UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK
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UNIGENE LABORATORIES, INC. and
UPSHER-SMITH LABORATORIES, INC.,

Plaintiffs,

- against -

APOTEX INC. and
APOTEX CORP.,

Defendants.
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06 CV. 5571 (RPP)

OPINION AND ORDER

ROBERT P. PATTERSON, JR., U.S.D.J.

In this patent infringement action brought by Plaintiffs Unigene Laboratories, Inc. and Upsher-Smith Laboratories, Inc. (collectively, "Unigene" or "Plaintiffs") against Defendants Apotex, Inc. and Apotex Corp. (collectively, "Apotex" or "Defendants"), Defendants, in their motion for summary judgment filed on April 17, 2009, assert that Claim 19 of legally issued U.S. Patent No. 6,440,392 ("the '392 patent"), which was reissued on June 30, 2009 under US RE40,812 ("the '812 reissued patent"), is invalid on the grounds of obviousness pursuant to 35 U.S.C. Section 103.[1] Plaintiffs, in their cross-motion filed on April 23, 2009 for summary judgment, counter that Claim 19 is not obvious as a matter of law.[2] Oral argument on the summary judgment motions was held on July 9,

[1] Defendants' memorandum of law in support of their motion for summary judgment, filed on April 17, 2009, is referred to as "Def. Memo." Plaintiffs' reply memorandum of law in opposition to Defendants' motion for summary judgment, filed on May 11, 2009, is referred to as "Pl. Opp. Memo." Defendants' response to Pl. Opp. Memo, filed on May 29, 2009, is referred to as "Def. Reply." Defendants' Rule 56.1 statement of material facts not in dispute filed in support of their motion is referred to as "Def. 56.1." Plaintiffs' response to Def. 56.1 is referred to as "Pl. Rep. 56.1."

[2] Plaintiffs' memorandum of law in support of their motion for summary judgment, filed on April 23, 2009, is referred to as "Pl. Memo." Defendants' reply memorandum of law in opposition to Plaintiffs' motion for

2009 ("07/09/2009 Tr."). For the following reasons, Plaintiffs' motion for summary judgment is granted, and Defendants' motion for summary judgment is denied. Accordingly, Plaintiffs' related motion to exclude the two late filed expert reports submitted by Defendants on April 23, 2009, which was argued before the Court on July 16, 2009 ("07/16/2009 Tr."), is dismissed as moot.

1. Factual Overview[3]

On August 27, 2002, the United States Patent and Trade Office ("PTO") issued the '392 patent, entitled "Nasal Calcitonin Formulations," based on a patent application filed on February 4, 2000. (Amended Complaint filed on July 2, 2009 ("Compl."), ¶12; Pl. 56.1 ¶6.) Plaintiff Unigene owns the '392 patent by assignment from Dr. William Stern, the sole inventor. (Compl. ¶13; Compl. Ex. A [Reissued Patent 06/30/2009]; Pl. 56.1 ¶8.)[4] The calcitonin formulation is currently sold as a nasal spray under the trademark Fortical ("Fortical"). (Compl. ¶15; Pl. 56.1 ¶2.) Fortical is manufactured by Plaintiff Unigene and provided to Plaintiff Upsher-Smith, who packages, distributes, and markets the product throughout the United States. (Compl. ¶16.) Fortical is a pharmaceutical product for administration to patients for the treatment of postmenopausal osteoporosis. (Compl. ¶17; Pl. 56.1 ¶3.)

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summary judgment, filed on May 18, 2009, is referred to as "Def. Opp. Memo." Plaintiffs' response to Def. Opp. Memo, filed on June 5, 2009, is referred to as "Pl. Reply." Plaintiffs' Rule 56.1 statement of material facts not in dispute filed in support of their motion is referred to as "Pl. 56.1." Defendants' response to Pl. 56.1 is referred to as "Def. Rep. 56.1."

[3] This Court has issued two prior opinions in this case, with which the parties are presumed to be familiar. On February 4, 2008, this Court determined that Defendants were not entitled to vitiate Plaintiffs' attorney client privilege under the crime-fraud exception. See Unigene v. Apotex, 2008 U.S. Dist. LEXIS 8215 (S.D.N.Y. Feb 4, 2008). On August 28, 2008, the Court issued an opinion interpreting the term "about 20mM of citric acid" as it is used in the '392 patent. See Unigene v. Apotex, 2008 U.S. Dist. LEXIS 66005 (S.D.N.Y. Aug 28, 2008).

[4] Due to the volume of expert reports and other exhibits cited to by the parties in support of their motions, the Court will cite to the parties' 56.1 statements, rather than to the provided exhibits.

On February 5, 2004, Plaintiff Unigene filed a reissue application seeking to correct an error in claim 1 of the '392 patent. (Pl. 56.1 ¶14.) On July 24, 2006, Plaintiffs Unigene and Upsher-Smith filed a complaint in the Southern District of New York, alleging infringement of the '392 patent by Defendants Apotex Inc. and Apotex Corp. pursuant to 35 U.S.C. § 271(e)(2)(A). (Compl. ¶22; Pl. 56.1 ¶¶1, 4.) Apotex Inc. is a large Canadian pharmaceutical company that manufactures generic pharmaceuticals and distributes them in the United States. (Compl. ¶¶21, 25.) Its subsidiary, Apotex Corp., assists Apotex Inc. in obtaining FDA approval for the pharmaceuticals Apotex Inc. plans to manufacture and distribute. (Id.)

Plaintiffs claim against Defendants is based on Defendants' submission of an Abbreviated New Drug Application ("ANDA No. 078200") on June 1, 2006, which sought FDA approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of a generic version of Fortical before the expiration of the '392 patent. (Compl. ¶¶21, 25; Pl. 56.1 ¶¶1, 4.) The same day, Defendants sent a Certification Letter to Plaintiffs, pursuant to federal statute, advising that Defendants had submitted an ANDA for a salmon calcitonin nasal spray, and stating the grounds on which Defendants believed the '392 patent to be invalid and unenforceable. (Compl. ¶¶ 24, 26.)

The only claim of the '392 patent at issue in this litigation is Claim 19. (Compl. ¶21; Pl. 56.1 ¶¶1-2, 4; Def. 56.1 ¶1.) Claim 19 of the '392 patent ("Claim 19" or "the claim-in-suit") teaches: "A liquid pharmaceutical composition comprising about 2,200 MRC units of salmon calcitonin, about 20 mM citric acid,[5] about 0.2% phenylethyl alcohol,

[5] From July 14-15, 2008, a Markman hearing was held before the Court to interpret the term "about 20mM of citric acid." In the Court's August 27, 2008 order and opinion, the Court determined that about 20 mM of

about .5% benzyl alcohol, and about .1% polyoxyethylene(20) sorbitan monooleate." (Pl. 56.1 ¶¶7, 16.)

On December 18, 2008 the PTO allowed the '392 reissue application with a substantially identical Claim 19. (Pl. 56.1 ¶¶18-23.) During the reissue proceedings, Plaintiffs submitted, and the patent examiner considered, all prior art cited by Defendants in their motion for summary judgment, as well as all of Defendants' expert reports. (Pl. 56.1 ¶¶21-22, 24-25, 95-96.) The Examiner's reasons for allowing the reissue of Claim 19 were that:

> The closest prior art, does not teach or suggest a formulation comprising calcitonin and citric acid or a salt thereof for intranasal administration in a concentration-dependent manner with enhanced bioavailability and shelf stability, wherein the concentration of citric acid or a salt thereof is the critical element. Applicants have discovered that the narrow concentration range of 10-25 mM of citric acid and/or a salt thereof gives the formulation both its enhanced bioavailabilty and shelf stability.

(Pl. 56.1 ¶23; '812 reissue patent [Table 1 [effect of concentration of citric acid on the bioavailability of salmon calcitonin], Table 3 [effect of the concentration of citric acid on the stability of salmon calcitonin stored at 50 degrees celcius].)

On June 30, 2009, the PTO reissued the '392 patent as US RE40,812.[6] (Pl. 56.1 ¶27.)

2. Summary Judgment Standard

The general standard for summary judgment applies in a patent case. See Brown v. 3M, 265 F.3d 1349, 1350 (Fed. Cir. 2001) (general summary judgment standard applies to patent invalidity); Spectra Corp. v. Lutz, 839 F.2d 1579, 1581 n.6 (Fed. Cir. 1988)

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citric acid meant "approximately 20mM." See Unigene v. Apotex, 2008 U.S. Dist. LEXIS 66005 (S.D.N.Y. Aug 28, 2008).

[6] The '812 reissue patent was submitted to the Court by the parties at oral argument on July 9, 2009.

("summary judgment is as appropriate in a patent case as in any other"). Accordingly, as to each motion for summary judgment, the burden is on the moving party to establish that there are no genuine issues of material fact in dispute and that it is entitled to judgment as a matter of law. See Fed. R. Civ. P. 56(c); Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 256 (1986 (purpose of the summary judgment procedure is not to deprive a litigant of a trial, but to avoid an unnecessary trial when there is only reasonably possible outcome.)

A court must grant summary judgment "if the pleadings, depositions, answers to interrogatories, and admissions on file, together with affidavits, if any, show that there is no genuine issue as to any material fact …." Miner v. Glens Falls, 999 F.2d 655, 661 (2d Cir. 1993); see also Welker Bearing Co. v. PHD, Inc., 550 F.3d 1090, 1095 (Fed. Cir. 2008). A dispute regarding a material fact is genuine "if the evidence is such that a reasonable jury could return a verdict for the nonmoving party." Aldrich v. Randolph Cent. Sch. Dist., 963 F.2d 520, 523 (2d Cir. 1992). After discovery, if the nonmoving party "has failed to make a sufficient showing on an essential element of [its] case with respect to which [it] has the burden of proof," then summary judgment is appropriate. See Celotex Corp. v. Catrett, 477 U.S. 317, 323 (1986).

The moving party bears the burden of establishing the absence of any genuine issue of material fact and all significant doubt over factual issues must be resolved in the opposing party's favor. Adickes v. S.H. Kress & Co., 398 U.S. 144, 157 (1970). The "fact that both the parties have moved for summary judgment does not mean that the court must grant summary judgment to one party or the other … Cross-motions are no more than a claim by each party that it alone is entitled to summary judgment, and the court must evaluated each motion on its own merits, taking care in each instance to view the evidence

in favor of the nonmoving party." Bubble Room, Inc. v. United States, 159 F.3d 553, 561 (Fed. Cir. 1998); Mingus Constructors Inc. v. United States, 812 F.2d 1387, 1391 (Fed Cir. 1987). As explained in detail below, the issue of obviousness is a challenge to the validity of the patent and requires the Court to determine whether the challenger has established a genuine issue of material fact as a matter of law as to whether or not the patent is obvious. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1137-38 (Fed. Cir. 1985).

3. Applicable Law

Defendants bear a higher burden of proof because a patent is presumed valid. 35 U.S.C. § 282. In an infringement action where the accused counters by charging invalidity of the patent, that challenger, to prevail, "must establish facts, by clear and convincing evidence, which persuasively lead to the conclusion of invalidity." Avia Group Int'l v. L.A. Gear California, 853 F.2d 1557, 1561 (Fed. Cir. 1988). The challenger bears the burden of persuasion and must demonstrate invalidity by clear and convincing evidence through final judgment. Id. at 1562; Perkin-Elmer Corp. v. Computervision Corp., 732 F.2d 888, 894 (Fed. Cir. 1984). This burden is significant because clear and convincing evidence "proves in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] highly probable." Intel Corp. v. U.S. Int'l Trade Comm'n, 946 F.2d 821, 830 (Fed. Cir. 1991).

Where a claim has also survived a reissue proceeding, and has thus been twice considered by the PTO, the burden of proving invalidity is made "heavier," and must be met by the party asserting invalidity. Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1139 (Fed. Cir. 1985); Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1555 (Fed. Cir. 1985). Indeed, the presumption of validity "carries with it a presumption that the

Examiner did [her] duty and knew what claims [she] was allowing." Al-Site Corp. v. VSI Int'l, Inc., 174 F.3d 1308, 1323 (Fed. Cir. 1999).

The presumption of validity is "most formidable" when the "party asserting invalidity relies upon prior art considered by the (PTO)." Central Soya Co., Inc. v. Geo. A. Hormel & Co., 723 F.2d 1573, 1577 (Fed. Cir. 1983); see also Al-Site Corp., 174 F.3d at 1323 ("challenger's burden is especially difficult when the prior art was before the PTO examiner during prosecution of the application"); American Hoist & Derrick v. Sowa and Sons, 725 F.2d 1350, 1359 (Fed. Cir. 1984) ("When no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job …").

Where the basis for alleging invalidity is a patent's purported obviousness under 35 U.S.C. § 103, courts must consider an array of factors in determining whether the totality of the evidence warrants overturning the presumption of validity. Brown and Williamson Tobacco Corp. v. Philip Morris, 229 F.3d 1120, 1124 (Fed. Cir. 2000). A claimed invention is unpatentable due to obviousness if the difference between it and the prior art is "such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a).

Whether the invention was obvious under Section 103 is a legal conclusion based on certain factual inquiries, In re Huang, 100 F.3d 135, 138 (Fed. Cir. 1996); see also Richardson-Vicks v. Upjohn Co., 122 F.3d 1476, 1483 (Fed Cir. 1997), InterConnect, 774 F.2d at 1137 (obviousness is a question of law), including: 1) the level of ordinary skill in the art; 2) the scope and content of the prior art, and; 3) the differences between the

claimed invention and prior art. Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966) ("Graham Factors"). In answering this question, the Supreme Court in KSR directed courts facing this question to reject a "rigid approach" in favor of an "expansive and flexible approach using "common sense" when assessing whether an invention would have been obvious to a person of ordinary skill in the art. KSR International v. Teleflex, 550 U.S. 398, 415-16 (2007).

If the challenger establishes a *prima facie* showing of obviousness under these primary factors, the court then weighs secondary considerations of nonobviousness, which can include: commercial success, long felt but unmet need, failure of others, and unexpected results. Graham, 383 U.S. at 17; Sud-Chemie, Inc. v. Multisorb Techs., 554 F.3d 1001 (Fed. Cir. 2009) (secondary considerations, including "unexpected results, copying, and commercial success," … "constitutes independent evidence of nonobviousness" and can be quite instructive in the obviousness inquiry"); In re Sullivan, 498 F.3d 1345, 1351 (Fed. Cir. 2007) (evidence to rebut prima facie case of obviousness include "unexpected results," "commercial success," and "long-felt but unresolved needs"); In re Glaug, 283 F.3d 1335, 1338 (Fed. Cir. 2002); Winner Int'l Royalty v. Wang, 202 F.3d 1340, 1350-51 (Fed. Cir. 2000) (only after prima facie case of obviousness is established does burden shift to nonmovant to rebut prima facie case with secondary considerations); Simmons Fastener Corp. v. Ill. Tool Works, Inc., 739 F.2d 1573, 1575 (Fed. Cir. 1984) ("Only after all evidence of nonobviousness has been considered can a conclusion on obviousness be reached"); see also Pfizer v. Apotex, 480 F.3d 1348, 1369 (Fed. Cir. 2007) ("evidence of unexpected results can be used to rebut a prima facie case of obviousness").

The obviousness inquiry must be approached from the correct temporal and objective perspectives. KSR, 500 U.S. at 421 (a patent is invalid only if a person of ordinary skill in the art, at the time of the invention, would have been able to construct the invention based on the prior art and some motivation). Indeed, "determinations of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." Crown Operations Int'l, Ltd. v. Solutia, Inc., 289 F.3d 1367, 1376 (Fed. Cir. 2002). Put differently, a challenger who relies on the "blueprint drawn by the inventor," beginning the analysis at the claimed invention and matching it to the prior art, has not demonstrated obviousness. Interconnect, 774 F.2d at 1138 (holding "[t]he invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time"); ATD Corp. v. Lydall, Inc., 159 F.3d 534, 546 (Fed Cir. 1998) (it is legal error to allow selection of prior art based on evaluating a claim and then working backwards to find the links to patch together a chain of references that could lead to the claim components).

Rather, the decision maker must step back in time to before the moment of actual invention, and out of the actual inventor's shoes into those of a hypothetical, ordinary skilled in the art person who has never seen the invention. W.L. Gore & Assocs., Inc. v Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983). The legal question is whether, in light of the differences between the invention and the prior art, and all relevant facts, the invention would have been obvious at that time to such a person. Panduit Corp. v. Dennison Manufacturing, 810 F.2d 1561, 1566-68 (Fed. Cir. 1987); see also Ruiz v. AB Chance Co., 234 F.3d 654, 662-63 (Fed. Cir. 2000) ("Secondary considerations" provide an important check against hindsight analysis).

Where the challenger alleges the patent is obvious because it is no more than a combination of known elements, the challenger, in addition to showing that the elements were known, must also give "some articulated reasoning with some rational underpinning" 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; In re Rouffet, 149 F.3d 1350, 1355 (Fed. Cir. 1998) ("when a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references"); In re Deuel, 51 F.3d at 1559 (to establish obviousness, a claimed specific compound" must be "precisely envisioned" by the prior art). "Knowledge of a problem and motivation to solve it" are insufficient to show "motivation to combine particular references to reach the particular claimed method." Innogenetics v. Abbott Labs, 512 F.3d 1363, 1373-74 (Fed Cir. 2008).

In determining "motivation" in the chemical context, the inquiry begins with the reasoned identification of a lead compound. Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd., 533 F.3d 1353, 1359 (Fed. Cir. 2008); Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed.Cir. 2008); In re Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995) ("normally a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound," this is because close or established "structural relationships may provide a requisite motivation or suggestion to modify know compounds to obtain new compounds").

The challenger must then offer some articulated reasoning to explain why a person of ordinary skill in the art ("POSA") would make the changes to the lead compound to

arrive at the claim-in-suit, including some suggestion for making the necessary molecular modifications. See Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007) (holding that obviousness requires the challenger to show a reason for making molecular modifications); see also Eisai, 533 F.3d at 1357; In re Deuel, 51 F.3d at 1558 (to make a prima facie showing of obviousness in instances where there is similarity between prior art and a claimed compound, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required.)

Such reasoning may include the interrelated teachings of multiple patents, the effects of demands known to the community or in the marketplace, and the knowledge as well as the inferences and creative steps of a POSA. KSR, 550 U.S. at 401. The Federal Circuit has explicitly "reemphasized the importance of the motivation to combine," warning:

> An … accused infringer may often find every element of a claimed invention in the prior art … [T]he suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness. At the heart of [the] validity dispute is whether one of skill in [the] art would have found motivation to combine the pieces from one … prior art patent with a piece of another … through a series of manipulations.

Yamanouchi Pharmaceutical v. Danbury Pharmacal, 231 F.3d 1339, 1343 (Fed. Cir. 2000).

Where the challenger bases the reasoning on similarities between chemical properties, the properties of the elements of the compound inform the court's assessment of motivation. In re Dillon, 919 F.2d 688, 697 (Fed. Cir. 1990). While the claimed properties need not be known in the prior art, the lack of disclosure may indicate a lack of motivation. Id. In the alternative, a challenger may show there existed a finite number of identifiable,

predictable solutions which were obvious to try, thus rendering the invention obvious. KSR, 550 U.S. at 421.

Lastly, summary judgment of invalidity for obviousness in favor of Defendants is only appropriate if Defendants show, by clear and convincing evidence, that the patent is a combination of elements known in the prior art, that there was a motivation to combine those elements, and that there exist no secondary considerations from which a reasonable juror could infer nonobviousness. See, e.g., KSR, 550 U.S. at 426. Summary judgment of validity in favor of Plaintiffs is appropriate "where the accuser fails to make a showing sufficient ultimately to prove, by clear and convincing evidence, that the challenged claim is obvious in light of the professed combination." Eisai v. Teva Pharms USA, 2006 U.S. Dist. LEXIS 73516, *8 (S.D.N.Y. 2006) (granting plaintiff's motion for nonobviousness), aff'd, 533 F.3d 1353 (Fed. Cir. 2008); Fromson, 886 F.2d at 1302.

4. Obviousness Discussion

As noted, Claim 19 is composed of 2,200 IU/ml of salmon calcitonin, about 20 mM of citric acid, about .2% phenylethyl alcohol, about .5% benzyl alcohol, and about .1% polyoxethylene sorbitan monooleate ("Polysorbate 80"). (Def. 56.1 ¶¶1, 3, 16.) Both parties agree that the salmon calcitonin serves as the active ingredient, the citric acid serves as a buffer, absorption enhancer, and stabilizer, the phenylethyl and benzyl alcohols are preservatives, and the Polysorbate 80 is a surfactant.[7] (Def. 56.1 ¶¶73-76.) In reissuing the patent in December of 2008, the USPTO concluded that:

[7] In their brief in support of their motion for summary judgment, Defendants first examine Plaintiffs' New Drug Application ("NDA") for Fortical as evidence of the function of each element of claim 19. (Def. Memo at 2; Def. 56.1 ¶¶6-11.) Plaintiffs' NDA lists salmon calcitonin as the "active ingredient," citric acid as a "buffer," phenylethyl alcohol and benzyl alcohol as preservatives, and Polysorbate 80 as a "surface tension modifier." (Id.) Defendants then mention that the '392 patent teaches citric acid as a stabilizer and absorption

> The closest prior art, does not teach or suggest a formulation comprising calcitonin and citric acid or a salt thereof for intranasal administration in a concentration-dependent manner with enhanced bioavailability[8] and shelf stability, wherein the concentration of citric acid or a salt thereof is the critical element. Applicants have discovered that the narrow concentration range of 10-25 mM of citric acid and/or a salt thereof gives the formulation both its enhanced bioavailability and shelf stability.
>
> (Pl. 56.1 ¶23.)

Defendants assert that claim 19 would have been obvious to one of ordinary skill in the art based on a combination of over 40 prior art references. Specifically, Defendants argue that prior art teaches that each of the five components had been used "just the way they were used in the Claim 19 of the patent."[9] (Def. Memo at p. 3; 07/09/2009 Tr. at 4.) Defendants put forth their obviousness argument despite the fact that all of the relevant prior art identified by Defendants' chemistry and patent law experts, as well as their expert reports,[10] were submitted to and considered by the USPTO during the reissue prosecution. (Pl. 56.1 ¶¶21-22, 24-25, 95-96.)

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enhancer as well. (Def.'s Memo at 2 -3.) However, as the Court noted at oral argument, and as Plaintiffs point out in their response to Defendants' 56.1 Statement (Pl. Rep. 56.1 ¶¶8-11), it is the '392 patent which is at issue in the present litigation, not Plaintiffs' NDA. (07/09/2009 Tr. 7.) Consequently, to prevail, Defendants' analysis must show that each element in claim 19, and not in the NDA, was obvious.

[8] Bioavailability refers to the "amount of the active drug (salmon calcitonin) absorbed into the bloodstream and available to act on the body. See Bayer Schering Pharma v. Barr Labs, 2009 U.S. App. LEXIS 17372, *3 (Fed. Cir. Aug 5, 2009). Hence, the use of an absorption enhancer with the active drug would increase the active drug's "bioavailability."

[9] The first two Graham factors "the level of ordinary skill in the art" and the "scope and content of the prior art" are not in dispute. Plaintiffs have accepted all art that Defendants cite as within the scope and content of the relevant prior art. (Pl.'s Memo at 10.) Further, Defendants have accepted Plaintiffs description of the level of the ordinary skill in the art. A POSA is "an individual with a Masters Degree in Chemistry, Pharmaceutical Chemistry, Biochemistry, or similar field with at least eight (8) years of development, or an individual with a Ph.D in Chemistry, Pharmaceutical Chemistry, Biochemistry or similar field with at least four (4) years of practical experience in pharmaceutical liquid dosage form development." (Def. Opp. Memo at 10.) Finally, the parties do not dispute the differences between the prior art and claim 19. Thus, the sole issue remaining for these summary judgment motions is the legal determination of what the prior art would have taught a POSA at the time of the invention.

[10] Two additional expert reports from Drs. Mitra and Klibanov, which were served on Plaintiffs on April 25, 2009 and which are the subject of Plaintiffs' motion to exclude, were not considered by the patent examiner. (Pl. Memo Opp. at 18 n.7.)

A. There is Little Guidance in the Prior Art for Selecting a Citric Acid Concentration for Use As An Absorption Enhancer and Shelf Stabilizer Of Salmon Calcitonin in Liquid Nasal Formulations.

Defendants argue that a POSA seeking to make a nasal calcitonin product as of the '392 patent's priority date, February 4, 2000, would have been motivated to make a drug comparable to Novartis' successful Miacalcin, which also used the same active ingredient, salmon calcitonin, in the exact same concentration (i.e. 2,200 I.U./mL). (Def. 56.1 ¶¶24-25.) Bioequivalence with Miacalcin would have ensured the new drug's eligibility for the FDA's abbreviated new drug application ("ANDA"). (Def. 56.1 ¶88.) FDA approval through an ANDA would decrease the drug's time to market and reduce approval costs by reducing or eliminating safety testing. (Id.) At the same time, the POSA would have been motivated to create a drug that did not infringe the Miacalcin patent.[11] (Def. 56.1 ¶¶87-88.)

However, other than having the 2,200 IU/mL of salmon calcitonin as being the active ingredient, none of the other ingredients of Miacalcin match that of Claim 19. (Def. Rep. 56.1 ¶35.) Specifically, Miacalcin contains 8.5 mg of sodium chloride, which acts as a tonicity agent, nitrogen, which acts as a sparging agent, .10 mg of Benzalkonium chloride ("BZK"), which acts as a preservative, absorption enhancer, and surfactant, Hydrochloric acid, which acts as a pH adjuster, and purified water, which acts as a carrier. (Pl. 56.1 ¶¶29-34.) Thus, even crediting Defendants' argument that Plaintiffs were endeavoring to

[11] Plaintiffs take issue with Defendants' use of Miacalcin, which had been marketed by Novartis since 1995 (Def. 56.1 ¶36), as a starting point for the obviousness analysis, arguing that at the time of the development of Fortical, there were four nasal calcitonin formulations, only one of which, Miacalcin, suggested the usefulness of the 2,200 I.U./ml concentration of calcitonin. (Pl. Opp. Memo at 10-11.) However, due to Fortical's similiary to Miacalcin in calcitonin concentration and its bioequivalence (Def. 56.1 ¶40), and due to the fact that the inventor of Fortical, Dr. Stern, testified in his deposition that his purpose in creating Claim 19 was to formulate a salmon calcitonin formulation that was bioequivaluent to Miacalcin (Def. 56.1 ¶47), the Court accepts Defendants' use of Miacalcin as the lead compound and a reasonable starting point for the obviousness analysis. See Eisai, 533 F.3d at 1359 ("post-KSR, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound").

make a bioequivalent to Miacalcin, the issue presented is whether it would have been obvious for a POSA to strip away the nonactive ingredients of Miacalcin, and insert the ingredients present in Claim 19 to arrive at Fortical. Defendants argue that the prior art teaches this, while Plaintiffs contend otherwise.[12]

In making their argument that it was obvious to have chosen 20mM of citric acid to replace BZK, Defendants rely on four patents as disclosing the use of "about 20 mM" citric acid with calcitonin. (Def. Memo at 4.) Defendants cite U.S. Patent No. 5,123,315 ("the Ceschel '315 patent"), U.S. Patent No. 5,026,825 ("the Grebow '825 patent"), U.S. Patent No. 5,719,122 ("the Chiodini '122 patent), and U.S. Patent No. 5,183,802 ("the Aliverti '802 patent") which, according to Defendants, "disclose the use of about 20 mM citric acid and/or its salts with calcitonin, specifically salmon calcitonin, in liquid nasal compositions." (Def. Memo at 4; Def. Rep. 56.1 ¶¶26-30.) However, nothing in those references suggests using 20mM of citric acid with salmon calcitonin to achieve the result obtained by the '392 patent, which was to have a nasal salmon calcitonin formulation with both shelf stability and enhanced bioavailability.

i. *No prior art uses citric acid for stability or as an absorption enhancer for enhanced bioavailability.*

Specifically, although the Ceschel '315 patent contains examples containing citric acid in a range between 15.8 mM and 34.1 mM, including one example of 20.5 mM, the Ceschel '315 patent explicitly states that the citric acid was not used as an absorption enhancing agent, but was merely the "acidic component of the buffer." ('315 Patent, col. 4,

[12] In undertaking obviousness analysis, it is crucial to remember that a patent comprised of multiple elements, like the one here, "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." KSR, 550 U.S. at 418. Rather, in cases involving the combination of familiar elements in a patent in accordance with known methods, the Supreme Court has opined that an invention will likely be obvious when it elicits predictable results. Id.

lines 18-22; Pl. Rep. 56.1 ¶27.) Similarly, the Grebow ‘825 patent teaches the use of between 50 to 200 mM of citric acid as one of many possible buffers for calcitonin in intranasal formulations (‘825 Patent, col. 11, lines 40-45; Pl. Rep. 56.1 ¶28); the Chiodini ‘122 patent teaches the use of 1.9mM of citric acid as one component of many different buffering agents in formulations containing a polyglycolysed glycercide absorption enhancer (‘122 Patent, Col. 6, lines 20-23; Pl. Rep. 56.1 ¶29), and; the Aliverti ‘802 patent teaches the use of 1.9 mM of citric acid as one component of many various buffering agents in formulations containing the compound ammonium glycyrrhizinate as an absorption enhancer (‘802 Patent, col. 8, lines 5-7; Pl. Rep. 56.1 ¶30.) Accordingly, for these four pieces of prior art relied upon by Defendants, citric acid was used as a buffer, and not as an absorption enhancer or shelf stabilizer.

Further, each of the four above-mentioned patents uses a different absorption enhancer or stabilizer than that present in Claim 19. The Chiodini ‘122 patent uses polyglycolysed glyceride (Pl. 56.1 ¶63), the Ceschel ‘315 acid uses ammonium tartrate (Pl. 56.1 ¶57), the Grebow ‘825 acid uses delta-aminolevulinic acid (Pl. 56.1 ¶66), and the Aliverti ‘802 patent uses Glycyrrhizinate (Pl. 56.1 ¶52). Accordingly, the ‘825, ‘122, ‘315, and ‘802 patents all teach citric acid as a potential buffering agent when used with other absorption enhancers, indicating that citric acid cannot act as both a buffer and an absorption enhancer for calcitonin. (Pl. Opp. Memo at 13.) See In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994) (reference will teach away if it suggests that line of development is unlikely to be productive of result sought by applicant).

Defendants nonetheless assert that “the prior art disclosed that citric acid was known to act as an absorption enhancer of calcitonin.” (Def. Memo at 7-8.) However,

none of the four references Defendants cite for this proposition provide sufficient reason for a POSA to have chosen citric acid as an absorption enhancer when formulating a nasal, liquid salmon calcitonin product equivalent to Miacalcin. U.S Patent 5,059,587 (the "Yamamoto '587 patent") discloses citric acid as one of 13 absorption enhancers for calcitonin in a powdered nasal composition – not a liquid formulation as claimed in Claim 19.[13] (Pl. 56.1 ¶77; Pl. Rep. 56.1 ¶50, Def. Rep. 56.1 ¶50.). U.S. Patent No. 4,476,116 ("the Anik '116 patent") discloses citric acid as among an extensive list of over 60 "chelating agents" for enhancing the absorption of polypeptides, but does not reference enhancing the absorption of calcitonin. (Pl. Rep. 56.1 ¶51; Def. Rep. 56.1 ¶51.) The Agarwal reference does not even mention salmon calcitonin and discloses dozens of compounds among fourteen classes that purportedly act as absorption enhancers of polypeptides when administered intranasally, and "citrates" is listed as one example among the class of "chelators." (Pl. Rep. 56.1 ¶52, Def. Rep. 56.1 ¶52.) U.S. Patent No. 6,008,189 (the "Inamoto '189 patent") describes semi-solid compositions of calcitonin designed to be administered intravaginally – not intranasally as done in Claim 19. (Pl. Rep. 56.1 ¶53.) Thus, Defendants' references fail to suggest that a POSA would have selected citric acid as an absorption enhancer in a liquid, nasal calcitonin formulation.

ii. *No prior use of citric acid as a shelf stabilizer*

Defendants argue that the Bell reference discloses that "citric acid was known to act as a stabilizer of calcitonin." (Def. Memo at 8; Def. 56.1 ¶¶55-57, Def. Rep. 56.1 ¶¶53-

[13] As this Court has previously determined in its February 4, 2008 opinion concerning the crime fraud exception, the administration of calcitonin in an oral dosage, or in a dosage through the cheek, rectum, or vagina, or in a dosage in a solid or powdered form, is far different from the administration of a liquid dosage nasally, and absorption enhancers that were applicable in such different contexts are not applicable in the liquid nasal context. See Unigene v. Apotex, 2008 U.S. Dist. LEXIS 8215 at *12-20.

57.) It does not. The Bell reference does not mention calcitonin, so it could not disclose that citric acid was a known stabilizer for that compound. The Ceschel '315 patent (relied upon by Defendants here) does disclose that extensive research was conducted to find a suitable stabilizing agent for a nasally administered calcitonin formulation. (Pl. Rep. 56.1 ¶27.) The Ceschel '315 patent reports that the compounds of the Anik '116 patent were tested and that such "absorption enhancing agents" were unable to assure suitable stability and that "only ammonium tartrate is a satisfactory stabilizing agent for liquid nasal compositions containing polypeptides." (Id.) Thus, there was no reason based on the teaching of the Ceschel '315 patent (which is inconsistent with Defendants' stated proposition here) for using citric acid in combination with calcitonin to achieve stability of a liquid nasal formulation. In re Gurley, 27 F.3d at 553 ("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.")

Accordingly, Defendants have not provided evidence that a POSA would choose about 20 mM of citric acid to achieve shelf stability or enhanced bioavailability of a liquid nasal calcitonin formulation. In re Deuel, 51 F.3d at 1558 (to make a prima facie showing of obviousness in instances where this is similarity between prior art and a claimed compound, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required.) No prior art uses citric acid as an absorption enhancer (or shelf stabilizer) in liquid nasal formulations of calcitonin. Therefore, there was no guidance in the prior art for selecting a citric acid concentration to match the absorption enhancing effect of BZK in Miacalcin. Although some prior art uses citric acid as a buffer in liquid nasal formulations of

calcitonin, Miacalcin does not contain a separate buffer, and the prior art cited by Defendants uses other compounds as absorption enhancers or stabilizers.[14]

B. It Would Not Have Been Obvious for a POSA to Have Modified Miacalcin to Arrive at Claim 19.

From the aforementioned analysis, it is clear that Defendants' obviousness arguments rely upon examining the blueprint drawn up by Dr. Stern in Claim 19, and from there, Defendants have picked and chosen prior art designed to match the parameters of Claim 19. Indeed, Defendants experts Drs. Mitra and Langer admitted as much in their depositions. (Pl. 56.1 ¶¶111-12.) Defendants' methodology is legally incorrect, as it is impermissible to use hindsight to establish an obviousness claim. KSR, 550 U.S. at 421 (factfinder should be aware … of the distortion caused by hindsight bias and must be cautioned of arguments reliant upon ex post reasoning); ATD Corp, 159 F.3d at 546 ("Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention."); Interconnect Planning, 774 F.2d at 1143 ("The invention must be viewed not from the blueprint drawn by the inventor, but in the state of the art that existed at the time.").

Viewed from the proper perspective, without the benefit of hindsight, it is apparent that even had Plaintiffs been motivated to make a bioequivalent version of Miacalcin without BZK, as Defendants argue, no prior art suggests replacing the components of

[14] Defendants submitted a booklet to the Court at oral argument on July 9, 2009. Contained in this booklet was a chart which listed the components of Claim 19 and their functions, and next to that was a list of prior art that purportedly taught these function. However, even on this chart, Defendants cited no prior art which taught the use of citric acid as an absorption enhancer and shelf stabilizer. Rather, the chart listed the function of citric acid solely as a "buffer," and next to this function, cited prior art which taught citric acid's use as a buffer.

Miacalcin with those found in Claim 19. See Takeda Chem. Indus., 492 F.3d at 1356 (in obviousness inquiry, it is 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"); see also Innogenetics, 2007 U.S. Dist. LEXIS 193, at *17 ("A generalized motivation to develop a method is not the kind of motivation required by the patent laws.")

In that regard, BZK performs the function in the Miacalcin formulation of an absorption enhancer, a preservative, and a surfactant. Thus, a POSA seeking to replace BZK and develop a bioequivalent compound had essentially three options: 1) find another ingredient which was both a preservative and an absorption enhancer; 2) use an ingredient(s) which was a preservative together with a separate ingredient(s) which was an absorption enhancer, or 3) find some other way to increase absorption of calcitonin by the body (i.e. result in an enhanced bioavailability). Additionally, a POSA would likely wish to include a non-BZK surfactant in the formulation.[15] (Pl. 56.1 ¶¶99-100.)

As Defendants' experts suggest, a POSA would first look to find a component that essentially replicates BZK in function as closely as possible, i.e., a POSA would look to find a component that serves as both a preservative and an absorption enhancer. (Pl. 56.1 ¶99.) The prior art discloses numerous compounds that act as both preservatives and absorption enhancers of calcitonin. (Pl. 56.1 ¶¶39, 45, 99, 101.) For example, benzethonium chloride is, like BZK, a salt surfactant used as a preservative. (Pl. 56.1 ¶45.) EDTA may also be used as a preservative and absorption enhancer, and the preservative benzyl alcohol is described to be a potential absorption enhancer. (Id.) Further, all three of

[15] Surfactants are "substances that absorb to surfaces or interfaces to reduce surface or interfacial tension." (Def. Rep. 56.1 ¶18.)

these compounds had been used in FDA-approved liquid nasal formulations at the time of Dr. Stern's invention, and would have been the logical starting point for a POSA. (Id.) Yet Defendants do not explain why their hypothetical POSA would ignore these logical options and instead proceed to focus on citric acid as the solution.

Next, with regard to the third option, that of finding another way to improve the absorption and bioavailability of calcitonin, enzyme inhibitors and peptide carriers were known methods of doing so. (Pl. 56.1 ¶39.) For example, one of Defendant's prior art references, the '825 Grebow Patent, uses enzyme inhibitor delta-aminolevulinic acid to improve absorption. (Pl. 56.1 ¶66.) Yet Defendants' POSA fails to explore this obvious option too.

Instead, in explaining their obviousness argument, Defendants jump straight to the second option, which was to use an ingredient(s) which was a preservative together with a separate ingredient(s) which was an absorption enhancer, as the path a POSA would select. However, this methodology too does not suggest citric acid to a POSA. Rather, there was numerous prior art containing calcitonin in liquid formulations for nasal administration that had been found to be absorption enhancers in these formulations, including: benzyl alcohol, ethanol, malic acid, sodium caprate, sodium salicylate, Macrogol (polyethlylene glycol) 400, thiamine hydrochloride, sodium pyrophosphate and ammonium glycyrrhizinate. (Pl. 56.1 ¶¶43, 52-54, 69). U.S. Patents 4,690,952 and 4,788,221 ("Kagatani patents") describe many of the aforementioned components as absorption enhancers, and the Kagatani patents also disclose the use of citric acid as a component of the buffer system. ('952 Patent, col. 2, lines 24-27; Pl. 56.1 ¶69.) Hence, not only does the prior art provide more logical places than citric acid for a POSA to start looking for an absorption enhancer of calcitonin, but the

prior art teaches away from the use of citric acid as an absorption enhancer, and instead, focuses upon its use as a buffer.

Yet Defendants ignore these absorption enhancers suggested by prior art and instead turn, without any explanation of a reasonable expectation of success, to general classes of absorption enhancers for polypeptides of which there were many, including: bile salts, surfactants, chelating agents, fatty acids, glycosides, glycyrrhetinic acid derivatives, fusidic acid derivatives and phospholipids." (Pl. 56.1 ¶¶40-42.) From this list of general classes of absorption enhancers, Defendants' POSA would ignore the vast majority of them (each of which contained many possibilities for a POSA), and select chelating agents from among these general categories due to the fact that the Anik '116 patent states that chelating agents can be used as absorption enhancers (not mentioning calcitonin) with peptides. (Pl. 56.1 ¶41.) From that list of more than 60 chelating agents, the POSA would have to then select citric acid. (Pl. 56.1 ¶47.) The POSA does this, according to Defendants, even though the Anik '116 patent prefers EDTA and its salts, and uses it in each of the patent's examples. (Pl. 56.1 ¶¶46-51.)

Defendants do not point to any prior art reference which uses citric acid for the same purpose as BZK is used in Miacalcin, i.e., as an absorption enhancer and preservative of calcitonin in liquid nasal formulations. Instead, Defendants POSA would ignore the many compounds noted above, which appear in prior art to be more likely to succeed, and choose citric acid as an absorption enhancer and stabilizer This giant leap demonstrates that Defendants' obviousness argument is impermissibly hindsight driven. And while Defendants argue that a POSA would be attracted to citric acid because it was used as a buffer in prior liquid nasal formulations in references testing different absorption

enhancers, Defendants ignore the fact that Miacalcin was formulated and approved without a buffer. It would have made little sense for a POSA, who was trying to replicate Miacalcin, to add new components with new functions. Accordingly, the aforementioned analysis demonstrates the many twists and turns a POSA would have had to have made to have arrived at Claim 19 when starting at, and trying to replicate, Miacalcin. Defendants have failed to present evidence to support their claim that Claim 19 was obvious.

Additionally, and as the patent examiner recognized, even if a POSA would have chosen citric acid either as an absorption enhancer or as part of a buffer, a POSA would have still had to select a concentration of citric acid suitable for these functions. In arguing that a POSA would have chosen a concentration of 20mM of citric acid, as Dr. Stern did in Claim 19, Defendants argue that: 1) some prior art use concentrations of citric acid near 20mM, and 2) that "routine optimization" would lead a POSA to 20mM citric acid. (Def. Memo at 14-15.)

Yet the prior art relied upon by Defendants suggest a wide variety of concentrations, none of which would have automatically led a POSA to select a concentration of 20mM. For example, the Anik '116 patent teaches that a chelating agent would be in the range of .26mM to 521 mM. (Pl. 56.1 ¶48.) Another patent (the Arvinte '788 patent) uses citric acid at concentrations of 0.0052 mM – 0.52 mM. (Pl. 56.1 ¶79.) The '122 Chiodini patent discloses a total citrate concentration of 17.6mM, the Ceschel '315 patent discloses a range of between 15.8 mM and 34.1 mM, the Veronesi patent discloses a range of 26 mM to 47 mM, and other patents disclose a range of anywhere from 1.9 mM to 260 mM. (Pl. 56.1 ¶¶48, 55, 62, 64, 71, 73, 75, 79, 82, 87-88, 91, 94.) Accordingly, while certain prior art suggests that a range of around 20 mM could be used,

other prior art suggests a far wider range of options. Thus, Defendants have not shown that it would have been obvious for a POSA to select a range of approximately 20 mM of citric acid.

C. Defendants' Obviousness Argument with Respect to the Other Components of Claim 19 Fares Little Better.

Citric acid, while the most novel and most contested component of Claim 19, is not the only contested component. Rather, the parties disagree as to whether it would have been obvious" for a POSA to use .2% phenylethyl alcohol, .5% benzyl alcohol, and .1% Polysorbate 80 in Claim 19.

First, in support of their argument that a POSA would have chosen benzyl and phenylethyl alcohol in their specific concentrations to act as preservatives for Claim 19, Defendants simply state that those two ingredients were considered safe and accepted by regulatory authorities, that they had been marketed in nasal compositions (although not in combination with salmon calcitonin), and that the choice of the concentrations for these two ingredients "would be obvious from the normal desire to optimize the range." (Def. Memo at 5-6, 16.)

However, no prior art reference provided by Defendants reveals a formulation containing both preservatives, rather, the art simply suggests using a single preservative. (Def. 56.1 ¶¶13-14, 75-76.) Nor do Defendants provide any reasons for why a POSA who started with Miacalcin (which only has one preservative, BZK), would add a second preservative. Defendants' reliance on In re Kerkhoven, 626 F.2d 846 (CCPA 1980) in this regard is misplaced. Unlike in In re Kerkhoven, Claim 19 is not simply a combination of two elements to form a third that does the same thing, rather it is a combination of five components at specific concentrations, each serving a function within the claimed

compound. (Pl. Rep. 56.1 ¶¶73-77, 89.) Accordingly, Defendants have failed to submit evidence, and it is their burden to do so, to explain why a POSA would have used the two preservatives contained in Claim 19.

Next, in support of their argument that it would have been obvious for a POSA to use Polysorbate 80 as a surfactant, as it was used in Claim 19, Defendants simply assert that Polysorbate 80 was considered safe and accepted by regulatory authorities and had been used in previously produced nasal compositions (although not in combination with salmon calcitonin). (Def. Memo at 5-6; Def. 56.1 ¶¶16-18, 21-22.) As to the concentration of about .1% of Polysorbate 80, Defendant's proof consists solely of attorney argument that the amount "would be obvious from the normal desire to optimize the range." However, despite Defendants' conclusory statements, the prior art provides little guidance for why a POSA would have selected polysorbate 80 and not some other surfactant, much less arrive at a concentration of about .1%.

In that regard, there were many surfactants known and available to a POSA, including at least four that were previously used in FDA-approved nasal products (Polysorbate 20, Polysorbate 80,[16] lecithin and gylceryl monooleate). (Pl. 56.1 ¶105.) Further, the Wade reference discloses that the antimicrobial activity of benzyl alcohol, a preservative present in Claim 19, is "reduced in the presence of nonionic surfactants, such as polysorbate 80." (Pl. 56.1 ¶89.) Given that teaching, the prior art taught away from using Polysorbate 80 together with benzyl alcohol, one of the preservatives used in Claim 19. Accordingly, the Court finds that it was not obvious that a POSA would have used Polysorbate 80 as the surfactant here.

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[16] Polysorbate 20 and Polysorbate 80 are commonly known by their commercial names, Tween 20 and Tween 80, respectively. See US Patent No. 2885675.

D. Summary

In deciding these motions for summary judgment, it is crucial to remember the burden placed upon Defendants, who are challenging the validity of Claim 19. Defendants must prove invalidity by clear and convincing evidence. The burden of proving invalidity is made heavier where, as in this case, a claim has survived a reissue proceeding. Additionally, the presumption of validity is most formidable when the party asserting invalidity relies upon prior art considered by the PTO, as Defendants do here.

Viewed in this context, it is eminently clear that Defendants have failed to meet their burden of proving obviousness as a matter of law. Rather, and as described above, Defendants obviousness attack is entirely hindsight driven. In that regard, Defendants start with Claim 19, and from that, attempt to find prior art that in Defendants' view might have taught a POSA to construct that claim. Not only is this impermissible hindsight, and legally incorrect, but upon examination, the prior art cited by Defendants in no way suggests that a POSA would have had a reasonable expectation of success, let alone an obvious one, to simply replace the BZK found in Miacalcin with citric acid to arrive at the bioequivalent compound that is the subject of this litigation, Claim 19. Further, Defendants have failed to show that the use of the three other components of Claim 19 (phenylethyl and benzyl alcohol and Polysorbate 80) would have been obvious to a POSA. Accordingly, Defendants' motion for summary judgment is denied.

It is further evident that Defendants have failed to make a sufficient showing ultimately to prove, by clear and convincing evidence, that Claim 19 is obvious. Two points are relevant here. First, and as is relevant to Defendants' motion for summary

judgment explained above, little to none of the prior art suggests using citric acid as a replacement for BZK for the functions BZK performed in Miacalcin.

Second, and as fully described in Part B of this section, infra, when viewed correctly, from a prospective basis rather than with hindsight, where the POSA is simply presented with a problem to solve and prior art, it is apparent that the road from Miacalcin to Claim 19 was not suggested by the prior art. In fact, in developing a bioequivalent to Miacalcin, a POSA would have had to have disregarded teachings from the prior art that would have led the POSA astray, see In re Omeprazole Patent Litig., 490 F. Supp. 2d 381 (S.D.N.Y. 2007) ("if the prior art teach way from combining known elements in the manner claimed by the invention at issue, discovering a successful way to combine them is less likely to be obvious"), and instead would have examined numerous paths, with hundreds of potential solutions, to result in Claim 19.

Based on the evidence presented, the Court concludes that no "reasonable jury would find that an ordinarily skilled artisan would have had a motivation to combine the above-cited references in order to achieve the benefits realized by the patented invention." See Network Appliance, Inc. v. Bluearc Corp., 374 F. Supp. 2d 825, 837-838 (N.D. Cal. 2005) (providing legal framework for determination of Plaintiff's summary judgment motion for nonobviousness). Accordingly, Plaintiffs' motion for summary judgment on nonobviousness is granted as a matter of law.

5. Plaintiffs' Motion to Exclude the Expert Reports Submitted by Defendants Subsequent to the Filing of the Motions for Summary Judgment is Denied as Moot.

On September 22, 2008, this Court issued the following scheduling order for the completion of expert discovery: Opening Expert reports were due October 14, 2008, reply

expert reports were due December 2, 2008, rebuttal expert reports were due January 5, 2009, and the completion of expert discovery was due on February 23, 2009. (Docket Number 124.) Defendants submitted their motion for summary judgment on April 17, 2009, and on April 23, 2009, Plaintiffs filed their own motion for summary judgment. That same day, after Plaintiffs filed their motion, Defendants submitted two additional expert reports from Drs. Klibanov and Mitre which purported to show that the "use of citric acid and/or its salts does not increase stability of calcitonin compositions as compared to compositions without citric acid and/or its salts." (Def. Memo of Law in Opposition to Plaintiff's Motion to Exclude, at 2.)

According to Defendants, these reports were introduced to "cover the very important issue of whether or not Dr. Stern has shown any 'surprising results' to rebut a prima facie case of obviousness." (Id. at 12.) Defendants go on to argue that "a prima facie case of obviousness can be rebutted by a showing of secondary considerations concerning nonobviousness. One of those secondary considerations is "surprising or unexpected results." (Id. at 12-13; see also 07/16/2009 Tr. 13-14, 23.) See Winner Int'l Royalty, 202 F.3d at 1350-51 (only after prima facie case of obviousness is established does burden shift to nonmovant to rebut prima facie case with secondary considerations).

However, as explained supra, Defendants have failed to present a prima facie case of obviousness. Accordingly, the issue of secondary considerations, along with Plaintiffs' motion to exclude, is moot. See, e.g., Takeda, 492 F.3d at 1363 ("In light of our conclusion that Alphapharm failed to prove that the claimed compounds would have been prima facie obvious, we need not consider any objective indicia of nonobviousness"). For this reason, Plaintiffs' motion to exclude the expert reports under Fed. R. Civ. P. 37 is denied.

Conclusion

Defendants' Motion for Summary Judgment is denied, and Plaintiffs' Motion for Summary Judgment is granted. Plaintiffs' Motion to Exclude is denied as moot. As Defendants have conceded infringement of Plaintiffs' '392 and '812 reissued patents, this Court finds that Plaintiffs are entitled to a permanent injunction prohibiting Defendants from further infringement. 35 U.S.C. § 271(e)(4)(B). Accordingly, judgment will be entered in favor of Plaintiffs. Defendants are hereby permanently enjoined from engaging in any activity that infringes on U.S. Patent No. 6,440,392, inclusive of U.S. Patent Number RE40,812.

IT IS SO ORDERED.

Dated: New York, New York
August 31, 2009

Robert P. Patterson, Jr.

U.S.D.J.

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