UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF FLORIDA

Case No. 10-20526-CIV-MORENO

VALEANT INTERNATIONAL (BARBADOS) SRL,

Plaintiff,

vs.

WATSON PHARMACEUTICALS, INC., WATSON LABORATORIES, INC.—FLORIDA, and WATSON PHARMA, INC.

Defendants.

MEMORANDUM OPINION

This action was filed by Valeant International (Barbados) SRL ("Valeant") against Watson Pharmaceuticals, Inc., Watson Laboratories, Inc.—Florida, and Watson Pharma, Inc. (collectively, "Watson"), alleging patent infringement. Valeant is the owner of several patents related to the drug known as Aplenzin®. Watson seeks to market the generic equivalent of that drug. Watson has conceded infringement but asserts as an affirmative defense that Valeant's asserted patents are invalid.

Aplenzin® is an antidepressant that contains bupropion hydrobromide as the active ingredient. Valeant owns four patents related to Aplenzin®: U.S. Patent Nos. 7,569,610, 7,563,823, 7,649,019, and 7,553,992 (collectively, "the patents-in-suit"). Each of the patents-in-suit contains several claims. In order to streamline the issues for trial, the parties agreed to try this case only with respect to five representative claims in the patents, with the resolution of the issues concerning those claims being dispositive as to all of the previously asserted claims as

between the parties. The representative claims of the patents-in-suit are: (1) Claim 3 of the '610 patent; (2) Claim 9 of the '823 patent; (3) Claim 10 of the '823 patent; (4) Claim 2 of the '019 patent; and (5) Claim 1 of the '992 patent. The representative claims relate to controlled release and once-a-day formulations of bupropion hydrobromide, methods of treating depression with those formulations, and a specific crystalline form of bupropion hydrobromide.

The Court has jurisdiction over the parties and the subject matter pursuant to 28 U.S.C. § 1338(a). Additionally, venue is appropriate under 28 U.S.C. §§ 1391 and 1400(b). Neither jurisdiction nor venue is contested by the parties. The Court conducted a bench trial from June 21, 2011 to June 28, 2011. This Memorandum Opinion constitutes the Court's findings of fact and conclusions of law on the issues raised during trial. Ultimately, the Court finds that Watson has failed to prove by clear and convincing evidence that Valeant's asserted patent claims are invalid, and accordingly, grants judgment in favor of Valeant.

I. Background

Bupropion was invented by Nariman Mehta in 1969 as a method of treating depression and was subsequently patented by Mehta in 1974 in U.S. Patent No. 3,819,706 (the "Mehta patent"). (Def. Ex. 135.) While the Mehta patent mentions a number of bupropion salts, it does not specifically mention bupropion hydrobromide. (Pl. Ex. 96 ¶¶53-54; Trial Tr. 437:25-438:11.) Bupropion has been sold since the 1980s as the bupropion hydrochloride salt, under the brand name Wellbutrin®. (Pl. Ex. 98 ¶18; Def. Ex. 602 at 10.) Today, both branded and generic versions of bupropion hydrochloride are on the market, including generic versions sold by Watson. (Pl. Ex. 94 at 86.)

Since the early 1980s, however, it was known that bupropion hydrochloride had stability problems when combined with pharmaceutical excipients. (Def. Ex. 128 at 20556-57; Def. Ex.

602 at 18-19.) Between 1984 and 2004 many attempts were made to improve the stability of bupropion hydrochloride formulations. (Trial Tr. 66:18-68:25; 301:10-303:16; Pl. Ex. 94 at 38.) One of the first such attempts was a 1984 patent application by Billinghurst where he tested several different bupropion salts to see if any had improved stability relative to the hydrochloride salt. (Def. Ex. 128; Pl. Ex. 94 at 38; Def. Ex. 379 at 40832.) Among the salts Billinghurst tested were a number of mineral acids[1], all of which were found to be unstable. (Trial Tr. 473:22-474:11.) As was the case in the Mehta patent, the hydrobromide salt was neither mentioned nor tested. (Trial Tr. 66:18-67:15.) Only the maleate salt, which is an organic carboxylic acid salt, was found to have improved stability. (Def. Ex. 602 at 18-19; Trial Tr. 434:21-436:10.) Due to toxicology concerns, however, it could never be formulated into a commercial product. (Def. Ex. 128 at 20557; Trial Tr. 435:10-23; Maes Dep. 130:20-131:24.) During the twenty years following Billinghurst's failed attempt to find an alternative salt with improved stability over bupropion hydrochloride, no new efforts were made to find a different bupropion salt; instead, other means were explored to improve stability of bupropion hydrochloride formulations, several of which were subsequently patented. (Trial Tr. 66:18-68:25; Def. Ex. 602 at 18-19.)

Despite the various attempts to improve the stability of bupropion hydrochloride formulations, the shelf life of commercial bupropion hydrochloride tablets has remained short, with once-a-day formulations having never achieved a shelf life longer than eighteen months. (Trial Tr. 299:23-300:4.) Thus, in 2003, Valeant (then Biovail) set out to address the longstanding stability issues with bupropion hydrochloride formulations. (Trial Tr. 298:20-299:20; 303:17-22; 380:16-21.) While Valeant tried a number of different approaches, it ultimately decided to revisit what Billinghurst had attempted but failed to discover in 1984—a

[1] Hydrochloride, hydrobromide, sulfates, and phosphates are all examples of mineral acid salts.

new bupropion salt that could be formulated into a commercial product with an extended shelf life. (Trial Tr. 303:14-22.) The goal of this new salt project was to extend the shelf life of Wellbutrin® without negatively impacting any of its other properties. (Trial Tr. 307:5-8.)

The first step in the project was to figure out what salts of bupropion could even be made. (Maes Dep. Tr. 64:15-16.) Because Valeant was not specialized in manufacturing new salts, it sought the assistance of an Italian chemical company known as Chemi S.p.A. ("Chemi"). (Maes Dep. Tr. 64:15-65:6.) Valeant and Chemi spent several months attempting to make new salts, many of which failed to result in a testable product. (Def. Ex. 95; Def. Ex. 98.) Their selection of salts was largely an empirical process, because it was difficult to predict exactly which salt would be the best. (Maes Dep. 84:2-6; 170:23-171:13.)

In 2004 the inventors from Valeant and Chemi made bupropion hydrobromide. They discovered that bupropion hydrobromide exists in many forms, both amorphous and crystalline. (Def. Ex. 604 at 10; Pl. Ex. 96 at 15; Trial Tr. 643:16-25; 671:2-15.) Among these forms was the very stable crystalline compound—Form I bupropion hydrobromide—covered by Claim 1 of the '992 patent. (Trial Tr. 224:16-225:8.) The inventors also tested bupropion hydrobromide and discovered that bupropion hydrobromide in a controlled-release formulation produces a much more stable product relative to corresponding bupropion hydrochloride formulations. (Trial Tr. 311:18-312:8; Pl. Ex. 95 at 015319, 154331.) They also discovered that bupropion hydrobromide once-a-day tablets can be formulated at all the recommended daily dosages, even the highest dosage, which had never been accomplished with bupropion hydrochloride. (Trial Tr. 312:25-316:13; Pl. Ex. 98 ¶34.)

As a result of this research project, Valeant was able to develop Aplenzin®, a once-a-day bupropion hydrobromide tablet covered by the patents-in-suit. The effective filing date of the

patents-in-suit is June 27, 2005. Valeant launched Aplenzin® in April 2009. Less than a year later Watson sought FDA approval to market a generic version of Aplenzin®, which Watson has conceded infringes the patents-in-suit. Therefore, the sole issue for trial was whether each of the asserted claims in the four patents-in-suit is invalid.

II. Discussion

"A patent shall be presumed valid." 35 U.S.C. § 282. By statute, the patents-in-suit "have a strong presumption of validity in infringement proceedings." *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999). This presumption of validity applies independently to each claim within a patent, even if other claims within the patent are held invalid. 35 U.S.C. § 282. Accordingly, Watson must prove invalidity for each asserted claim.

To overcome the presumption of validity, the challenger has the burden of proving by clear and convincing evidence that the patent is invalid. *Microsoft Corp. v. i4i Ltd. Partnership*, 131 S. Ct. 2238, 2242 (2011). Clear and convincing evidence is evidence that places in the fact finder "an abiding conviction that the truth of [the] factual contentions [is] highly probable." *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984) (internal quotations omitted). "[I]f the fact trier of the issue is left uncertain, the party with the burden loses." *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008). This burden "is constant and remains throughout the suit on the challenger" and "does not shift at any time to the patent owner." *TP Labs., Inc. v. Prof'l Positioners, Inc.*, 724 F.2d 965, 971 (Fed. Cir. 1984). Moreover, when the Patent Office has considered the prior art during prosecution of the patents, the burden on the challenger to establish invalidity is even heavier. *Glaxo Ltd. v. Apotex, Inc.*, 376 F.3d 1339,

1348 (Fed. Cir. 2004); *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 468 F.3d 1366, 1378 (Fed. Cir. 2006).

Here, Watson challenges the validity of the five representative patent claims on the basis that they are (1) anticipated by the prior art; and/or (2) obvious in view of the prior art. The Court will address each argument in turn.

A. Anticipation

Watson contends that Claim 3 of the '610 patent and Claim 1 of the '992 patent are invalid for anticipation under 35 U.S.C. § 102(b).[2] Generally speaking, "Anticipation means that the claimed invention was previously known, and that all of the elements and limitations of the claims are described in a single prior art reference." *Hakim v. Cannon Avent Group, PLC*, 479 F.3d 1313, 1319 (Fed. Cir. 2007); *see also Sanofi*, 470 F.3d at 1375 ("[Anticipation] requires a finding that 'each and every limitation is found either expressly or inherently in a single prior art reference.'") (quoting *Celeritas Techs. Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed.Cir.1998). Anticipation is a question of fact. *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006).

For a prior art reference to anticipate a claimed invention, the reference "must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements arranged as in the claim." *Net MoneyIN, Inc. v. Verisign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (internal quotations omitted). "[T]he reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without *any* need for picking, choosing, and combining various disclosures not directly related to

[2] Claim 3 of the '610 patent is directed to an improved method of treating depression using a once-a-day bupropion hydrobromide dosage form. Claim 1 of the '992 patent is directed to a specific and highly stable crystalline compound of bupropion hydrobromide—Form I bupropion hydrobromide.

each other by the teachings of the cited reference." *In re Arkley*, 59 C.C.P.A. 804, 455 F.2d 586, 587 (C.C.P.A. 1972). Any difference between the prior art reference and the claimed invention, no matter how slight, defeats an anticipation challenge to validity. *NetMoneyIN*, 545 F.3d at 1371. As explained by the Federal Circuit in *Net MoneyIN*:

> Thus, it is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention.

Id. In other words, elements of a claim that are not present in the single piece of prior art on which the anticipation defense is based may not be supplied by the knowledge of one skilled in the art or the disclosure of another reference. *See Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984); *see also Eli Lilly and Co. v. Sicor Pharms., Inc.*, 705 F. Supp. 2d 971, 992 (S.D. Ind. 2010) ("In showing that all elements of an invention were anticipated, the challenging party may not rely upon the knowledge of one skilled in the art or the disclosure of another reference to supply missing elements.").

Here, Watson asserts that Claim 3 of the '610 patent and Claim 1 of the '992 patent are anticipated by the 1974 Mehta patent. (Def. Ex. 135.) The Court finds that Watson has not met the exacting standard for anticipation with respect to either claim.

1. Claim 3 of the '610 patent is not anticipated

Claim 3 of the '610 patent is a dependant claim which incorporates by reference the elements of Claim 1 of the '610 patent. When the two claims are integrated Claim 3 reads as follows:

> A method of treating depression, comprising administering an effective amount of bupropion hydrobromide in a once-daily dosage to treat depression to a subject in need thereof.

(Def. Ex. 003 at 786051.) Thus, Claim 3 requires that the bupropion hydrobromide comprise a once-daily dosage form. Yet it is undisputed that the Mehta patent contains no disclosure of any once-daily dosage form. (Def. Ex. 135.) Indeed, Watson has admitted as such in its post-trial filings. (Dkt. No. 141 at 6.) This alone precludes a finding that Claim 3 of the '610 patent is anticipated by the Mehta patent, as the claimed invention must be *identically* disclosed in the cited prior art reference. *NetMoneyIN*, 545 F.3d at 1371.

Watson argues that Claim 3 is nevertheless anticipated because once-daily dosing of bupropion was well known in the prior art by 2004 and thus would "immediately have been envisaged by a person of ordinary skill in the art in 2004 reading the Mehta '706 patent." (Dkt. No. 141 at 5.) This argument, however, is exactly the kind of argument that has been rejected by the Federal Circuit. *See, e.g., Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984); *NetMoneyIN*, 545 F.3d at 1371. Thus, the Mehta patent does not anticipate claim 3 of the '610 patent.

2. Claim 1 of the '992 patent is not inherently anticpated

B. Obviousness

Watson also contends that Claims 9 and 10 of the '823 patent, Claim 2 of the '019 patent, and Claim 3 of the '610 patent are invalid for obviousness.[3] A patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §

[3] The asserted claims of the '823 and '019 patents relate to combining bupropion hydrobromide with pharmaceutical excipients to produce controlled release and once-a-day bupropion hydrobromide formulations. Claim 3 of the '610 patent relates to use of these formulations to treat depression.

103(a). "Obviousness is a question of law based on underlying facts." *Group One, Ltd. v. Hallmark Cards, Inc.*, 407 F.3d 1297, 1303 (Fed. Cir. 2005). Obviousness is determined with respect to the subject matter as a whole, not separate pieces of the claim. *Sanofi-Syntehelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008).

1. Legal Standard

To establish a prima facie case of obviousness, the party challenging the patent must prove by clear and convincing evidence that a person of ordinary skill in the art would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that said artisan would have had a reasonable expectation of success in doing so. *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). Underpinning this legal inquiry are four groups of factual findings: (a) the scope and content of the prior art; (b) the level of ordinary skill in the art; (c) the differences between the claimed subject matter and the prior art; and (d) secondary considerations of non-obviousness, such as commercial success, long-felt but unsolved needs, and failure of others.[4] *DyStarTextilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006); *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). "If a patent challenger makes a prima facie showing of obviousness, the owner may rebut based on 'unexpected results' by demonstrating 'that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have

[4] The Court notes that many of these facts are not disputed by the parties here. For instance, the parties do not dispute whether any of the cited references constitutes prior art and do not dispute that all prior art in this case existed as of June 27, 2004 (i.e. the "critical date," or one year before the patent applications at issue were submitted). In addition, the parties' experts offer substantially similar definitions of a person of ordinary skill in the art. Therefore, the Court finds that a person of ordinary skill in the art has either a graduate degree in pharmaceutical science or a related discipline with at least two years of experience in pharmaceutical development or physical chemistry, or alternatively possesses a bachelor's degree in one (or more) of the same fields with at least five years of experience in pharmaceutical development or physical chemistry.

found surprising or unexpected.'" *Procter & Gamble Co.*, 566 F.3d at 994 (quoting *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

In *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 407 (2007), the Supreme Court rejected a rigid application of the teaching, suggestion, or motivation test, and reaffirmed that the *Graham* factors "continue to define the inquiry that controls" an obviousness analysis. Nevertheless, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." Therefore, "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). In addition, the *KSR* Court held that an invention may be found obvious if it would have been "obvious to try." *KSR*, 550 U.S. at 421. A patent claim is obvious to try if "there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions" and pursuit of those solutions "leads to the anticipated success." *Id.*

Thus, since *KSR*, the Federal Circuit has emphasized that "predictability is the touchstone of obviousness." *DePuy Spine, Inc. v. Medtronic Sofamar Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009). "[T]he 'predictable result' discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose." *Id.* (internal citation omitted). In the instant case, the intended purpose of the claimed inventions was to create a bupropion formulation with improved stability over the prior art bupropion hydrochloride formulations. Therefore, for Watson to establish that the asserted patent claims are obvious, Watson must prove by clear and

convincing evidence that an ordinarily skilled artisan in 2004 would have been motivated to combine the prior art references to achieve the claimed inventions—in this case a controlled release or once-a-day bupropion hydrobromide formulation—and that said artisan would have had a reasonable expectation that a bupropion hydrobromide formulation would achieve the anticipated success—in this case greater stability over bupropion hydrochloride formulations.

2. Watson has not established a prima facie case of obviousness

Taking into account the *Graham* factors, the Court finds that Watson has not made the required showing. Specifically, Watson has not proved by clear and convincing evidence that a person of ordinary skill in the art in 2004 would have had a reasonable expectation that changing the salt in a bupropion formulation from hydrochloride to hydrobromide would result in increased stability.

As a general rule, salt selection is an unpredictable art. Numerous prior art references produced at trial support this principle. (*See* Def. Ex. 132 at 20550 ("Berge") (Selecting a salt form that exhibits the desired combination of properties is a difficult semiempirical choice.); Def. Ex. 173 at 20737 ("Gould") (same); Def. Ex. 166 at 3683048 ("Bighley") (same); Def. Ex. 345 at 740703 ("Davies") ("There is yet, no reliable way of predicting exactly what effect changing the salt form . . . will have on its biological activity . . . ."); Def. Ex. 383 at 79314 ("Verbeek") ("Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound."); Pl. Ex. 82 at 1 ("Black") ("[T]he ability to predict which salt forms will have desirable properties is essentially nonexistent.").)

Watson has not cited to any witness testimony or prior art that contradicts this general rule, and while Watson has cited several prior art references that refer to bupropion-related compounds, none with the exception of Billinghurst address the issue of stability. Thus, Watson relies on the

testimony of its pharmaceutics expert, Dr. Graham Buckton. At trial Dr. Buckton testified that the prior art suggested moving to a bupropion hydrobromide formulation as a way to solve the known stability problems with bupropion hydrobromide formulations. Dr. Buckton cited several prior art references in support of this conclusion.

The first is a 1986 publication by Philip L. Gould titled, "Salt Selection of Basic Drugs" ("Gould"). (Def. Ex. 173). Gould contains a chart with three suggestions for improving the stability of a salt. (Def. Ex. 173 at 20747.) Gould's first suggestion is to reduce hygroscopicity by increasing the acid's hydrophobicity and using a carboxylic acid instead of a sulphonic or mineral acid. It is undisputed, however, that hydrobromide is a mineral acid salt, not a carboxylic acid salt, so this teaching may have actually directed one away from the hydrobromide. (Trial Tr. 442:18-443:10.)

Gould's second suggestion for improving stability is to use an acid with a higher pKa to reduce the acidity of the acqueous solution. It is undisputed, however, that hydrobromic acid is one of the few acids with a *lower* pKa than hydrochloric acid (and would thus increase acidity), so this teaching may also have directed one away from the hydrobromide. (Pl. Ex. 103 at 103.349; Trial Tr. 443:16-444:13.)

Gould's third suggestion is to raise the melting point of the salt. As one of three possibilities for doing so he suggests choosing a small counter ion, listing the chloride and the bromide as examples. In a 2003 version of the same chart reproduced by P. Heinrich Stahl, however, the bromide ion is no longer referenced as an example of a "small counter ion." (Def. Ex. 130 at 20598.) At trial Dr. Buckton could offer no explanation for the subsequent omission of the bromide ion from the Gould chart, nor did he explain why he chose to rely on the outdated

1986 version of the Gould chart, rather than the 2003 Stahl version that was contemporaneous with the time of the invention. (Trial Tr. 74:19-76:17.)

In addition, Gould's suggestion to raise the melting point of the salt would not lead to the selection of a hydrobromide as a means to improve the stability of a hydrochloride salt, because the relative melting points of chlorides and bromides are not possible to predict. For example, lithium bromide and sodium bromide have lower melting points than their chloride containing counterparts; conversely, ammonium bromide has a higher melting point than ammonium chloride. Moreover, bupropion hydrobromide actually has a *lower* melting point than bupropion hydrochloride. (Pl. Ex. 94 at 13.)

Thus, none of the suggestions in Gould would have led an ordinarily skilled artisan in 2004 to reasonably expect that switching from a hydrochloride to a hydrobromide would improve salt stability. In fact, Gould's suggestions may have actually led one away from choosing a hydrobromide to solve the known stability problem with bupropion hydrochloride.

The second prior art reference cited by Dr. Buckton is a 1996 publication by Lyle D. Bighley titled, "Salt Forms of Drugs and Absorption" ("Bighley"). (Def. Ex. 166.) Although Bighley teaches that salt selection is a difficult choice (Def. Ex. 166 at 3683048), Dr. Buckton cited Bighley at trial as purportedly containing a reason to select bupropion hydrobromide to improve stability of bupropion hydrochloride formulations. (Trial Tr. 99:3-25.) In particular, Dr. Buckton pointed to the following statement under the heading Preparation of Other Mineral Acids: "Mineral acids other than hydrochloric, such as sulfuric, phosphoric, and hydrobromic, have been employed principally to reduce hygroscopicity and perhaps the acidity of a resulting solution." (Def. Ex. 166 at 3683080.)

This section, however, contains no discussion of stability. Rather, stability is addressed in the following section, and while that section mentions several possible options to improve stability, using a hydrobromide salt is not one of them. (Def. Ex. 166 at 3683080.) Furthermore, given that Billinghurst had already tested a number of bupropion mineral acids, albeit not the hydrobromide, and found all of them to be unstable, Bighley's statement about reducing hygroscopicity by using other mineral acids would provide little guidance to an ordinarily skilled artisan in 2004 looking to solve the known stability problems with bupropion hydrochloride.

Moreover, the relative hygroscopicity of chlorides and bromides is not predictable. In some cases bromides are more hygroscopic than chlorides; in other cases chlorides are more hygroscopic than bromides; and in still other cases, they are comparable. For example, potassium bromide is more hygroscopic than potassium chloride, while on the other hand lithium bromide is more hygroscopic than lithium chloride. (Def. Ex. 94 at 12.) And in the Harding and Bastin references cited by Dr. Buckton (and discussed more thoroughly below), hydrobromides and hydrochlorides are shown to be comparable, not different, in terms of hygroscopicity. (Trial Tr. 78:21- 81:21.)

Bighley also provides a decision tree to guide formulators in selecting a suitable salt. (Def. Ex. 166 at 3683076.) The decision tree indicates that if chemical instability is encountered in a mineral acid salt—a category to which hydrochloride and hydrobromide belong—the path to follow is to make an organic salt, not to try another mineral acid salt. (Pl. Ex. 94 at 15-16; Trial Tr. 446:23-447:24.) In fact, Bighley teaches that mineral acid salts produce a *more* hostile environment and tend to be *less* stable than a sulfonate or carboxylate salt. (Def. Ex. 166 at 3683062, 3683067.) This is consistent with Gould's teaching that instability due to hygroscopicity should be addressed by trying a carboxylic acid (an organic acid). (Def. Ex. 173

at 20747.) Thus, nothing in Bighley suggests that a hydrobromide formulation would be reasonably expected to improve the stability of a hydrochloride formulation.

Dr. Buckton also cited to a 2000 publication by Richard J. Bastin, but this prior art offers no guidance on how to improve the stability of a hydrochloride salt, let alone bupropion hydrochloride. (Def. Ex. 176.) The final prior art reference cited by Dr. Buckton as suggesting to try bupropion hydrobromide to solve the known stability problems with bupropion hydrochloride is U.S. Patent No. 6,110,940, filed May 17, 1995 (the "Harding patent"). (Def. Ex. 138.) In his expert report, Dr. Buckton cited Harding for its purported teaching that a hydrobromide salt of an indole compound was stable while the hydrochloride salt supposedly was not. (Def. Ex. 602 at 31.) At trial, however, Dr. Buckton was forced to concede that the Harding patent in fact taught that the indole hydrochloride salt was stable. (Trial Tr. 78:21-82:8.) In an effort to explain this apparent inconsistency, Dr. Buckton admitted that it is not possible to predict the stability of bupropion hydrobromide based on information about the stability of different drugs. (Trial Tr. 81:25-82:22.)

Dr. Buckton thus confirmed that one cannot predict how the stability of bupropion formulations will be affected by a change in salt based on teachings about the corresponding salts of other drugs. That admission is consistent with the many prior art references that teach that salt selection is inherently unpredictable and, in particular, with the statement made in the Davies reference: "There is, as yet, no reliable way of predicting exactly what effect changing the salt form of an active drug will have on its biological activity, and the supposition that the same salt form of two related parent compounds will behave in exactly the same way may not be correct." (Def. Ex. 345 at 740703.)

Watson has cited to no other prior art references suggesting that switching the salt from hydrochloride to hydrobromide would result in a more stable bupropion formulation. Watson attempts to overcome this important deficiency by arguing that obviousness can be based on the availability of high-throughput screening as a means to rapidly create and test many salts at once. At trial, Dr. Buckton testified that given the availability of these high-throughput screens in 2004, a person or ordinary skill in the art would have included bupropion hydrobromide in a screen for alternate salt to solve the stability problems with bupropion hydrochloride. (Trial Tr. 89:6-13.)

High-throughput screening, however, does not identify which salts, if any, are suitable for a particular purpose; rather, it simply identifies which salts can be formed. After screening, one would still have to run numerous tests on the resulting salts to determine their individual properties. (Trial Tr. 409:18-410:5; Def. Ex. 602 at 15; Maes Dep. 170:23-171:13.) As Dr. Anderson testified, even if one used high-throughput screening, which Valeant did not use in its development of bupropion hydrobromide, one would simply be left with "a bunch of salts . . . . You then have to study them, and there's a lot of work there." (Trial Tr. 409:18-410:5.) So while high-throughput screening would have allowed one to create and test many salts at once, it would not have allowed one to reasonably predict the individual properties of the resulting salts in advance.

It is for this reason that the Federal Circuit has rejected the argument that obviousness can be based on the availability of after-the-fact testing. *See Sanofi*, 550 F.3d at 1087 (rejecting argument that a claimed compound may be found obvious if one skilled in the art could have produced the claimed compound and then done routine testing to assess whether it had the desired properties and instead requiring that obviousness be assessed based on what was

predicted about the properties in advance of testing). Indeed, because predictability is the touchstone of obviousness, the obviousness analysis must focus on whether—based on the prior art—the favorable properties of the claimed invention could be reasonably predicted in advance of any testing. *See id.* Therefore, the availability of high-throughput screening is simply not probative of the issue of obviousness.

It is for these same reasons that Watson's argument based on the alleged popularity of hydrobromides in 2004 must also fail. A salt may be popular for many reasons, so the fact that hydrobromide may have been the third most commonly used salt in 2004—without explaining *why* it was so prevalent—is simply not probative as to whether a bupropion hydrobromide formulation would have been reasonably expected to improve the stability of bupropion hydrochloride formulations.

Accordingly, the Court finds that Watson has not proved by clear and convincing evidence that an ordinarily skilled artisan in 2004 would have reasonably expected a bupropion hydrobromide formulation to have improved stability over the bupropion hydrochloride formulations. Thus, Watson has not established a prima facie case of obviousness.

3. Secondary considerations support a finding of non-obviousness

Even assuming, *arguendo*, that Watson has established a prima facie case of obviousness, the Court finds that Valeant has introduced sufficient evidence of unexpected results to rebut such a showing. The evidence adduced at trial demonstrated that Valeant's claimed inventions have significant unexpected advantages over the bupropion hydrochloride formulations, including a longer (doubled) shelf life, reduced risk of seizures, the ability to formulate a single tablet at all dosage strengths (including the highest dosage), improved resistance to dose dumping, and easier manufacturability due to reduced corrosivity. (Trial Tr. 310:16-322:13.)

Watson argues that Valeant has failed to demonstrate the required nexus between these unexpected results and the asserted patent claims. The Court finds this argument to be without merit. A nexus does not require that a claim expressly recite the advantages of the patented invention; it is enough that they flow directly from the invention. *See Preemption Devices, Inc. v. Minnesota Mining & Mfg. Co.*, 732 F.2d 903, 907 (Fed. Cir. 1984) ("'[S]ales pitch features . . . do not properly belong in claims, the sole function of which is to point out distinctly . . . [the] composition of matter which is patented, not its advantages. It is entirely proper, nevertheless, in evaluating non-obviousness, for a court to take into account advantages flowing directly from the invention patented.") (internal quotations omitted). Here, the unexpected results flow directly from the patented inventions, all of which relate to the novel combination of bupropion hydrobromide and pharmaceutical excipients to provide controlled release and once-a-day formulations of bupropion hydrobromide. Thus, there is a nexus between the unexpected advantages and the asserted patent claims.

In addition, other secondary considerations support a finding of non-obviousness. In particular, the repeated failure of others during the twenty years following Billinghurst to solve the known stability problems with bupropion hydrochloride suggests that the claimed inventions would not have been obvious. *See Advanced Displays Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000); *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopedics, Inc.*, 976 F.2d at 1574-75 (reasoning that competitors' failure to develop the patented invention suggested non-obviousness). Furthermore, the fact that three other companies, including Watson, have copied Aplenzin despite the availability of bupropion hydrochloride supports a finding of non-obviousness. *See Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 991 (Fed.

Cir. 1988) ("Copying the claimed invention, rather than one in the public domain, is indicative of unobviousness.").

4. The Pfizer *case is distinguishable*

At the center of Watson's obviousness challenge is its argument that this case is controlled by *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007). The patent examiner was made expressly aware of the *Pfizer* case during prosecution of the patents in suit, however, and concluded that the facts of *Pfizer* were very different from the facts in this case and therefore irrelevant to the present proceedings. (Def. Ex. 80 at 000783.) The Court agrees.

In *Pfizer* the asserted patent claims all related to amlodopine besylate, which was created to solve the known stability problems with amlodopine maleate. *Id.* at 1353-54. The Federal Circuit found the claims to be obvious in view of the "particularized facts" of the case. *Id.* at 1367-68. Saliently, in *Pfizer* the court found that numerous prior art teachings specifically indicated that switching to the besylate salt would result in improved stability over the maleate salt. *Id.* at 1362-64. Here, however, as discussed above, Watson has offered no similar teachings suggesting that switching from the hydrochloride salt to the hydrobromide salt would result in a more stable bupropion formulation. Thus, for this and several other reasons the Court need not discuss, *Pfizer* is distinguishable and does not control here.

Accordingly, reviewing the evidence adduced at trial in light of the *Graham* factors, the Court concludes that Watson has not established by clear and convincing evidence that Valeant's claimed asserted patent claims are invalid for obviousness.

III. Conclusion

For the reasons discussed above, the Court finds that Watson has failed to prove by clear and convincing evidence that Valeant's asserted patent claims are invalid. Accordingly, the Court will enter judgment in favor of Valeant and against Watson on Valeant's claims of infringement.

DONE AND ORDERED in Chambers at Miami, Florida, this 7th day of November, 2011.

FEDERICO A. MORENO
CHIEF UNITED STATES DISTRICT JUDGE

Copies Provided To:
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