 2003, before any clinical testing, the Institutional Review Board approved the safety of research with 100 mg disodium EDTA in human patients in the fasted state. (Tr. 2B.24:5-22). The informed consent notice to human participants did not identify in its section on "possible disadvantages and risks" that EDTA could cause intestinal damage in the fasted state at 100 mg. (DTX 10, at Bates No. 556). As Plaintiffs' head of regulatory affairs told FDA, the "100 milligram dose used in the risedronate DR tablet[] edetate[22] disodium is not expected to effect the permeability and absorption of risedronate and/or other drugs . . . by altering intestinal permeability." (Tr. 2B.126:14-20). In other words, none of Plaintiffs' toxicologists or regulatory personnel thought that the literature posed safety concerns that discouraged investigation in humans. Nor did the independent Institutional Review Board.[23] A person of ordinary skill in the art, reading the references in context, would have believed that a pharmaceutical composition containing 100 mg EDTA delivered to the small intestine without

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[22] Edetate is another name for EDTA. (Tr. 1B.138:3-4).

[23] Plaintiffs never mentioned to the human participants that very high doses of EDTA cause harmful spreading of the tight junctions as reported in Lin and Janner, nor did they mention the danger of using EDTA as a permeability enhancer as reported in Muranishi and Van Hoogdalem. Rightly so, because these studies were irrelevant. Plaintiffs were not testing permeability enhancement, nor any dose above 700 mg; rather, they were testing EDTA as a chelator at 100 mg.

food was likely safe for its intended use. Every scientist and toxicologist consulted in 2003 agreed.

Based on the publications available in 2005, the credible expert testimony,[24] and the relevant evidence, the literature did not discourage the use of EDTA in the claimed amount nor suggest that EDTA would be unproductive as a chelator of calcium in the small intestine. Accordingly, the literature did not teach away. *See Ricoh Co. v. Quanta Computer Inc.*, 550 F.3d 1325, 1332 (Fed. Cir. 2008) (finding that reference criticizing speed above 5 m/s for one method of reading an optical disk (recrystalization) did not teach away from using speed above 5 m/s for a different, claimed method (laser pulses) of reading an optical disk); *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1355 (Fed. Cir. 2012) (finding prior art that taught away from using conventional non-enteric coated oral dosage forms did not teach away from all non-enteric coated formulations, nor one particular claimed powder formulation); *In re Gartside*, 203 F.3d 1305, 1320 (Fed. Cir. 2000) (finding reference that taught low to moderate temperatures were undesirable for catalytic reactions did not teach away from use of all catalytic systems, nor the claimed system which used high temperatures).

[24] Dr. Dillberger's analysis was highly credible. Dr. Rodricks was not lacking in credibility, but his primary opinion was that there was uncertainty and "unknowns facing a POSA," (Tr. 2A.49:25-50:3), regarding the claimed dose of EDTA. Lack of certainty, without more, does not establish that prior art teaches away. *Warner Chilcott Co., LLC v. Teva Pharm. USA, Inc.*, --- F. App'x ---, No. 2014-1439, 2014 WL 6435042, at *6 (Fed. Cir. Nov. 18, 2014) ("Plaintiffs rely on the testimony of their experts and assert that there was uncertainty regarding the safety and efficacy of a once-monthly regimen, . . . [L]ack of certainty does not preclude a conclusion of obviousness.").

B. Long-felt, Unmet Need

A claimed invention's "satisfaction of a long-felt need" is evidence of nonobviousness. *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009) "[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem." *Tex. Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). "[W]e look to the filing date of the challenged invention to assess the presence of a long-felt and unmet need." *Procter & Gamble Co.*, 566 F.3d at 998.

There was a long-felt need for a drug that "took the compliance problem out of the equation."[25] Before ATELVIA® was released, over half the patients took their medicine incorrectly, and one-third failed to comply with the instruction to wait half an hour after administration before eating breakfast. (PTX 118, at 491, Figure 2 (1998 study of daily-administered alendronate)). The evidence at trial established that taking the predecessor drug ACTONEL® incorrectly would result in a dose that was ineffective because of the food effect. On the other hand, taking ATELVIA® in the fasted state—i.e. taking it incorrectly—nonetheless would result in a dose that is effective at treating osteoporosis, (PTX 188, at 272; Tr. 3A.20:10-12), even if there were additional side effects of upper abdominal pain, (*see* Tr. 3A.20:13-17).

Other products were released before the priority date that also made compliance easier, with fasting administration once weekly and once monthly rather than once daily. (*See* Joint Stipulation of Facts ¶¶ 48 (FOSAMAX® 2000), 55 (ACTONEL® 2002), 59 (BONIVA® 2005)). But the effectiveness of those formulations would not improve for a patient who either refused to fast

[25] Warner stipulated that they are "not arguing that Atelvia can be administered 'with or without food.'" (Final Pretrial Order 18, ¶ 102, Dkt. No. 207). Thus, they do not assert satisfaction of a long-felt need for a bisphosphonate that can be taken regardless of food intake. FDA has approved ATELVIA® to be administered with food only. (Joint Stipulation of Facts ¶ 75).

or could not understand the fasting rule, whether once monthly or once daily. Although ATELVIA® patients must still comply with administration rules regarding co-administered drugs that interfere with absorption, (PTX 409, at 9 (ATELVIA® label); Tr. 3A.61:2-6), it does satisfy a need for a drug that lessens the consequence of failure to comply with the feeding or fasting rules. This satisfaction of a need to take compliance out of the equation for treatment of osteoporosis is entitled to some weight.

C. Unexpected Results

An inference that a patent is not obvious may be supported by "a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). "[T]he applicant's showing of unexpected results must be commensurate in scope with the claimed range." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); *see also In re GPAC Inc*., 57 F.3d 1573, 1580 (Fed. Cir. 1995) ("For objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention.").

ATELVIA® researcher Dr. Michael McClung, who conducted a two-year study on the drug, testified that patients taking either ATELVIA® per label or contra label unexpectedly performed better than ACTONEL® per label in the second year of the study. (DTX 182, at 305; Tr. 3A.31:18-32:3). He relied on data from one bone location (lumbar spine) using one measure of bone density, which showed a statistically significant difference in patient bone density in the

ATELVIA® groups and the ACTONEL® group between year one and year two. (DTX 182, at 302-05). However, other locations (total hip and femoral neck) and other measures of bone density (urine and serum concentration) did not show statistically significant differences between year one and year two. (Tr. 3A.79:2-80:17). McClung opined that the reason for the difference in bone density was that the researchers saw the patients less frequently in year two, and were unable to remind patients of the dosing instructions, resulting in a drop in compliance. He concluded that ATELVIA® performed unexpectedly well compared to ACTONEL® in year two because the consequence of failing to comply with dosing rules for ATELVIA® was not as dire as with ACTONEL®. (Tr. 3A.37:8-10). However, he admitted that "there's no way to prove that. One cannot assess that component of compliance." (Tr. 3A.35:23-24).

This allegedly unexpected result is about essentially the same concept as the evidence of long-felt need to diminish the consequence of noncompliance. It is rendered less weighty because other measures of bone density and other locations of measurement did not show a statistically significant difference between year one and year two. (Tr. 3A.79:2-80:17). And the reason for the improvement in bone density in some samples for patients taking ATELVIA® in year two could also be due to the study's comparison of *daily* ACTONEL® to *weekly* ATELVIA®. No single head-to-head clinical study has been conducted which compared once-weekly ATELVIA® directly with once-weekly ACTONEL®. (Joint Stipulation of Facts ¶ 76). McClung acknowledged the possibility that long-term compliance with dosing rules may be easier if the patient only needs to comply once weekly rather than every day. (Tr. 3A.42:3-43:1; Tr. 3A.46:3-12; DTX 182, at 306). Thus, any improvement in patient bone density in year two may be due to

dosing frequency rather than the claimed invention.[26] "Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). Because these unrelated factors could equally be the reason for the observed result, and because other testing methods and locations diminished the value of the observed result, there is an absence of sufficient evidence of nexus to the patient compliance issue. Accordingly, the Court gives the evidence little weight.

D. Simultaneous Invention: The Takeda Invention

"Independently made, simultaneous inventions, made 'within a comparatively short space of time,' are persuasive evidence that the claimed apparatus 'was the product only of ordinary mechanical or engineering skill.'" *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) (quoting *Concrete Appliances Co. v. Gomery*, 269 U.S. 177, 184 (1925)). "[T]hough not determinative of statutory obviousness, [simultaneous invention is] strong evidence of what constitutes the level of ordinary skill in the art." *Geo. M. Martin Co.*, 618 F.3d at 1305-06. (quoting *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000)). It "is directly tied to the level of knowledge attributable to one of ordinary skill in the art." *Ecolochem*, 227 F.3d at 1379.

In the instant case, there was a real battle by the parties about the invention by a Japanese company called Takeda. Takeda invented a drug with risedronate and disodium EDTA

[26] The Harris study addressed the safety and efficacy of once-daily ACTONEL® compared to once-weekly ACTONEL®. (PTX 166, at 763; Tr. 3A.27:4-9). It did not address the effect on compliance of moving from once-daily to once-weekly administration. (PTX 166, at 758 (All "subjects were instructed to take the study drug once a day."))

that exhibited "pharmaceutically effective absorption." Japanese Patent Application No. 2003-359,539 (DTX 35) was filed on October 20, 2003, several years before the challenged patents. The story of why Takeda did not get its patent is not a pretty picture: Proctor & Gamble used its commercial muscle to pressure Takeda to abandon its patent application to avoid its publication and stop it from becoming prior art to Proctor & Gamble's research into ATELVIA®. The pressure succeeded and the Takeda application never became prior art.

Teva sought to use this saga to show inequitable conduct, and thereby invalidate the patent. This Court, following the caution and law of the Federal Circuit on this issue, did not permit an amendment to the pleadings to proceed on the claim of inequitable conduct on the theory that killing a foreign patent application to prevent it from becoming prior art would have had to be disclosed to the patent examiner. However, this Court ruled that the evidence was admissible for any other proper purpose.

The Takeda invention "pertains to a pharmaceutical composition that is capable of preventing the effect of food or drug materials on absorption of physiologically active non-peptide substances." (*Id.* at 3). Dependent claim 10 covers "an enterically coated pharmaceutical composition internally containing" "physiologically active non-peptide substances [that] are bisphosphonates" and an "absorption promoter [that] is a chelating agent." (*Id.* at 2). It lists "examples of chelating agents" as "organic acids and salt thereof, EDTA and EGTA." (*Id.* at 12). The preferred bisphosphonate is "monosodium risedronate." (*Id.* at 9).

The Takeda application describes the food effect exhibited by compounds like bisphosphonates and tetracyclines, and instructs that chelating agents defeat the food effect by "minimizing absorption variation due to interaction with food." (*Id.* at 10). This invention is characterized by similar absorption of the active ingredient in the fasted and fed states:

absorption of the non-peptide active ingredient "when co-administered with food" is "most preferably, about 60 % or more" of absorption "on an empty stomach." (DTX 35, at 18). Although the actual Takeda product formulation used sodium citrate as a chelator, its patent application encompassed formulations containing EDTA combined with risedronate sodium with the preferred effect of absorption in the fed state that is 60% of absorption in the fasted state.

Both Plaintiffs' and Defendant's formulation scientists agreed that the pharmaceutical composition discussed in the Takeda application exhibited "pharmaceutically acceptable -- effective absorption." (Tr. 4B.75:12-13 (Dr. Davis); Tr. 1B.42:6-10 (Dr. Yates)). Takeda did not have access to any of Plaintiffs' nonpublic research (or that of its predecessor Proctor & Gamble). (Tr. 2B.137:13-18 (Technology Manager Michael Burns); 2B.140:11-141:5; DTX 52).

Plaintiffs knew that Takeda's 2003 patent application disclosed the same invention as that which Proctor & Gamble, and now Warner, intended to patent. When they discovered that Takeda was working on a risedronate product with "pharmaceutically effective absorption," it "threw the organization into a panic." (Tr. 2B.143:13-25 (Burns)). A business decision was made to pressure Takeda (one of Proctor & Gamble's business partners in Japan) to abandon its patent and its research in this area "to preserve Proctor and Gamble's future global interests." (Tr. 2B.141:18-22). Technology Manager Michael Burns stated the clear explanation: "Takeda was already doing work in this area and we had to squash it for patent reasons." (DTX 63).

Why was Proctor & Gamble thrown into a "panic" when they discovered the Takeda application? Why did they need to "squash" the Takeda application? And why was the Takeda patent application abandoned so as not to become prior art? The answer is clear: they knew that Takeda had created the same invention and would achieve priority. This strong evidence of simultaneous invention is "directly tied to the level of knowledge attributable to one of ordinary

skill in the art." *Ecolochem*, 227 F.3d at 1379. A skilled artisan would have known how to conquer the bisphosphonate food effect and achieve "pharmaceutically effective absorption."

E. Skepticism

When "noted experts express[] disbelief in" a claimed invention, such evidence would support an inference of nonobviousness. *United States v. Adams*, 383 U.S. 39, 52 (1966). Two employees at Teva resisted testing the claimed amount of EDTA. (PTX 262, at Bates No. 94478; PTX 260, at Bates No. 94391). However, there is no evidence in the record regarding the employees' scientific credentials, (Tr. 2B.8:7-10; Tr. 2B.14:1-8), and thus no evidence that they were persons of skill in the relevant art. Moreover, no evidence suggested a requisite nexus between employee skepticism and the effectiveness of the claimed invention, as distinguished from concerns regarding the cost of investing in additional research to support an inactive ingredient level above the Inactive Ingredient Guide, as believed necessary to receive FDA approval for its ANDA application. (PTX 260, at Bates No. 94392; Tr. 3B.13:8-19; Tr. 3B.29:13-15). *See Muniauction, Inc. v. Thomson Corp*., 532 F.3d 1318, 1327 (Fed. Cir. 2008). Consequently, there is an absence of evidence that skilled artisans, as defined above, were skeptical the invention would be successful as claimed, and the testimony is therefore accorded little weight. *See Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 711 F .3d 1348, 1368 (Fed. Cir. 2013) (finding relevant the "skepticism of *skilled* artisans") (emphasis added).

Patentee Burgio's testimony that Plaintiffs' development partner Sanofi Aventis stopped funding ATELVIA®—without documentary evidence or witness testimony regarding the reason Sanofi cut funding—lacks sufficient basis to constitute skepticism about the merits of the claim.

The third proffered basis—that FDA required Plaintiffs to conduct additional testing on ATELVIA®—is minimally probative of skepticism regarding whether the invention would work

as claimed.[27] Safety testing is required for every new drug. (Tr. 2B.43:12-15; Tr. 2B.61:16-25). Requests for additional testing "reflect[] attention to the FDA's normal duties ensuring the safety and efficacy of new drugs by requiring actual data to corroborate statements in a new drug application." *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

F. Failure of Others and Copying

"The purpose of evidence of failure of others is to show indirectly the presence of a significant defect in the prior art, while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1081-83 (Fed. Cir. 2012) (internal quotation marks omitted).

Before ATELVIA® was approved and launched, Teva had produced a formulation containing 35 mg risedronate sodium and 100 mg disodium EDTA. (Tr. 3B.34:11-15). The Regulatory Affairs division chose not to test this formulation in humans because it believed that FDA would require additional research to include a level of EDTA above the Inactive Ingredient Guide in its ANDA formulation. (Tr. 3B.44:24-45:4). Teva then produced batches with 40 mg EDTA and 5 mg EDTA—for which safety research was already available, (PTX 253, at Bates No. 77147)—and tested each in humans, neither of which achieved "pharmaceutically effective absorption." (PTX 258). After ATELVIA® launched, Teva tested its 100 mg EDTA batch in

[27] So, too, the correspondence from after the priority date indicating that FDA was satisfied with EDTA's safety is of minimal relevance. (*See, e.g.*, PTX 347, at Bates No. 1777908).

humans. (Tr. 3B.44:12-17). These circumstances do not reflect difficulties understanding and implementing the technology. *See DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1371-72 (Fed. Cir. 2006). Teva first produced a formulation with 100 mg EDTA, which it chose not to administer because of constraints in funding additional research believed necessary to get FDA approval. (*See* Tr. 3B.38:9-14). This was not confusion or "failure" in the application of the science. There is an absence of evidence of nexus to the claimed invention; accordingly, the evidence is due little weight.

4. Differences Between The Claims and the Prior Art

Although the elements are discussed individually in order to maintain an organized explanation of its reasoning, the Court considers the claims of the '459 and '460 patents and the prior art as a whole and without hindsight in reaching its conclusions. And, although discussed in separate sections, the Court considers the objective considerations of nonobviousness, the level of ordinary skill in the art, the scope of the prior art, and the differences between the claims and the prior art in a holistic manner. While the content and scope of the prior art have been noted in certain instances above in this opinion, the analysis of the prior art and the claimed subject matter is discussed in detail below. Citations to the record will not be repeated when the facts are discussed below.

A. The Selection of "35 mg risedronate sodium"

For the same reasons that the Court found above in its anticipation opinion, the *Brazilian Application* disclosed 35 mg risedronate sodium as an acceptable choice for the bisphosphonate dose. Thus, the claimed dose represents the selection of one of a limited subclass of named ingredients disclosed by the prior art as acceptable for a formulation. *See Merck & Co. v.*

Biocraft Labs., Inc., 874 F.2d 804, 807 (Fed. Cir. 1989) ("That the [prior art] discloses a multitude of [1,200] effective combinations does not render any particular formulation less obvious."); *Purdue Pharma Products L.P. v. Par Pharm., Inc.*, 377 F. App'x 978, 982 (Fed. Cir. 2010) ("Purdue's main argument is that a person of skill in the art would not have selected tramadol out of the myriad other possible active ingredients . . . [But the prior art] lists tramadol as one of fourteen different opioid analgesics to use in a controlled-release formulation that provide effective blood levels for twenty-four hours. As such, [the prior art] itself renders the selection of tramadol obvious regardless whether or not the patent lists tramadol as a preferred embodiment."). There was no evidence adduced that choosing risedronate, as opposed to another bisphosphonate disclosed by the *Brazilian Application*, was necessary for the invention to work effectively. The challenged patents describe other effective formulations containing ibandronate (DTX 2, '459 patent, col. 30 (Example XI describing an embodiment of the invention containing 100 mg ibandronate)) and alendronate (DTX 2, '459 patent, col. 29 (Example X describing an embodiment of the invention containing 70 mg alendronate sodium and 100 mg disodium EDTA). In claiming 35 mg risedronate, Plaintiffs chose the most common and convenient version of one of fourteen disclosed acceptable bisphosphonates.

B. The Selection of "100 mg disodium EDTA"

The *Brazilian Application* did not disclose a formulation with precisely 100 mg disodium EDTA. Rather, as the Court found above, it disclosed a range between 20 and 175 mg EDTA when EDTA is paired with risedronate based on relative molar weights. The claimed amount of 100 mg EDTA is within the prior art disclosed range.

It is evidence of obviousness where "a range [is] disclosed in the prior art, and the claimed invention falls within that range."[28] *Tyco Healthcare Grp. LP v. Mut. Pharm. Co., Inc*., 642 F.3d 1370, 1372-73 (Fed. Cir. 2011) (internal citations omitted). "Where the difference between the claimed invention and the prior art is some range or other variable within the claims, the patentee must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results." *Iron Grip Barbell Co., Inc. v. USA Sports, Inc*., 392 F.3d 1317, 1322 (Fed. Cir. 2004) (internal alterations omitted). Merely "optimizing" a variable is obvious unless the result is "unexpectedly good." *Peterson*, 315 F.3d at 1330; *see also* MPEP § 2144.05 ("Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical."). The inference that a prior art range for a particular variable disclosed the claimed value to a skilled artisan, "can be rebutted if it can be shown that the prior art teaches away from the claimed range, or the claimed range produces new and unexpected results." *Ricoh Co. v. Quanta Computer Inc*., 550 F.3d 1325, 1331 (Fed. Cir. 2008) (quoting *Ormco Corp. v. Align Tech., Inc*., 463 F.3d 1299, 1311 (Fed. Cir. 2006)); *Tyco Healthcare Grp. LP v. Mut. Pharm. Co.*, 762 F.3d 1338, 1346 (Fed. Cir. 2014). But where selection of the claimed amount within the prior art range results in "only a difference in degree from the prior art results," the claimed amount is not critical. *Galderma Labs. v. Tolmar*, 737 F.3d 737-39 (Fed. Cir. 2013).

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[28] Of course, the Court considers all evidence relevant to obviousness or nonobviousness collectively before making any determination. The burden of proof never leaves the party challenging the validity of the patent and that "burden is always the same, clear and convincing evidence." *Sciele Pharma Inc. v. Lupin Ltd*., 684 F.3d 1253, 1260 (Fed. Cir. 2012); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig*., 676 F.3d 1063, 1076-77 (Fed. Cir. 2012) (finding no "formal burden-shifting framework").

As the Court found above in its anticipation opinion, there is clear and convincing evidence that the selection of the claimed amount of 100 mg EDTA from the prior art range of 20 to 175 mg EDTA is not critical. The expert testimony demonstrated that, due to the cellular calcium buffer, no precise ratio of EDTA to other ingredients is required to achieve its purpose of blocking calcium after a meal without harming the intestinal tight junctions. The challenged patents confirm that a range of EDTA is effective regardless of the dose of risedronate it is paired with, the type of bisphosphonate, or the location of release within the small intestine. Nor did the prior art teach away or suggest that EDTA was unsuitable for its claimed use. Although there were safety concerns using EDTA at far higher doses than necessary to be effective in the small intestine (and when using EDTA as a permeability enhancer) the weight of authority, such as the *Poiger Reference*, established that EDTA was not dangerous when used as a chelator at doses below 250 mg. This implicit knowledge in the art is confirmed by Takeda's simultaneous invention, which used EDTA as a suitable chelator of calcium to defeat the bisphosphonate food effect. There was an absence of evidence that the selection of 100 mg EDTA produced any unexpected result. No evidence established that the selection of 100 mg EDTA was better than the prior art range by more than a matter of degree.

The absence of food effect studies documenting the relative effectiveness of other doses of EDTA does not diminish the persuasiveness of the expert testimony. Even the inventor Burgio did not deny that a wide range of EDTA would work effectively depending on the location of release within the lower gastrointestinal tract. (Tr. 4A.114:25-115:4). Burgio himself declared under oath to the PTO that his formulation produced "pharmaceutically effective absorption," even though he lacked a food effect study directly comparing absorption between the fed and

fasted states. (Tr. 4B.36:5-39:4). He relied, as the Court does, on persuasive inferences derived from established scientific theory.

C. "pharmaceutically effective absorption"

The limitation is defined as: "an amount of a chelating compound high enough to significantly bind the metal ions and minerals in food but low enough not to significantly alter absorption of the bisphosphonate as compared to absorption in the fasted state. That is, absorption is similar with or without food. Given the high variability of bisphosphonate absorption, fed exposure within about 50% of fasting exposure is expected to be 'pharmaceutically effective absorption.'" As the Court found in its anticipation opinion, the *Brazilian Application* did not clearly and convincingly use this term or contain all elements within its definition.

When the prior art must be modified to reach the claimed result "a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006). "Such a suggestion may come expressly from the references themselves. It may come from knowledge of those skilled in the art that certain references, or disclosures in the references, are known to be of special interest or importance in the particular field. It may also come from the nature of a problem to be solved, leading inventors to look to references relating to possible solutions to that problem." *Pro-Mold and Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir.

1996) (internal citations omitted); *see Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362 (Fed. Cir. 2007).

To show a reasonable expectation of success, a skilled artisan must be motivated to do more than "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *Medichem*, 437 F.3d at 1165. "Similarly, prior art fails to provide the requisite 'reasonable expectation' of success where it teaches merely to pursue a 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." *Id.* (internal citations and quotation marks omitted). "What does matter is whether the prior art gives direction as to what parameters are critical and which of many possible choices may be successful." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014). But "[o]bviousness does not require absolute predictability of success. . . . [A]ll that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

i. Motivation to Modify

The *Brazilian Application* used EDTA to: "a) reduc[e] the formation/solubilization of insoluble complexes of bivalent [calcium and magnesium] ions with bisphosphonates, and b) increase [] permeability of the intestinal mucosa." It does not require the claimed element that "absorption is similar with or without food." The evidence at trial revealed reasons to modify the *Brazilian Application* to exclude enhancing intestinal permeability and to achieve "absorption [that] is similar with or without food."

By 2005, it was understood that altering the integrity of the tight junctions was undesirable because of the risk of bacterial infection of the more permeable intestinal membrane. The weight of the literature conclusively found that using EDTA at the very high doses necessary to enhance intestinal permeability in humans was disfavored. Thus, a person of ordinary skill in the art would have been motivated to avoid "significantly alter[ing] absorption of the bisphosphonate as compared to absorption in the fasted state."

Not only did the bisphosphonate literature as a whole discourage enhancing intestinal permeability, it also strongly favored eliminating the bisphosphonate food effect. All bisphosphonates, including ACTONEL®, FOSAMAX®, and BONIVA®, instructed patients to administer the dose without food because the cations found in food formed insoluble complexes with bisphosphonate. But some patients did not want to fast before taking their dose and other patients had trouble remembering the dosing instructions. This well-known and well-understood food effect problem would have motivated skilled artisans to seek a formulation wherein "absorption is similar with or without food."

This was not merely an abstract motivation to eliminate the food effect for bisphosphonates generally, but a motivation to use chelating agents in combination with bisphosphonates to achieve similar absorption in the fed and fasted states. AstraZeneca's *WO '111* patent suggested that pairing chelating agents with bisphosphonates would help achieve "less variation in absorption" of a bisphosphonate. The reference stated that formulations of a bisphosphonate combined with a chelating agent such as EDTA would allow for "oral administration [that] may be given during fasted or fed conditions" to "allow the patient to take

the medicament more conveniently, e.g. together with food intake."[29] (DTX 206, at 2). In other words, it explicitly suggested using a chelating agent to achieve similar absorption of bisphosphonates regardless of food intake.

So, too, the 1978 *Poiger Reference* would have motivated a person of skill in the art to modify the *Brazilian Application* to include "absorption [that] is similar with or without food." Poiger solved the tetracycline food effect in humans using EDTA solely to significantly chelate metal ions in food, without increasing absorption of the active ingredient. The result was similar absorption in the fed and fasted states, significantly better than the fed:fasted ratio of 50% assumed to be pharmaceutically effective. Tetracycline—like the active ingredient in ATELVIA®—is captured by calcium molecules when a patient has eaten, leading to negligible amounts of absorption. Poiger showed that tetracycline administered with the chelating agent disodium EDTA blocked the formation of tetracycline-calcium complexes, just as the *Brazilian Application*, Lin, and Janner suggested with bisphosphonate-calcium complexes.

A person of ordinary skill in the art, who would have understood the cause of the bisphosphonate food effect and the desire to solve it, would have been motivated by the *Poiger Reference's* success achieving "almost equivalent" absorption "irrespective of the diet" using EDTA as a chelator of calcium. Although Poiger was not within the bisphosphonate literature, it was squarely within the literature relied upon by the *Brazilian Application*. Both parties' experts agreed that a person of ordinary skill in the art would have understood that the first section of the *Brazilian Application* was about using EDTA to block the calcium in food from capturing the

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[29] Plaintiffs argues that *WO '111* would have led a person of ordinary skill in the art away from using EDTA because it cited another reference, which in turn discussed the dangers of EDTA as a permeability enhancer. This argument is not persuasive. *WO '111* explicitly suggests use of the calcium chelator EDTA.

bisphosphonate. (Tr. 1A.129:3-17 (Dr. Yates); Tr. 1A.133:9-11; Tr. 4B.87:22-25 (Davis)). A skilled artisan would know that the *Poiger Reference* and the *Brazilian Application* involve the same subject matter: using EDTA to reduce the interference caused by the calcium in food on active ingredient absorption. The *Poiger Reference* was directly pertinent to the problem the inventor was attempting to solve. (Tr. 2A.17:11-16; Tr. 1B.13:11-14 ("[T]he mechanism by which bisphosphonate absorption is reduced with calcium is actually the same mechanism by which tetracycline absorption is reduced, which is the formation of insoluble calcium complexes.")).

The motivation to use EDTA as a chelator of calcium to achieve "absorption [that] is similar with or without food" is confirmed by Takeda's simultaneous research on a dose of bisphosphonate and chelating agent intended to minimize variation in bisphosphonate absorption between the fed and fasted state.

All of these known factors would have motivated a person of ordinary skill in the art to (1) seek similar absorption of bisphosphonate regardless of food intake; (2) use EDTA solely as a chelator to bind calcium from food; and (3) avoid increasing permeability by excluding very high doses that would spread the tight junctions. The totality of the evidence establishes a motivation to modify the *Brazilian Application* to include the limitation "pharmaceutically effective absorption."

ii. Reasonable Expectation of Success in Achieving Similar Absorption

An "expectation of success need only be reasonable, not absolute[,] . . . [enough to] convince a reasonable finder of fact that the skilled artisan would have had that reasonable expectation of success that [the modification] would work for its intended purpose." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Thus, the question is whether a person

skilled in the art would have had a reasonable expectation of achieving similar absorption of a bisphosphonate regardless of a patient's food intake by using EDTA as a chelator to block dietary calcium.

As the Court discussed above, a skilled artisan would have expected a relatively low dosage range of EDTA to block calcium after a meal without harmfully altering the tight junctions. As the totality of the literature indicated, and as Dr. Yates testified, a skilled artisan would have recognized that comparatively low doses of EDTA, like 75 mg, were sufficient to chelate calcium in the small intestine after a meal. A skilled artisan would also have expected that substantially more than 175 mg EDTA would be needed to alter the tight junctions. For example, the *Poiger Reference* disclosed a formula for calculating how much EDTA would be needed to block dietary calcium so that it would not interfere with absorption of an active ingredient: a one-to-one ratio of EDTA to expected calcium. Defendant's formulation scientist Dr. Yates testified that those of skill in the art routinely calculate the expected concentration of ingredients at different locations, a practice called stoichiometry. (Tr. 1B.30:18-25). To calculate the amount of EDTA necessary to bind to calcium on a one-to-one basis, a skilled artisan would need access to information regarding: (1) the amount of expected calcium in the small intestine; and (2) the amount of time the active ingredient was exposed to calcium before full absorption. This information was available to one of ordinary skill in the art in the *Mahé Reference* and the *Mitchell Reference*.[30] Poiger performed similar calculations to determine the amount of EDTA

[30] For example, the *Mahé Reference* taught that the amount of calcium is least variable and most predictable in the terminal ileum, where the exposure to calcium is a concentration of 0.1 millimolar every ten minutes after ingestion of a high-calcium drink. The *Mitchell Reference* taught that risedronate absorption took about 30 minutes in the lower gastrointestinal tract and that it could be effectively absorbed in the terminal ileum. Accordingly, risedronate released in

necessary to bind to the calcium in milk he released into the stomach. (DTX 162, at 130). Based on this literature, a person of ordinary skill would have expected a range of between 75 and 175 mg to chelate calcium without affecting tight-junction permeability.

Poiger's experimental design was not perfect for studying the difference between absorption in the fed and fasted states using EDTA: he compared EDTA delivered via capsule with EDTA in solution; he adjusted the pH of dissolved EDTA to avoid side effects of disodium EDTA; he compared different amounts of EDTA in the fed state and in the fasted state; he tested EDTA with milk rather than with food; and there is limited explanation of contrary studies. But Poiger showed that EDTA could competitively inhibit calcium from food via chelation, allowing an active ingredient—otherwise captured by calcium—to reach the bloodstream. Without EDTA, a patient in Poiger's study who fasted received more than four times the dose of the active ingredient compared to when the patient had eaten. But with EDTA, absorption of the dose in the

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the terminal ileum would encounter a concentration of about 0.3 millimolar of calcium. Applying Poiger's one-to-one ratio of EDTA to expected calcium indicates that 0.3 millimolar concentration of EDTA will significantly bind to calcium in the terminal ileum of the small intestine after a high-calcium meal. Dr. Yates testified that this amount of EDTA, 0.3 millimolar, equates to slightly more than 100 mg. (Tr. 1B.30:12-17). This amount is below that disclosed as harmful to the tight junctions by a factor of five or greater. (DTX 167, at 283 ("Ultrastructural alterations of intestinal epithelium are known to occur at EDTA concentrations of 25 [millimoles]."); *id.* at 281 ("EDTA was effective at doses of 10 mg/kg and higher."); PTX 175, at 1251 ("2 [millimoles] EDTA and higher concentrations were sufficient to provoke a statistically significant . . . increase of [intestinal] permeability," whereas lesser doses are insufficient)).

Plaintiffs argue that a skilled artisan would not use Mahé's calculation of the amount of calcium in the intestine. These arguments include that Mahé purportedly underestimated the amount of calcium based on earlier studies and also that Mahé overestimated the amount of calcium by using more calcium than in the typical breakfast. This effort to diminish Mahé as providing a reasonable expectation of success is not persuasive. A skilled artisan would have used Mahé and other references to estimate the amount of calcium. (*See* Tr. 3B.35:19-23).

fasted state was better than a fed:fasted ratio of 50%. And even with 250 mg disodium EDTA on a fasted stomach, there was no statistically significant increase in absorption in the fed state—i.e. no spreading of tight junctions.

This is powerful evidence for a skilled artisan, who could foresee success in using EDTA as a competitive calcium chelator to defeat the interference caused by dietary calcium and thus achieve similar absorption without causing intestinal harm. The fact that the dosage and form of EDTA changed between trials may have cautioned that success at the observed magnitude was not guaranteed. But Poiger's teaching regarding the use of EDTA to achieve "almost equivalent" absorption that was "constant irrespective of the diet" provided guidance about the critical parameters sufficient to give a skilled artisan a reasonable expectation of success of achieving absorption that is similar in the fed and fasted states. "Obviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success." *In re Droge*, 695 F.3d 1334, 1337-38 (Fed. Cir. 2012). A person of ordinary skill in the art would have had a reasonable expectation of success that a dose of EDTA could reliably chelate the expected amount of calcium in the small intestine after a meal without separating the tight junctions and substantially increasing absorption. The expected result of such a formulation would be "absorption [that] is similar with or without food."

The expectation of success is not diminished by the patentee's purportedly lengthy and arduous road to achieving similar absorption regardless of food.[31] For many of the hurdles the

[31] Plaintiffs argued that the purportedly confounding effect of "solid calcium" would have prevented a reasonable expectation of success. (*See* Pls.' Pretrial Proposed Findings of Fact ¶¶ 94-96, 100-101, 136-138). However, they submitted no proposed findings of facts on "solid calcium" to the Court in their final proposed findings of fact and conclusions of law and have thereby abandoned this argument. *See In re Omeprazole Patent Litig*., 483 F.3d 1364, 1375 (Fed. Cir. 2007).

inventor described during his testimony, the prior art *Brazilian Application* had already posited a solution. For instance, Burgio described the challenge of finding doses of EDTA effective for chelating calcium that were also low enough to be safe, and their realization that the solution was to use an enteric coating to bypass the stomach. Compared to Ezra and Janner's teaching regarding the high doses of EDTA necessary for release in the stomach, Burgio "thought there was a better way to think about doing it. . . [to] go with a lower dose and push the actual delivery of both the bisphosphonate and the chelator to the lower GI tract," "where everybody had taught it couldn't be done." (Tr. 4A.80:11-14; Tr. 4A.116:24-117:2). However, the *Brazilian Application* had come to exactly the same conclusion years before: "This invention solves the problem encountered in the current state of the art[,] presenting an innovative technique in which the chelating agent becomes available only in the small intestine, which is the principal site of bisphosphonate absorption. The purpose of targeting the release of chelating agents into the small intestine is to eliminate the interaction of these agents with the contents of the stomach." (DTX 205, at 3). And Takeda came to the same conclusion nearly simultaneously, if not before. (DTX 35, at 7).

Regarding the choice to use less EDTA, Burgio testified that "based on the Janner and Ezra information, I would have expected that you needed much more EDTA as you go further up the GI tract into the stomach and jejunum and duodenum to get [] 'pharmaceutically effective absorption.'" (Tr. 4A.93:16-20). Here, too, the prior art *Brazilian Application* recommended the solution: lower the dose from the "extremely high (more than 100 mg/kg of body weight)" doses in Janner to less than 175 mg EDTA. The reason for this is that the "contents of the stomach also contain calcium and magnesium ions, the interaction of the contents with the chelating agents compromises the potentiating action of absorption, since a large part of the chelating agents is

'consumed' before they reach the small intestine. . . [R]elease of chelating agents only into the small intestine permits a reduction in the dosage administered for the desired result, which is increased absorption of the bisphosphonates." [32] (*Id.*).

Burgio also described how the inventors expected "pharmaceutically effective absorption" to occur in the ascending colon—where they expected calcium levels to be lowest—but that testing failed to achieve "pharmaceutically effective absorption" in the ascending colon. Release of the formulation in the ascending colon resulted in a ratio of fed to fasted absorption of 34%, whereas release in the small intestine produced a ratio of fed to fasted absorption of 73%. (PTX 352, at s3). Thus, absorption of risedronate when released in the ascending colon, although far from negligible, was "subpar" and was not "pharmaceutically effective absorption." (Pls.' Proposed Findings ¶ 8).

A skilled artisan would have reasonably expected success in choosing the prime location to release the risedronate. First, the *Mahé Reference* suggested that the level of calcium after a meal was most predictable and stable in the small intestine, particularly the ileum, and not the ascending colon. And the *Brazilian Application* suggested delivery of the chelating agent "only into the small intestine." (DTX 205, at 3). While the inventors chose to begin with the ascending

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[32] Plaintiffs argue that the *Brazilian Application* does not contain human testing data indicating that lower doses would be successful. But a full clinical study need not be conducted to show an expectation of success. *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success."). Rather, the test is whether there is clear and convincing evidence that a person of ordinary skill in the art would have a reasonable expectation of success in using the treatment at issue. *Procter & Gamble Co.*, 566 F.3d at 994; *see also Duramed Pharm., Inc. v. Watson Labs., Inc.*, 413 F. App'x 289, 294 (Fed. Cir. 2011) ("A reference, however, is prior art for all that it discloses, and there is no requirement that a teaching in the prior art be scientifically tested, or even guarantee success, before providing a reason to combine. Rather, it is sufficient that one of ordinary skill in the art would perceive from the prior art a reasonable likelihood of success.").

colon, *Mahé* and the *Brazilian Application* provided a reasonable expectation of success by release in the small intestine. *See Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1334 (Fed. Cir. 2014) ("The evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success with the 150 mg monthly dose, even if the level of success may have turned out to be somewhat greater than would have been expected."). Based on the *Poiger Reference*, the *Mahé Reference*, and the expert testimony regarding a skilled artisan's knowledge of the mechanics of EDTA, there is clear and convincing evidence that a skilled artisan would have reasonably expected success using an amount of EDTA sufficient to bind calcium, without significantly affecting the permeability of the cellular membrane, such that absorption would be similar in the fed and fasted state.

V. CONCLUSION

The Court now considers, as a whole, the knowledge of one of ordinary skill in the art, the scope and content of the prior art compared to the claimed invention, and the objective considerations of nonobviousness. The parties agree that the *Brazilian Application* contains "all of the elements of the asserted claim[s]" except "pharmaceutically effective absorption." The *Brazilian Application* disclosed an enterically coated formulation containing a combination of a bisphosphonate and a chelating agent. It named the claimed "methacrylic acid" copolymer as an acceptable enteric coating, as one that releases immediately "only in the small intestine." It explicitly named the claimed ingredient risedronate sodium as an acceptable bisphosphonate and explicitly named the claimed ingredient disodium EDTA as an acceptable chelating agent. It disclosed use of an "effective quantity" of risedronate, which a person of ordinary skill would know included the most commonly prescribed and convenient dose: the claimed amount of 35 mg. And it disclosed a preferred range of disodium EDTA equivalent to between 20 and 175 mg,

which includes the claimed amount of 100 mg. The selection of 100 mg was not critical; there is no special benefit to choosing 100 mg rather than another amount within the prior art range. Instead, a wide range of levels of EDTA would be effective in blocking the calcium in food from capturing the active ingredient without increasing permeability. The literature did not teach away from using disodium EDTA, nor did it suggest using this amount of EDTA would be dangerous. It taught only that very high doses of EDTA were harmful and that using such very high doses of EDTA for the specific purpose of spreading the tight junctions was undesirable.

The *Brazilian Application* discussed two separate mechanisms to increase bisphosphonate absorption: (1) chelation, wherein EDTA binds to calcium molecules in food after a patient has eaten and blocks the calcium molecules from capturing the bisphosphonate; and (2) permeability enhancement, wherein large doses of EDTA spread the tight junctions, increasing overall intestinal absorption. As in the *Brazilian Application*, the challenged patents require "an amount of a chelating compound high enough to significantly bind the metal ions and minerals in food." However, the challenged patents also require "an amount of a chelating compound . . . low enough not to significantly alter absorption of the bisphosphonate as compared to absorption in the fasted state." Thus, the challenged patents chose one of the two methods set forth in the *Brazilian Application*.

Considering the level of skill in the art and the scope and content of the prior art, there is clear and convincing evidence that a person of ordinary skill in 2005 would have been motivated to avoid the high levels of EDTA necessary to enhance permeability because the literature taught that such "extremely high" doses were undesirable. At the same time, a skilled artisan would have known that EDTA's chelation mechanism would eliminate the bisphosphonate food effect. *WO '111* explicitly suggested that chelating agents produced less variable bisphosphonate

absorption after a meal. Lin and Janner discussed how EDTA would prevent bisphosphonate-calcium complexes—long known as the cause of the food effect—from forming. The *Brazilian Application*, too, instructed delivery "only into the small intestine" to "eliminate[] the interaction of [bisphosphonate] with the contents of the stomach," wherein the chelating agent "capture[s] the bivalent ions in preference to the bisphosphonate, permitting the bisphosphonate to remain free for absorption by the body." The experts on both sides agreed this disclosure informed a person of skill in the art that EDTA would block calcium after a meal, thus overcoming the food effect. And Takeda's simultaneous invention confirms the knowledge in the art that chelating agents like EDTA are effective at chelating calcium after a meal and achieving a similar ratio of fed:fasted bisphosphonate absorption.

The *Poiger Reference*, among others, was a strong predictor of success that EDTA could capture dietary calcium after a meal and allow an active ingredient to be absorbed without enhancing intestinal permeability. Based on Poiger's formula and the other prior art references, a skilled artisan could have predicted success using the same dosing range as claimed. And the *Mahé Reference* and the *Brazilian Application* suggested the small intestine as the likely successful delivery location. Based on these and the other references detailed above, there is clear and convincing evidence that a skilled artisan would have been motivated to modify the prior art to contain the claimed limitations and would have reasonably expected success in so doing.

The Court balances this evidence of a known, desirable use for EDTA against the evidence that ATELVIA® met a need for an osteoporosis drug that lessened the consequence of failure to fast before administration. In light of all the circumstances, some satisfaction of a need is not sufficient to outweigh the extensive evidence in the prior art showing that coadministration

of EDTA and a bisphosphonate would have the benefit of reducing the food effect and the evidence of Takeda's simultaneous invention of a formulation that would meet the need to a similar extent. *See Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 883 (Fed. Cir. 1998). Weighing all relevant objective considerations, Plaintiffs' asserted objective considerations "do not, in the circumstances of this case, tip the scales of patentability." *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 36 (1966).

The asserted claims of the '459 and '460 represent the most common version of a bisphosphonate the prior art disclosed as acceptable combined with the most well-known and widely used chelating agent, as recommended by the prior art. That combination was used for a purpose that skilled artisans understood EDTA addressed: chelating calcium after a meal. "When there is . . . market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 421 (2007). The expected result of this identified solution was similar absorption in the fed and fasted states. That Takeda did just that—pursuing known options with identified ingredients—is why Proctor & Gamble was thrown "into a panic" and "squash[ed] [the application] for patent reasons."

The claims are thus a combination of known elements, arranged in a known way, to produce expected results. The patentee selected this combination of known ingredients, within the ranges disclosed as acceptable in the prior art, and patented the resulting blood concentration. And the specific doses of ingredients chosen from the prior art range was similarly unremarkable. Such a combination "is likely the product not of innovation but of ordinary skill and common sense." *KSR*, 550 U.S. at 420; *see Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (finding obvious the patentee's selection of amount of omeprazole

from a range and class of active ingredients in the prior art combined with a particular amount of sodium bicarbonate from a range and class of buffering agents disclosed in same prior art, and claiming the resulting expected serum concentration of omeprazole). Applying the clear and convincing standard of proof, claim 16 of the ’459 patent and claim 20 of the ’460 patent, considered as a whole, are obvious.

An appropriate Order will issue.

/s/ Faith S. Hochberg
Hon. Faith S. Hochberg, U.S.D.J.