United States Court of Appeals for the Federal Circuit

UNIGENE LABORATORIES, INC. AND UPSHER-SMITH LABORATORIES, INC.,
Plaintiffs-Appellees,

v.

APOTEX, INC. AND APOTEX CORP.,
Defendants-Appellants.

2010-1006

Appeal from the United States District Court for the Southern District of New York in case no. 06-CV-5571, Judge Robert P. Patterson, Jr.

Decided: August 25, 2011

BRUCE C. HAAS, Fitzpatrick, Cella, Harper & Scinto, of New York, New York, argued for plaintiffs-appellees. With him on the brief was STEVEN C. KLINE.

MANNY D. POKOTILOW, Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd., of Philadelphia, Pennsylvania, argued for defendants-appellants. With him on the brief were ROBERT S. SILVER, JAMES J. KOZUCH and MARC B. BASSLER. Of counsel was WILLIAM JOSEPH CASTILLO.

Before RADER, *Chief Judge*, MOORE, and O'MALLEY *Circuit Judges*.

RADER, *Chief Judge*.

The United States District Court for the Southern District of New York heard a dispute between Apotex, Inc. and Apotex Corp. ("Apotex"), the appellants, and Unigene Laboratories, Inc. and Upsher-Smith Laboratories, Inc. (collectively, "Unigene"), the appellees, over claim 19 of U.S. Patent No. RE40,812E ("'812E patent"). On cross-motions for summary judgment, the district court granted Unigene's motion that the patent would not have been obvious at the time of invention. *Unigene Labs., Inc.,v. Apotex, Inc.* ("Summary Judgment Opinion"), No. 06-CV-5571, Dkt. No. 175, slip op. at 28-29 (S.D.N.Y. Aug. 31, 2009). The trial court also denied Apotex's motion to breach the attorney-client privilege under the crime-fraud exception. *Unigene Labs., Inc.,v. Apotex, Inc.* ("Crime-Fraud Opinion"), No. 06-CV-5571, Dkt. No. 89, slip op. at 18 (S.D.N.Y. Feb. 4, 2008). In addition, the district court determined that Apotex had waived several counter-claims. *Unigene Labs., Inc.,v. Apotex, Inc.* ("Counterclaim Opinion"), No. 06-CV-5571, 2010 WL 2730471 (S.D.N.Y. July 7, 2010). Because the district court correctly decided all of these motions, this court affirms.

I.

Unigene owns the '812E patent through assignment from inventor Dr. William Stern ("Stern"). The '812E patent is a reissue of U.S. Patent No. 6,440,392 ("'392 patent"). The reissue occurred on June 30, 2009, while this case was before the district court.

Covered by the '812E patent, Fortical® is an Food and Drug Administration ("FDA") approved pharmaceutical nasal spray with the active ingredient salmon calcitonin

("salmon calcitonin" or "calcitonin"). Unigene filed for FDA approval under 21 U.S.C. § 355(b)(2) and now holds the New Drug Application ("NDA") for Fortical®. Unigene's NDA claims Miacalcin® as its reference drug, meaning that for FDA approval, Unigene had to prove that Fortical® was a bioequivalent of Miacalcin®. Upsher-Smith is the exclusive patent licensee, with rights to market and sell Fortical® in the United States. Fortical® treats, among other things, postmenopausal osteoporosis.

Fortical® is a bioequivalent of Novartis International AG's Miacalcin® calcitonin nasal spray. Miacalcin® has been marketed since 1995, before the '812E patent's February 4, 2000 priority date. Unigene developed Fortical® as an alternative to Miacalcin®.

Both Miacalcin® and Fortical® use salmon calcitonin at a concentration of 2,200 I.U./mL as their active ingredient. Salmon calcitonin is a natural polypeptide hormone. Calcitonins help regulate calcium ions in the blood and therefore address calcium-related conditions like osteoporosis. To be effective, polypeptides, like salmon calcitonin, must reach the bloodstream. Delivery to the bloodstream, however, is not easy because calcitonins are readily degraded by bodily fluids, are relatively unstable in pharmaceutical compositions, and are poorly absorbed through tissues. Miacalcin® and Fortical® are both nasal sprays.

Fortical® and Miacalcin® have different formulations. For instance, Miacalcin® also contains 8.5 mg of sodium chloride, which acts as a tonicity agent; nitrogen, which acts as a sparging agent; hydrochloric acid, which acts as a pH adjuster; and purified water, which acts as a carrier. Of particular importance to this appeal, Miacalcin® contains 0.10 mg of benzalkonium chloride ("BZK") which functions as a preservative, absorption enhancer, and

surfactant. In contrast, Fortical® contains 20 mM of citric acid, which functions as an absorption enhancer and stabilizer/buffer; polyoxyethylene(2) sorbitan monooleate ("polysorbate 80"), which acts as a surfactant; and phenylethyl alcohol and benzyl alcohol, which serve as preservatives.

Apotex, a Canadian pharmaceutical company, filed Abbreviated New Drug Application ("ANDA") No. 078200 with the FDA on June 1, 2006. Apotex's ANDA certified under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("paragraph IV certification") intends to make, use, offer to sell, sell, and/or import a generic version of Unigene's Fortical® product before the expiration of the '812E patent. Because a paragraph IV certification is an act of infringement under 35 U.S.C. § 271(e)(2), *see also Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1351 (Fed. Cir. 2004), Unigene lodged a Complaint for infringement in the district court. The only asserted claim in the litigation is claim 19. Claim 19 reads:

> A liquid pharmaceutical composition for nasal administration comprising about 2,200 MRC units of salmon calcitonin, about 20 mM citric acid, about 0.2% phenylethyl alcohol, about 0.5% benzyl alcohol, and about 0.1% polyoxyethylene(2) sorbitan monooleate

'812E patent col.18 ll.1-5.

Apotex's original Answer of September 20, 2006 contained numerous affirmative defenses. In addition to allegations of invalidity under 35 U.S.C. §§ 101, 102, 103, and 112, Apotex alleged noninfringement and inequitable conduct. The inequitable conduct assertions cited the failure to disclose an allegedly material piece of prior art and making allegedly misleading statements during

patent prosecution. Apotex filed an Amended Answer on May 8, 2007 with two more inequitable conduct allegations, one based on an error in Table 3 of the '392 patent and another based on the failure to disclose a piece of prior art.

In September 2007, during fact discovery, Apotex moved to breach Unigene's attorney-client privilege under the crime-fraud exception. In support of these allegations, Apotex referred to Unigene's alleged failure to disclose U.S. Patent No. 5,912,014 ("'014 patent") to the U.S. Patent and Trademark Office ("Patent Office") and to errors in Table 3 of the '392 patent, the same conduct upon which Apotex premised some of its inequitable conduct claims at issue in this appeal.

The prior art '014 patent, with Dr. Stern as a co-inventor, carries the title "Oral Salmon Calcitonin Pharmaceutical Products." The '014 patent claims enteric-coated solid pharmaceutical formulations of salmon calcitonin, administered orally. The '014 patent discloses a solid oral tablet that the specification touts as a more convenient and comfortable dosage method for patients. The '014 patent teaches an oral formulation that resists degradation during the digestion process to keep the salmon calcitonin active. The '014 patent discloses experiments measuring the effects of citric acid on buffer pH, bioavailability of salmon calcitonin, and absorption of salmon calcitonin in the presence of enhancers. These experiments injected 0.5 mL of liquid formulation containing citric acid, taurodeoxycholic acid, mannitol, and calcitonin into the exposed duodenum of anesthetized rats. The experiments showed an increase in calcitonin's bioavailability when the amount of citric acid was increased and noted that bioavailabilty was "minor" in the presence of enhancers when compared to citric acid alone.

Table 3 of the '392 patent, reproduced below, shows the effect of citric acid concentration on the stability of salmon calcitonin stored at 50°C. Table 3 shows the percentage of calcitonin in formulations with different amounts of citric acid over fifteen days. As published '392 patent, Table 3 had two errors, indicated by the strike-through lines:

EFFECT OF THE CONCENTRATION OF CITRIC ACID ON THE STABILITY OF sCT STORED FOR VARYING PERIODS AT 50° C (Percent sCT Recovered)					
Citric Acid (pH 3.7)	0 mM	10 mM	~~20~~ 25 mM	50 mM	100 mM
Days at 50° C					
0	100	100	100	100	100
3	83	94	91	90	87
6	53	90	87	83	77
9	24	82	78	73	66
15	22	74	68	61	~~20~~ 52

J.A. at 31. The error on the top axis, characterized as clearly typographical in nature by the district court, labels a column "20 mM" instead of "25 mM." Second, the point of Apotex's allegations, a data point on the table reads 20 percent instead of the 52 percent actually measured. The column containing the second error shows that a salmon calcitonin solution with 100 mM of citric acid degrades over time, as the percentages of recovered calcitonin decrease from 100 percent to 52 percent over time. Whether the 15 day measurement is 20 percent or 52 percent, the recovery is still below the 66 percent recovered after 9 days.

The record indicates that Dr. Stern immediately informed the Patent Office when he became aware of the errors in Table 3. Specifically, Dr. Stern submitted a declaration on September 7, 2007, explaining an "inadvertent error during automated data analysis." He explained

further that the error did not affect the trend of salmon calcitonin reduction.

The district court declined to find that these errors or non-disclosures were sufficient to pierce the attorney-client privilege. The district court found the '014 patent to be either immaterial to the '392 patent or cumulative to the other cited references. *Crime-Fraud Opinion*, at 11. While both the '014 patent and '392 patent related to pharmaceutical formulations of salmon calcitonin, the district court found that the '392 patent's formulations were "considerably different" than formulations in the '014 patent and were, therefore, immaterial. *Crime-Fraud Opinion*, at 11. The district court also found that Apotex's proffered evidence of fraudulent intent regarding the '014 patent was insufficient to establish a prima facie case of fraud. *Id.* at 12.

The district court also found that the errors in Table 3 of the '392 patent were immaterial. *Id.* at 14-15. The district court found the corrected version of the table consistent with Unigene's assertions at the Patent Office. *Id.* at 16. The district court concluded that the errors were not material with respect to patentability or common law fraud. *Id.* The district court also determined that evidence of Stern's submission of a second declaration to clarify errors in Table 3 lacked deceptive intent, making that conduct insufficient to support an assertion of common law fraud. *Id.* at 17-18.

Unigene and Apotex cross-moved for summary judgment on obviousness. The Patent Office granted reissue of the '392 patent on June 30, 2009, at which point the district court granted Unigene's motion to amend the Complaint to replace all references to the '392 patent with the reissued '812E patent. Apotex filed an Answer to Unigene's Amended Complaint on July 20, 2009 that

included several additional counts of inequitable conduct. Without addressing these new claims, the district court granted Unigene summary judgment of nonobviousness and entered judgment.

The district court found that the '812E patent would not have been obvious at the time of invention as a matter of law. *Summary Judgment Opinion* at 29. In considering forty-plus pieces of prior art submitted by Apotex (also considered by the Patent Office during prosecution of the '812E patent), the district court found that no prior art teaches using 20 mM citric acid to achieve "both shelf stability and enhanced bioavailability" in a nasal salmon calcitonin formulation. *Summary Judgment Opinion* at 15.

The district court also found that it would not have been obvious to a person of ordinary skill in the art to modify Miacalcin® to reach the formulation of claim 19. The record shows that a person of ordinary skill was an individual with a masters degree in chemistry, pharmaceutical chemistry, biochemistry, or a similar field with at least eight years of practical experience in pharmaceutical liquid dosage form development, or an individual with a Ph.D. in the same fields with at least four years of practical experience in pharmaceutical liquid dosage form development. Specifically, the district court determined first that BZK serves as an absorption enhancer, a preservative, and a surfactant in Miacalcin®. Then, the court relied on expert testimony to conclude that a person of ordinary skill would have been motivated to find other FDA-approved compounds that serve as both absorption enhancers and preservatives of calcitonin. Further, the district court found that the prior art taught alternative methods of improving bioavailability and absorption of calcitonin.

In response to the court's summary judgment rulings, Apotex moved for reconsideration in light of its counterclaims of inequitable conduct. The district court granted Apotex's motion to consider its counterclaims. Nonetheless the district court re-entered judgment for Unigene. The district court held that all of Apotex's defenses and counterclaims, those asserted in 2006-07 and those Apotex sought to add in 2009, had been conceded, waived, barred, abandoned, or improperly raised. Apotex appeals the district court's rejection of the three added inequitable conduct counterclaims ("Count XII, Count XIII, and Count XIV"). This court has jurisdiction under 35 U.S.C. § 1295(a)(1).

II.

This court applies its own law to review a district court's application of the crime-fraud exception to the attorney-client privilege. *In re Spalding Sports Worldwide, Inc.*, 203 F.3d 800 (Fed. Cir. 2000). This court reviews a district court's determination of material protected by the attorney-client privilege for an abuse of discretion. *Apotex Corp. v. Merck & Co.*, 507 F.3d 1357, 1362 (Fed. Cir. 2007).

A party must establish *Walker-Process* fraud, also known as common law fraud, to successfully pierce the attorney-client privilege under the crime-fraud exception. *See Walker-Process Equip., Inc. v. Food Mach. & Chem. Corp.*, 382 U.S. 172, 177 (1965). A finding of common law fraud in the patent context "must be based on independent and clear evidence of deceptive intent together with a clear showing of reliance." *Spalding*, 203 F.3d at 803; *see Nobelpharma AB v. Implant Innovations, Inc.*, 141 F.3d 1059, 1070 (Fed. Cir. 1998) (holding that both fraudulent misrepresentations and omissions can support a finding of common law fraud). Such independent and clear evidence

must establish a prima facie case of fraud, which is "generally held *not* to exist" unless the accusing party can show:

> (1) a representation of material fact, (2) the falsity of that representation, (3) the intent to deceive or, at least, a state of mind so reckless as to the consequences that it is held to the equivalent of intent (scienter), (4) a justifiable reliance upon the misrepresentation by the party deceived which induces him to act thereon, and (5) injury to the party deceived as a result of his reliance on the misrepresentation

Spalding Sports, 203 F.3d at 807 (citing *Nobelpharma*, 141 F.3d at 1069-70). This court need only examine Apotex's proffered evidence of intent to uphold the district court's refusal to invoke the crime-fraud exception.

The record does not show clear evidence of intent for either of the alleged fraudulent acts by Unigene. As noted by the district court, the record contains only an essentially "unsupported allegation" that Dr. Stern intentionally left the '014 patent off of the initial information disclosure statement of the '392 patent. *Crime-Fraud Opinion*, at 12. The second allegation of fraud rests on a similarly flimsy foundation.

In the first place, the typographical error in Table 3 of the '392 patent, corrected on reissue, does not call for the extreme remedy of piercing the attorney-client privilege. The district court found the "evidence tend[ed] to prove that this error was an honest mistake, though perhaps a careless one." *Id.* at 16. Indeed, Dr. Stern submitted a declaration during the reissue proceedings to explain the error in Table 3. Further, as the trial court found, the

error itself did not alter the arguments made by Unigene to the PTO. Accordingly, the district court concluded that the record did not show any evidence of intent to deceive the Patent Office. *Id.* at 18.

The district court did not abuse its discretion in these findings on the crime-fraud exception to the attorney-client privilege. This court need not reach the district court's materiality determinations because the record is devoid of sufficient intent evidence.

III.

This court reviews a district court's denial of a party's motion to amend its pleadings under the law of the regional circuit. *Panduit Corp. v. All States Plastic Mfg. Co.,* 744 F.2d 1564, 1575 (Fed. Cir. 1984). The United States Court of Appeals for the Second Circuit reviews a district court's denial of a request to amend pleadings for an abuse of discretion. *Parker v. Columbia Pictures Indus.*, 204 F.3d 326, 339-40 (2d Cir. 2000). Apotex appeals the court's refusal to add Counts XII, XIII, and XIV to its Answer to Unigene's Amended Complaint. Apotex does not challenge the district court's rulings with respect to the allegations of inequitable conduct asserted in its Original and First Amended Answers. The district court's decision was based on its determination that Unigene's Amended Complaint did not change the scope of the original Complaint and therefore did not provide an opportunity for Apotex to expand the breadth of its affirmative defenses or counterclaims.

The record shows that the district court acted well within its discretion in finding that Apotex's added counterclaims were not "colorable grounds for relief." *Blaskiewicz v. Cnty. of Suffolk*, 29 F. Supp. 2d 134, 138 (E.D.N.Y. 1998) (citation omitted). The trial court is especially well positioned to assess whether the Amended

Complaint it authorized materially changed the scope of the original Complaint. Counts XII, XIII, and XIV all relate to inequitable conduct. The district court found that the filing of an Amended Complaint, which merely renamed the patent in suit post-reexamination, did not so materially alter the proceedings as to authorize previously unasserted counterclaims. The district court found Count XII improper because, *inter alia*, the new claim provided inadequate notice to Unigene. The district court barred Counts XIII and XIV, which mirror Apotex's crime-fraud allegations, based on the same fatal absence of materiality and intent already addressed in the Crime-Fraud Opinion. This court agrees that the record shows insufficient evidence of fraudulent intent and erects an insurmountable obstacle to Apotex's new counterclaims. Accordingly, the district court did not abuse its discretion by denying Claims XII, XIII, and XIV.

IV.

This court reviews the district court's grant of summary judgment without deference. *Eisai Co. Ltd. v. Dr. Reddy's Labs.,* 533 F.3d 1353, 1356 (Fed. Cir. 2008). Summary judgment is appropriate if the movant can show both the absence of genuine issues of material fact and entitlement to judgment as a matter of law. Fed. R. Civ. P. 56(c). This court reviews the evidence in the light most favorable to the party opposing the motion, with all doubts resolved in favor of the nonmovant. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1360-61 (Fed. Cir. 2008).

Obviousness under 35 U.S.C. § 103(a) is a legal question based on underlying factual determinations. *Eisai*, 533 F.3d at 1356 (citing *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1478, 1479 (Fed. Cir. 1997)). An obviousness analysis measures the difference between the

claimed invention and the prior art to determine whether "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. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006) (citing *In re Kahn*, 441 F.3d 977, 985 (Fed. Cir. 2006)). The factual underpinnings, often referred to as the *Graham* factors, include 1) the scope and content of the prior art; 2) the level of ordinary skill in the art; 3) the differences between the claimed invention and the prior art; and 4) evidence of secondary factors, also known as objective indicia of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention. *Id.* at 421 (describing that a person of ordinary skill possesses "ordinary creativity, [and is] not an automaton"); *see also Bayer Schering Pharm. AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1350 (Fed. Cir. 2009) (Newman, J., dissenting) ("The statutory criterion is whether the invention would have been obvious to persons of ordinary skill at the time of the invention, not whether it is sufficiently simple to appear obvious to judges after the discovery is finally made . . . .").

A person of ordinary skill at the time of the invention interprets the prior art using common sense and appropriate perspective. *KSR*, 550 U.S. at 421. In *KSR* the Supreme Court observed:

> When there is a design need or 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. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Id. Accordingly, when design need and market pressure may dictate a commonsensical path using a finite number of identified predictable solutions to one of ordinary skill, deviations from that path are likely products of innovation.

This court has observed that teachings from prior art, suggestions beyond the literal teachings of those art references, or even motivations from the store of common knowledge of one of ordinary skill in the art field ("TSM")—flexibly viewed and applied—provide the sources of evidence that an ordinary skilled artisan might have found and combined at the time of the invention. *Ortho-McNeil*, 520 F.3d at 1364-65 ("[A] flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis . . . ."); *see also KSR*, 550 U.S. at 419 ("The obviousness analysis cannot be confined by a formalistic conception of the words, teachings, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents.").

In this case, the patent claims a new composition or formulation to deliver an FDA-approved active ingredient. Thus, the claimed invention is not obvious if a person of ordinary skill would not select and combine the prior art references to reach the claimed composition or formula-

tion. *Eli Lilly v. Zenith Goldline Pharm.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006) ("to establish a prima facie case of obviousness based on a combination of elements in the prior art, the law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention").

To render a claim obvious, prior art cannot be "vague" and must collectively, although not explicitly, guide an artisan of ordinary skill towards a particular solution. *Bayer Schering.*, 575 F.3d at 1347. Indeed, "most inventions that are obvious were also obvious to try," *id.*, and a combination is only obvious to try if a person of ordinary skill has "a good reason to pursue the known options." *KSR*, 550 U.S. at 421. When a field is "unreduced by direction of the prior art," and when prior art gives "no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful," an invention is not obvious to try. *Bayer Schering*, 575 F.3d at 1347 (citing *O'Farrell*, 853 F.2d at 903); *see also Ortho-McNeil*, 520 F.3d at 1364 (stating the number of options must be "small or easily traversed").

A prima facie case of obviousness in the chemical arts is often based on a known compound, called a "lead compound," which serves as a starting point for a person of ordinary skill developing the claimed invention. *See Eisai*, 533 F.3d at 1357. Where the patent at issue claims a chemical compound, a lead compound is often used to show structural similarities between the claimed compound and prior art. *Id.* (citing *Eli Lilly*, 471 F.3d at 1377). In the context of a composition or formulation patent where the patented formulation was made to mimic a previously FDA-approved formulation, the functional and pharmaceutical properties of the "lead compound" can be more relevant than the actual chemical structure (though not always mutually exclusive). Thus,

the term "reference composition" is more appropriate than "lead compound" when considering obviousness for a chemical composition that the infringer deliberately imitates. In this case, Miacalcin® serves as the "reference composition" for Dr. Stern's development of the claimed composition. In Miacalcin®, BZK acts as a preservative, absorption enhancer, and surfactant. Claim 19 of the '812E patent is the result of Dr. Stern's effort to design around Miacalcin®. It is undisputed that "about 20 mM citric acid" in claim 19 functions as an absorption enhancer and surfactant in Fortical®.

Although claim 19 does not assign any particular functionality or property to its list of components, a person of ordinary skill, someone in the field of pharmaceutical liquid dosage form development, would have had reasons—specifically, design need and market demand—to create an FDA-approved liquid nasal composition that delivers salmon calcitonin. *See KSR*, 550 U.S. at 421. In this case, the design need is to achieve a bioequivalent composition. The market demand is to achieve a composition that treats the same symptoms as the reference formulation. Specifically, on February 4, 2000, someone developing a pharmaceutical nasal liquid dosage form with the active ingredient of salmon calcitonin would have known that a bioequivalent of Miacalcin®, largely determined by equivalent bioavailability of salmon calcitonin, would have the best chance to gain FDA approval quickly. *See* 21 § C.F.R. 320.23(b) ("Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions . . . ."); *id.* ("Bioavailability means the rate and extent to which the active ingredient or active moiety

is absorbed from a drug product and becomes available at the site of action."). Creating a bioequivalent of Miacalin® would allow approval of the new pharmaceutical liquid dosage form as an ANDA under 21 U.S.C. § 355(j)(2)(A)(vii) or an NDA under 21 U.S.C. § 505(b)(2)—both enjoying the additional advantage of using the clinical data or literature submitted in support of Miacalcin®. Alternatively, a composition requiring full clinical trials to demonstrate safety and effectiveness would require approval as an NDA under 35 U.S.C. § 505(b)(1), a significantly longer process. This court appreciates that the Hatch-Waxman Act encourages and rewards replication of protected compounds in some circumstances—an activity that rarely, but can, lead to innovative products.

While claim 19 contains several excipients in addition to salmon calcitonin, at oral argument, Unigene acknowledged that "citric acid is a very important part" of claim 19's case for inventiveness and nonobviousness. Oral Argument at 21:48-22:00, available at *http://www.cafc.uscourts.gov/oral-argument-recordings/2010-1006/all*. While the district court found other elements in combination were also nonobvious, this court agrees that the inclusion of "about 20 mM citric acid" in the composition provides the strongest case for nonobviousness.

Apotex asserted for the first time at oral argument that claim 19 is obvious in light of three pieces of prior art: Miacalcin®, the Day reference, and the '014 patent. *Id.* at 4:50. As discussed above, Miacalcin® serves as the reference composition.

On the basis of the record before this court, this court agrees that no reasonable juror could conclude that the '014 patent would give a person of ordinary skill sufficient reason or motivation to use about 20 mM citric acid in a

liquid nasal salmon calcitonin composition. *See KSR*, 550 U.S. at 421. The '014 patent claims a solid oral dosage of salmon calcitonin, not a liquid formulation. While the experiments discussed in the '014 patent found that "the bioavailability of salmon calcitonin increased nearly 10 fold when the amount of citric acid in the formulation was increased only 5 fold," '014 patent col.11 ll.33-35, a person of ordinary skill (not Dr. Stern, a co-inventor of the '014 patent) would not glean from the '014 results a reason to use about 20 mM citric acid in a nasal calcitonin formulation. The '014 patent itself describes a solid oral formulation of salmon calcitonin. Although the '014 patent mentions citric acid, that discussion refers to concentrations of citric acid much higher than those in claim 19. Moreover, the '014 patent examined citric acid for bioavailability in the context of a liquid injection into a rat duodenum, not a human use in a liquid pharmaceutical formulation. These significant differences would not cause a person of ordinary skill to replace BZK in Miacalcin® with 20 mM of citric acid in the normal course of research and development.

To a person of ordinary skill in the art, citric acid, even at about 20 mM concentrations, would not be an obvious substitute for BZK's functions as an absorption enhancer and as a surfactant because citric acid has a vague role in even the closest prior art. *See Eli Lilly*, 471 F.3d at 1380. U.S. Patent No. 5,124,315 ("'315 patent") describes liquid pharmaceutical compositions for nasal administration containing a polypeptide as an active ingredient. Example 5 of the '315 patent uses 20.5 mM of citric acid in a liquid nasal formulation containing salmon calcitonin as its active ingredient. '315 patent col.3 l.43. The '315 patent makes clear however that "citric acid was not used as an absorption enhancing agent, but it is

merely the acidic component of the buffer." *Id.* at col.4 ll.18-23.

In fact, the '315 patent teaches away from using about 20 mM citric acid as an absorption enhancing agent or stabilizing agent in a liquid formulation with a salmon calcitonin active ingredient. The '315 patent discusses U.S. Patent No. 4,476,116 ("'116 patent"), directed toward nasal compositions having enhanced peptide absorption. The '116 patent lists over fifty examples, including citric acid, of pharmaceutically acceptable chelating agents to serve as absorption agents. '116 patent col.11 l.1. Both parties agree that the '315 patent reports that the compounds listed in the '116 patent yielded "discouraging" test results, and that "only ammonium tartrate is a satisfactory stabilizing agent for liquid nasal compositions containing polypeptides as active ingredient [sic]." '315 patent col.2 ll.13-16, 19-21. One of ordinary skill in the art reading the '315 and '116 patents would have considered about 20 mM citric acid undesirable in a liquid nasal formulation containing salmon calcitonin.

The Day reference, a publication about pharmaceutical preformulation and formulation, lists benzyl alcohol and phenylethyl alcohol as two of nine listed preservatives on a table of "Excipients used in aqueous nasal products." J.A. at 11397. BZK is one of the nine listed preservatives in Day, along with benzethonium chloride, chlorobutanol, methylparaben, phenylmercuric acetate, propylparaben, and thimerosal. Citric acid is not included in the list of preservatives, but appears instead as a pH adjuster or buffer. The Day reference also lists polysorbate 20 and 80 as one of three surfactants used as excipients in aqueous nasal products. With reference to this prior art, there is no evidence to support the conclusion that a person of ordinary skill would expect a combination of citric acid, benzyl alcohol, phenylethyl alcohol, and

polysorbate 80 to contain a buffer, pH adjuster, preservative, and surfactant, but no absorption enhancer or excipient to promote bioavailability.

Thus, the "about 20.0 mM citric acid" limitation alone supports the district court's grant of summary judgment of nonobviousness. When used as an absorption enhancer in the '116 patent, citric acid was one of over fifty options. *See KSR*, 550 U.S. at 421. Further, when the prior art used citric acid at about 20 mM, as in the '315 patent, it was used only as a buffer. There is no genuine dispute of material fact that a person of ordinary skill attempting to make a liquid composition to deliver salmon calcitonin into a human body through nasal administration, would not have considered using about 20 mM citric acid with the narrowly claimed amounts of benzyl alcohol, phenylethyl alcohol, and polysorbate 80, because the formulation would not be expected to perform properly to meet the specificity of a pharmaceutical use. Thus, even accepting that there was a design need and market pressure to develop a pharmaceutical formulation that is bioequivalent to Miacalcin®, there is no evidence in the record that claim 19 would be an obvious solution to those motivations.

V.

Accordingly, this court affirms the district court's grant of summary judgment of nonobviousness in favor of Unigene, affirms the district court's denial of summary judgment of obviousness, affirms the district court's denial of Apotex's crime-fraud motion, and affirms the district court's dismissal of Apotex's new claims and defenses.

AFFIRMED

Each party shall bear its own costs.