UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

SANOFI-SYNTHELABO; SANOFI-SYNTHELABO, INC.; and BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,	:	02 Civ. 2255 (SHS)
Plaintiffs,	:	OPINION & ORDER
-against-	:	
APOTEX INC. and APOTEX CORP.,	:	
Defendants.	:	

SIDNEY H. STEIN, U.S. District Judge.

After trial on the merits, this Court finds that Apotex, Inc. and Apotex Corporation (collectively, "Apotex") have failed to prove by clear and convincing evidence that U.S. Patent No. 4,847,265 is invalid or unenforceable on any of the grounds asserted. Accordingly, Sanofi-Aventis, Sanofi-Synthelabo, Inc. and Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership (collectively, "Sanofi") are entitled to permanent injunctive relief and, as shall be determined by the Court in a future proceeding, damages.

This action concerns a patent dispute between Sanofi – which invested in the research and development to patent and bring to market the drug known as Plavix® – and Apotex, which seeks to market the generic equivalent of that drug. On the basis of the record established by the parties and the applicable law, the Court enters the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

FINDINGS OF FACT[1]

I. History of this Action

Plavix®, approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in November 1997, is prescribed for the reduction of thrombotic events such as heart attacks and strokes for patients who have recently suffered those events or who have arterial disease or acute coronary syndrome. (See Stipulated Statement of Facts ("Fact Stmt."), attached as Exhibit A to Joint Pretrial Order dated May 27, 2005 at ¶ 12.) The active ingredient of Plavix® is clopidogrel bisulfate. (Id.) Sanofi obtained a patent claiming clopidogrel bisulfate on July 11, 1989, naming Sanofi employees Alain Badorc and Daniel Fréhel as inventors. (Id. at ¶¶ 8-9.) That patent, U.S. Patent No. 4,847,265 ("the '265 patent"), claims clopidogrel bisulfate by its chemical name in Claim 3: "Hydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl)(2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer." ('265 patent at col. 12, ll. 37-41.) Sanofi-Aventis is the owner of the patent-in-suit, which expires on November 17, 2011. The foreign priority filing date of the '265 patent – the date on which Sanofi filed its earlier application for the corresponding French patent – is February 17, 1987. The '265 patent is exclusively licensed to Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership. (Fact Stmt. at ¶¶ 3, 13.)

Apotex sought approval from the FDA to manufacture and sell clopidogrel bisulfate tablets before the expiration of the '265 patent by filing an Abbreviated New

[1] To the extent that any findings of fact may be deemed conclusions of law, they shall also be considered conclusions of law; to the extent that any conclusions of law may be deemed findings of fact, they shall also be considered as such. See Miller v. Fenton, 474 U.S. 104, 113-14, 106 S. Ct. 445, 88 L. Ed. 2d 405 (1985).

Drug Application ("ANDA") with the FDA in November 2001. (Id. at ¶¶ 14-15.) In the ANDA, Apotex certified pursuant to the requirements of 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that it believed the '265 patent to be invalid. (Id. at ¶ 16; see also Glaxo Group Ltd. v. Apotex, Inc., 376 F.3d 1339, 1344 (Fed. Cir. 2004).) Apotex was the first to file an ANDA for clopidogrel bisulfate (Decl. of Dr. Bernard Sherman, dated Aug. 16, 2006 ("Sherman Decl.") at ¶ 17), thereby securing the right to 180 days of market exclusivity provided by the Hatch-Waxman Act to the first ANDA filer to challenge a patent. See 21 U.S.C. § 355(j)(5)(B)(iv); see also In re Tamoxifen Citrate Antitrust Litig., 429 F.3d 370, 376 (2d Cir. 2005).

In response to that ANDA filing by Apotex, Sanofi filed this litigation against Apotex on March 21, 2002 pursuant to 35 U.S.C. § 271(e), and asserted that Apotex's filing of the ANDA constituted infringement of the '265 patent, specifically Claim 3. (See Fact Stmt. at ¶ 17.) Apotex counterclaimed, asserting that the '265 patent is both invalid for three separate reasons and unenforceable as well.

First, Apotex alleges that the '265 patent is anticipated pursuant to 35 U.S.C. § 102(b) by an earlier patent held by Sanofi that covered a genus of chemical compounds called thienopyridines, within which clopidogrel bisulfate falls. (See Fourth Amended Answer and Amended Counterclaim ("Answer"), filed Nov. 17, 2006, at 3, 13.) The earlier patent, U.S. Patent No. 4,529,596 ("the '596 patent"), issued in July 1985 and expired in July 2003. (Fact Stmt. at ¶ 28.)

Second, Apotex contends pursuant to 35 U.S.C. § 103 that the subject matter claimed in the '265 patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. (See Answer at 3, 13.)

Third, Apotex contends that the patent is invalid under the judicial doctrine of obviousness-type double patenting. (Id. at 6, 15.)

Finally, Apotex also asserts that the '265 patent is unenforceable on the basis of Sanofi's alleged inequitable conduct before the U.S. Patent and Trademark Office ("PTO"). The alleged conduct consists of failing to name Dr. Jean-Pierre Maffrand as an inventor, making false statements to the PTO regarding the unexpected pharmacological properties of clopidogrel bisulfate, failing to disclose relevant prior research that Sanofi had conducted on a similar chemical compound, and failing to disclose a journal article that Apotex alleges is a material prior art reference. (Id. at 4-6, 8-15.)

With regard to infringement, the parties have stipulated that Apotex's clopidogrel bisulfate product infringes Claim 3 of the '265 patent. (See May 7, 2004 Stipulation and Order; Fact Stmt. at ¶ 18.) The ensuing procedural history of this action – including an account of the extensive settlement negotiations between the parties and the consequences for this litigation – is described in detail in this Court's Opinion dated August 31, 2006; familiarity with that Opinion is assumed. See Sanofi-Synthelabo v. Apotex Inc., No. 02 Civ. 2255, 2006 U.S. Dist. LEXIS 65127, at *9-16 (S.D.N.Y. Aug. 31, 2006). In brief, Apotex initiated an at-risk launch of its generic clopidogrel bisulfate product on August 8, 2006. Shortly thereafter, Sanofi moved for a preliminary injunction prohibiting Apotex from distributing its generic product. After an evidentiary hearing was held, the Court granted Sanofi's motion for preliminary injunctive relief on August 31, 2006, but denied its request for a recall of the approximately six-month supply of product that Apotex had already shipped to distributors in the United States. Id. at *89-91.

Apotex then moved to stay the preliminary injunction, but both this Court and the U.S. Court of Appeals for the Federal Circuit denied that motion. Apotex then appealed the order granting the preliminary injunction to the Federal Circuit, which affirmed the grant of the preliminary injunction in an opinion dated December 8, 2006. See Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368 (Fed. Cir. 2006), reh'g denied, 2007 U.S. App. LEXIS 2807 (Fed. Cir. Jan. 19, 2007). The parties then tried the merits of this action before this Court without a jury from January 22 through February 15, 2007. That trial – as well as the evidentiary hearing held in August 2006 – adduced the following facts.

II. Sanofi's Efforts to Develop Antiplatelet Aggregation Drugs

A. Ticlopidine

In 1972, Dr. Jean-Pierre Maffrand, then a Sanofi chemist in charge of a small research team, was asked by his supervisor to synthesize compounds structurally similar to tinoridine, a drug with known anti-inflammatory properties, in an effort to discover a superior anti-inflammatory drug. (Maffrand Tr. 1570-74.)[2] Tinoridine is a member of a class of compounds known as thienopyridines. (Maffrand Tr. 1575-76.) The chemical structure of a thienopyridine is characterized by the fusion of a thiophene ring to a pyridine ring. (Maffrand Tr. 1575-76.)

During 1972 and 1973, Sanofi synthesized a number of thienopyridine compounds. (Maffrand Tr. 1573-74.) Tests on those compounds revealed that unlike tinoridine, they possessed no anti-inflammatory properties. Some of the compounds, however – one of which Sanofi named "ticlopidine" – exhibited antiplatelet aggregation activity. (Maffrand Tr. 1573-75.) Put simply, the compound helped ensure that platelets

[2] References to (____ Tr. ____) refer to the page number of the trial transcript for the relevant witness. Similarly, references to (____ PI Tr. ____) refer to the page number of the transcript of the preliminary injunction hearing for the relevant witness.

in the blood would not aggregate together as much as they otherwise would. This was an important discovery. Researchers at Sanofi were convinced that platelets play a major role in events such as myocardial infarction and brain ischemia and Dr. Maffrand and his colleagues were interested to find an antiplatelet aggregation agent that would be "[a] better drug than aspirin." (Maffrand Tr. 1574-75.) In 1977, Sanofi obtained a patent on ticlopidine; that patent expired in 1994.

Ticlopidine was introduced as a drug in France in 1978 and in the United States in 1991, where it was marketed under the brand name "Ticlid." (Maffrand Tr. 1578-79; 1581-82.) Soon after the launch of ticlopidine in France, Sanofi became aware of rare but potentially fatal side effects associated with ticlopidine, specifically blood disorders known as neutropenia and thrombotic thrombocytopenic purpura ("TTP"). (Schneller Tr. 763, 815-16; Maffrand Tr. 1580-81.) As a result, the FDA required Ticlid to carry a "black box" warning that ticlopidine could cause life-threatening blood disorders. (Maffrand Tr. 1581.) The potential for these serious side effects meant that patients taking ticlopidine had to be clinically monitored for signs of blood disorders. (Maffrand Tr. 1581.) The sub-optimal side effect profile of ticlopidine – i.e., the risk of developing serious blood disorders – left open the need in the market for a drug that was as effective or more effective than ticlopidine, but with a lower risk of side effects.

B. PCR 1033

In 1975, Sanofi synthesized a thienopyridine named PCR 1033. That compound is the methyl analog of ticlopidine, which means that one of the two hydrogen atoms on the bridge carbon of a ticlopidine molecule – the carbon linking the thienopyridine and phenyl substituents – is substituted with a methyl (CH_3) group. (Maffrand Tr. 1584.)

The addition of the methyl group makes the bridge carbon asymmetric. Here, some knowledge of the basic principles of stereochemistry is required and has been best set forth by the Federal Circuit in its opinion affirming the preliminary injunction in this action:

> Stereochemistry refers to the three-dimensional spatial arrangement of a molecule's constituent atoms. Molecules that have the same chemical substituents, but different spatial arrangements, are referred to as stereoisomers. If they contain an asymmetrical carbon atom, they exist as non-superimposable mirror images of each other and are referred to as enantiomers. Enantiomers are optically active because they are capable of rotating plane-polarized light; enantiomers that rotate polarized light to the right are referred to as dextrorotatory enantiomers, or d-enantiomers; enantiomers rotating polarized light to the left are referred to as levorotatory enantiomers, or l-enantiomers. A mixture of equal amounts of both types of enantiomers is referred to as a racemic mixture, or racemate, and it exhibits no optical activity.

Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d at 1372.

Unlike ticlopidine, PCR 1033 is a racemate composed of the 50:50 mixture of its enantiomers. (Maffrand Tr. 1584, 1599-1600, 1682-83.) To make PCR 1033 suitable for testing, Sanofi chemist Alain Cabrol attempted to prepare the hydrochloride salt of PCR 1033, but that effort failed. (Maffrand Tr. 1599-1600; 1699; Badorc Tr. 1810.) Instead, Sanofi prepared PCR 1033 as a maleate salt. (Maffrand Tr. 1600.) When tested, Sanofi found that PCR 1033 was a more potent antiplatelet aggregation agent than ticlopidine, but that it was also less well-tolerated than ticlopidine; side effects were observed during the initial pharmacological testing of PCR 1033 in different species. (Maffrand Tr. 1587.) Around the beginning of 1976, Sanofi ceased efforts to develop PCR 1033 because of those side effects. (Maffrand Tr. 1587.)

In 1978, Maffrand asked Alain Badorc, a Sanofi chemist, to try to obtain the enantiomers of PCR 1033. (Maffrand Tr. 1587-88; Badorc Tr. 1807.) Maffrand testified

at trial that "we wanted to try our luck" to see if either enantiomer had a better ratio of antiplatelet activity to tolerance than the racemate. (Maffrand Tr. 1588.) At that time, Maffrand knew that a two-fold increase in a single enantiomer's therapeutic activity was the quantitatively best possible increase that could be attained through separation of the enantiomers of a racemate, and that such a result "is not the most frequent case." (Maffrand Tr. 1591-93; Harden Tr. 2304-06.) For that reason, Sanofi's preferred mode of searching for superior antiplatelet drugs at that time had been to modify the substituents of racemic compounds (thereby creating new compounds) – not to isolate the individual enantiomers of particular racemates – because a modified compound was the more likely path to significantly greater gains in antiplatelet activity. (Harden Tr. 2304; Maffrand Tr. 1592-94.)

Badorc successfully separated the enantiomers of PCR 1033 on his first attempt by means of a technique known as diastereomeric salt formation. (Badorc Tr. 1809; Maffrand Tr. 1702) That method involves combining the enantiomers of a racemic base with an enantiomerically pure chiral acid to form a diastereomeric salt (i.e., a salt with two chiral centers) in two distinct stereoconfigurations. (Davies Tr. 1934.) The resulting diastereomers, if formed, do not have identical physical properties; their different solubilities in a particular solvent, for example, may facilitate their separation. (Davies Tr. 1934-35; McClelland Tr. 1105-06.) However, the Court credits the testimony of Dr. Stephen G. Davies, an expert for Sanofi, who stated, "[t]he problem is that it is very hard to find situations where one [diastereomer] crystallizes out and the other one does not . . . . you are trying to get one to do something while leaving the other one behind." (Davies Tr. 1935-36.) If the diastereomers are successfully separated, a base is added to one of

the two separated diastereomeric salts to reconstitute the original base, which is then in an enantiomerically pure form. (McClelland Tr. 1108-1109; Davies Tr. 1936-37.)

Badorc prepared the diastereomeric salts of PCR 1033 by using tartaric acid dissolved in ethanol. (Badorc Tr. 1808-09.) The levorotatory enantiomer was designated PCR 3071 and the dextrorotatory enantiomer was designated PCR 3072. (Maffrand Tr. 1598.) To facilitate further testing, Badorc prepared the hydrochloride salts of PCR 3071 and PCR 3072. (Badorc Tr. 1810.) As noted, previous efforts to prepare the hydrochloride salt of the racemate – PCR 1033 – had failed. (Maffrand Tr. 1600, 1699.) Testing on the enantiomers revealed that PCR 3071 exhibited antiplatelet activity and PCR 3072 was inactive; the active enantiomer, however, was less well tolerated than ticlopidine and was not appropriate for administration to humans. (Maffrand 1598-99.) Sanofi discontinued the development of those enantiomers in 1981. (Maffrand Tr. 1599.)

C. PCR 3549

In 1978 – after Sanofi had synthesized PCR 1033 but before it had discontinued the development of PCR 3071 and PCR 3072 – Sanofi synthesized the ethyl analog of ticlopidine, which was designated PCR 3233. (Maffrand Tr. 1601-02.) Attempts to make the hydrochloride salt of PCR 3233 – an oily base – failed, but, after several failed attempts, Badorc eventually obtained its nitrate salt, which was designated PCR 3549. (Maffrand Tr. 1604; Badorc Tr. 1812.) Testing revealed that PCR 3549 was more potent than ticlopidine and better tolerated than PCR 1033, but was still less well tolerated than ticlopidine. (Maffrand Tr. 1604-05.) In November 1978, Maffrand asked Badorc to prepare the enantiomers of PCR 3549 to see if either enantiomer had a better risk/benefit profile than the racemate. (Maffrand Tr. 1605-06; Badorc Tr. 1811.) Badorc tried to

separate the enantiomers of PCR 3549 using diastereomeric salt formation – the technique that he had used successfully to resolve the enantiomers of PCR 1033 – but several attempts failed. (Maffrand Tr. 1606; Badorc Tr. 1813-14.) Badorc then tried to obtain the enantiomers of PCR 3549 by a different method – chemical asymmetric synthesis. (Maffrand Tr. 1606; Badorc Tr. 1819-20.) That method involves taking a precursor compound that is enantiomerically pure and modifying the compound to obtain the desired compound, but without altering the stereochemical configuration of the precursor compound. (Davies Tr. 1932-33; Badorc Tr. 1819-20.) At that time, Badorc believed – and he testified at trial that he still believes – that he successfully synthesized the enantiomers of PCR 3549 by that method. (Badorc Tr. 1823-24.) Badorc further testified that he confirmed his successful synthesis of the enantiomers of PCR 3549 in 1978 by measuring the rotatory power of each enantiomer, which were equal in absolute value (Badorc Tr. 1824); that result – the equal and opposite optical rotation of two products – is evidence of the presence of two enantiomers. (Davies Tr. 1981; Hendrickson Tr. 1474.) In addition, the nitrate forms of each enantiomer had equivalent melting points that were each higher than the melting point of PCR 3549. (Davies Tr. 1981.) Furthermore, "the chance is minimal, if not nonexistent," that two parallel asymmetric syntheses – such as those Badorc performed – would result in products demonstrating the same level of rotatory power and the same melting points. (Davies Tr. 1819.) The Court credits the testimony from Dr. Davies that this data provided strong evidence that Badorc had indeed obtained the enantiomers of PCR 3549 by means of asymmetric synthesis. (Davies Tr. 1981-82.)

Sanofi designated the levorotatory enantiomer PCR 3620 and the dextrorotatory enantiomer PCR 3621 and tested them for platelet aggregation inhibition activity. (Badorc Tr. 1826.) That testing showed that the platelet aggregation inhibiting activities of PCR 3620 and PCR 3621 were each comparable to PCR 3549, meaning neither improved on the racemate. (Maffrand Tr. 1615-16.) For that reason, Sanofi discontinued development of PCR 3620 and PCR 3621 and focused its efforts on PCR 3549. (Maffrand Tr. 1616-17.) PCR 3549, however, proved to be less well-tolerated than ticlopidine at similar dosage levels, and lower doses of PCR 3549 were insufficiently therapeutic. For those reasons, Sanofi abandoned its efforts to develop PCR 3549. (Maffrand Tr. 1616-17.)

D. PCR 4099

Sanofi synthesized several other thienopyridines in addition to PCR 1033 and PCR 3549. After having created two carboxylic acid derivatives of ticlopidine – in 1976 and 1978, respectively – which showed no platelet inhibition, Sanofi synthesized a new compound in 1980 that had an ethyl ester ($O=C-O-CH_2-CH_3$) substituent on the bridge carbon. (Maffrand Tr. 1637-39.) That compound – PCR 3935 – proved active in tests of antiplatelet aggregation activity (Maffrand Tr. 1638), and, after attempts to prepare it as both hydrochloride and bisulfate salts had failed, Sanofi prepared it as a hydrobromide salt. (Maffrand Tr. 1640.) Concerned, however, that PCR 3935 might be converted in the human body into carboxylic acid – which could render the compound therapeutically inactive – Sanofi synthesized a new compound in July 1980 by replacing the ethyl ester substituent of PCR 3935 with a methyl ester ($O=C-O-CH_3$) substituent. (Maffrand Tr. 1638-40.) Sanofi designated that compound – a racemic mixture prepared as a

hydrochloride salt – as PCR 4099. (Maffrand Tr. 1640-41.) The non-salt (free base) form of PCR 4099 is described by the chemical formula methyl α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o-chlorophenyl-acetate, or "MATTPCA." The nomenclature "methyl α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o-chlorophenyl-acetate" is equivalent to "methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl)(2-chlorophenyl)-acetate." (Fact Stmt. at ¶ 31.)

Testing showed that PCR 4099 exhibited more antiplatelet activity and was better tolerated than ticlopidine. (Maffrand Tr. 1641.) Nonetheless, Sanofi continued to synthesize and test other racemic carboxylic acid and ester derivatives of ticlopidine, as well as derivatives with amide ($O=C-NR_2$) substituents. (Maffrand Tr. 1641-43.) In total, Sanofi synthesized approximately 70 carboxylic acid, ester, and amide derivatives of ticlopidine, all of which were racemic mixtures. (Maffrand Tr. 1636-1637; 1642.) Many of these compounds were subjected to a battery of tests of pharmacological activity, including four tests known as the bleeding-time test, the silk-thread test, the collagen test, and the ADP test.[3] (Maffrand Tr. 1641; Hanson Tr. 2226, 2232-33, 2238-39, 2243, 2246-67.) These were screening tests "designed to quickly screen a large number of candidate compounds in order to identify a manageable number of compounds [for] more sophisticated testing." (Hanson Tr. 2226-27; see also Maffrand Tr. 1644, 1646.) Sanofi's expert Dr. Stephen R. Hanson gave testimony at trial – which the Court credits – that conclusions drawn from such tests are "tentative" and that "it would be risky to extrapolate the results of these tests" – performed only in rats – to other animals or humans. (Hanson Tr. 2227.)

[3] ADP refers to adenosine diphosphate.

III. The '596 Patent and Its Non-U.S. Counterparts

In July 1982 and July 1983, Sanofi applied for French and U.S. patents, respectively, on the class of thienopyridines having carboxylic acid, amide, and ester substituents. An internal Sanofi memorandum authored by Dr. Maffrand and dated February 11, 1982 stated that the patent would cover "PCR 4099 and its analogues." (Defendant's Exhibit ("Def. Ex.") 632.) The memorandum also noted that based on pharmacological testing, "[t]he most interesting esters were: PCR 4099, 4316, SR 24593, [and] SR 24597" and "[t]he most interesting amides were: PCR 4317, 4535, [and] 4516." (Id.) The application that was filed in the United States matured into the '596 patent, which issued on July 16, 1985 and listed Maffrand, Aubert, and Ferrand, among others, as inventors. The '596 patent is entitled "Thieno [3,2-c] Pyridine Derivatives and Their Therapeutic Application," and describes a genus of compounds that exhibit blood-platelet aggregation inhibition and anti-thrombotic activity. (Fact Stmt. at ¶ 27; '596 patent at col. 8, ll. 26-39.)

Sanofi also obtained European patent EP099802 ("the '802 patent") and Canadian Patent No. 1,194,875 ("the '875 patent") over the same class of compounds. These patents were also published more than a year before February 17, 1987, the foreign priority filing date of the '265 patent.

A. The Specification of the '596 Patent

The general formula described in column 1 of the '596 patent specification – which has two variables (X and Y) – depicts a racemate in non-salt (free base) form. The general formula covers an extremely large number of compounds covered by providing for various substituents in place of the X and Y groups. (McClelland PI Tr. 494; Davies

Tr. 1913-14). Each of the X and Y variables can be one of a number of enumerated substituents, with thirty-seven possibilities for the X variable and 1710 possible choices for Y. Multiplying these variables by the number of pharmaceutically acceptable acid addition salts yields an even higher number. Dr. Maffrand testified at trial that the patent covers "millions of compounds if we take into account all the combinations possible of products and salts." (Maffrand Tr. 1771.) Similarly, Sanofi's expert Dr. Davies testified that the patent covers "several millions of compounds." (Davies Tr. 1914.)

The general formula does not describe any individual enantiomer and does not describe how to obtain the enantiomers of any racemate; as drawn, the general formula describes a racemic mixture only. (Davies Tr. 1913.) However, the specification states that with respect to the general formula, "[t]he invention relates both to each enantiomer and their mixture." ('596 patent at col. 1, ll. 40-41.) The specification also sets forth that the thienopyridine compounds within the genus covered by Claim 1 can be made into addition salts with pharmaceutically acceptable mineral or organic acids or a mineral base. ('596 patent at col. 1, ll. 42-51.)

In addition, the '596 patent specification gives twenty-one examples of compounds included within the genus compound "to exemplify and to illustrate the different substituents which were claimed in the general formula." (Maffrand, PI Tr. 138; '596 patent at cols. 3-8.) These different compounds are described in the patent as different salts forms – including hydrobromide, hydrochloride, and bisulfate salts. (Maffrand, PI Tr. at 139-140.) Specifically, three of the examples are shown as hydrochloride salts and four of the examples are shown as bisulfate salts. (Snyder Tr. 236.) The first of the twenty-one examples in the '596 patent – Example 1 – is PCR

4099, prepared as a hydrochloride salt. (Maffrand, PI Tr. at 139.) Neither Example 1, nor any other example set forth in the specification, refers to the individual or separated enantiomers of PCR 4099 or, for that matter, of any other exemplified compound. Furthermore, there is no example in the '596 patent of a methyl ester – such as PCR 4099 – prepared as a bisulfate salt. (Banker Tr. 1328.) In addition, the pharmaceutical formulations provided as non-limiting examples at the end of the specification do not show a bisulfate salt in the solid dosage form. (McClelland Tr. 1178-79; '596 patent at col. 12, ll. 3-28.)

The specification of the '596 patent also describes the compounds covered by the patent as exhibiting "an excellent tolerance and a low toxicity." ('596 patent at col. 8, ll. 42-43.) In the 1980s, Sanofi scientists commonly used the terms "tolerance" and "tolerated" to denote a compound's relative toxicity and described compounds that performed well in sub-acute and acute toxicity tests as "not very toxic" or "better tolerated."[4] Dr. Maffrand testified that he considers "toxicity" to be "included in tolerance." (Maffrand Tr. 1664.) Dr. Frédéric Lacheretz, the deputy head of Sanofi's toxicology department in the mid-1980s, testified that the terms "'more toxic than' [or] 'less well-tolerated than' . . . mean the same thing." (Lacheretz Tr. 2392.) In addition, Dr. Hanson testified that the terms toxicity and tolerance are "not necessarily mutually exclusive." (Hanson Tr. 2224.) Similarly, Apotex's expert, Dr. Gilbert Banker, agreed that "not toxic" means that a substance "won't make you sick, won't affect your physiologic functions, won't deleteriously affect your organs or even produce untoward

[4] The practice of referring to "tolerance" in the context of acute toxicity testing is not unique to Sanofi. Patents of companies other than Sanofi use the term "well-tolerated" to refer to results obtained through acute toxicity testing. See, e.g., U.S. Patent No. 4,242,360 (Dec. 30, 1980) at col. 3, ll. 12-23 (basing an assessment of tolerance on the results of acute toxicity testing) (Pl. Ex. 447); see also Snyder Tr. 714-17.

side effects," and that non-toxic has the same meaning as "well tolerated." (Banker Tr. 1294.)

The Court credits Dr. Hanson's testimony that "[u]nless you're talking about a formally-described toxicology or tolerance study, the term tolerance . . . is commonly used as a general term that can describe toxic side effects as well as less severe side effects." (Hanson Tr. 2225-26.) Furthermore, the Court finds that the use of the terms "well-tolerated" and "less well-tolerated" is not restricted to descriptions of a drug's performance in tests at therapeutic doses only. (Graham Tr. 2424.) Apotex has failed to persuade the Court that those terms cannot appropriately be used to describe performance in tests at supra-therapeutic doses, including subacute and acute toxicity tests. (See Graham Tr. 2424; Hanson Tr. 2224; Lacheretz Tr. 2359; Rodricks Tr. 2495.)

B. The Claims of the '596 Patent

As described above, Claim 1 sets forth a general formula that covers millions of compounds, including "their addition salts with pharmaceutically acceptable mineral or organic acids . . . including both enantiomeric forms or their mixture." ('596 patent at col. 12, ll. 30-68, col. 13, ll. 1-19.) Claim 8 covers the same genus of compounds as Claim 1, but claims their "therapeutic compositions." Claim 8 reads:

> A therapeutic composition having blood-platelet aggregation inhibiting activities and anti-thrombotic activities containing an effective amount of a compound of claim 1, or an addition salt thereof with a pharmaceutically acceptable mineral or organic acid with mineral bases, or one of the two enantiomers or their mixture and a pharmaceutically acceptable carrier.

('596 patent at col. 14, ll. 5-11.)

Claims 2 through 7 correspond to particular racemates, and Claim 2 specifically claims MATTPCA, or the free base of PCR 4099:

> Methyl α-(4,5,6,7-tetrahydro-thieno(3,2,c)-5-pyridyl)-o.chlorophenyl-acetate.

('596 patent at col. 13, ll. 19-20.)

Claims 2 through 7 do not include the language "both enantiomeric forms or their mixture" or "their addition salts." Claim 2, therefore, does not expressly claim any salt form of MATTPCA. (Davies Tr. 1917-19; Byrn Tr. 2134.) In addition, Claim 2 does not include a stereochemical descriptor (e.g., "*d*-" or "*l*-") that identifies it as referring to an individual enantiomer.

C. Tests of Pharmacological Activity Reported in the '596 Patent

As noted above, prior to Sanofi's application for the '596 patent, several racemic compounds covered by the general formula of Claim 1 were tested for platelet aggregation inhibition activity. Results of those tests – the bleeding-time test, the silk-thread test, the collagen test, and the ADP test – were reported in the specification to the '596 patent. (Hanson Tr. 2226, 2232-33, 2243, 2246.)

Table I reports the results of the ADP test in which nine compounds, including PCR 4099 – which is listed as Derivative 1, were tested; most of the compounds demonstrated significant activity. At the doses at which they were tested, Derivative 4 demonstrated activity that was not meaningfully different from that of PCR 4099. (Snyder Tr. 633-35; '596 patent at col. 9, ll. 31-55.) In the collagen test reported in Table II, twelve compounds were tested, and, again, most of the tested compounds demonstrated significant activity. At the doses that were tested, Derivatives 9, 4, and 10 demonstrated activity quantitatively superior to that of PCR 4099, although Sanofi's expert Dr. Hanson described the activity levels of those compounds as comparable to that of PCR 4099. (Hanson Tr. 2244-46; '596 patent at col. 10, ll. 1-31.) In the bleeding-time

test, reported in Table III, six compounds were tested. All the tested compounds, including PCR 4099, demonstrated maximal inhibition of blood clotting activity. (Snyder Tr. 641; Hanson Tr. 2232-33, 2237-38; '596 patent at col. 10, l. 55, col. 11, l. 5.) In the silk-thread test reported in Table IV, most of the six tested compounds demonstrated significant activity. At the doses that were tested, two of the six compounds, Derivative 3 and Derivative 10, demonstrated activity quantitatively superior to that of PCR 4099. (Snyder Tr. 641-42; '596 patent at col. 11, ll. 35-51.) Again, Sanofi's expert Dr. Hanson testified, however, that "[f]or compounds No. 3, 10, [PCR] 4099, and No. 2, all of which did very well, it is not possible to further rank their effects." (Hanson Tr. 2241.)

As noted above, Dr. Hanson testified that the pharmacological activity data presented in Tables I-IV of the '596 patent is not an appropriate scientific basis on which to rank the relative performance of the compounds – except in cases where a high dose produces little or no activity. (Hanson Tr. 2226-27, 2241, 2246.) These were screening tests used to make rough determinations of activity versus inactivity. In addition, because the screening tests were performed in rats, inferences as to how the tested compounds would perform if administered to humans would be tentative because many drugs behave differently in rats and human beings. As a result, it "would be risky to extrapolate the results of these tests" to any other animal or to human beings. (Hanson Tr. 2227-29.)

Furthermore, the tests did not provide enough data points to construct a dose-response curve for each compound; a dose-response curve is a tool used to compare the relative potency of different compounds. (Hanson Tr. 2235.) The lack of data points

made it impossible to derive an "ED_{50}" value, the dose at which each compound produces half its maximal response, which is a similar tool of comparison. (Snyder Tr. 630-32; Maffrand Tr. 1646; Hanson Tr. 2236-37.) Finally, nearly all of the compounds were tested at only one or two dose levels (Snyder Tr. 642-43), making it impossible to draw conclusions about how the compounds would perform at lower doses. (Hanson Tr. 2238.) For these reasons, the Court finds that a person of ordinary skill in the art would not discern a preference for PCR 4099 based on the pharmacological testing data in the '596 patent. (Hanson Tr. 2250.)

D. The Canadian '875 Patent

As noted above, the '875 patent is the Canadian counterpart to the '596 patent. (Def. Exs. 206; 1235.) Claim 1 describes a "procedure for preparing derivatives of general formula (I)" – the same general formula claimed in Claim 1 of the '596 patent. With regard to the general formula, the '875 patent also claims "the two enantiomers or their mixture." In addition, after describing the procedure for preparing certain compounds, the claim states that "then the corresponding derivative sought is obtained, which is isolated and, if desired, its enantiomers separated and/or it is salified by mineral or organic acid action." (Def. Ex. 1235.)

E. The European '802 Patent

U.S. Patent No. 5,989,578 ("the '578 patent") – a patent held by Sanofi which issued in 1999 – states that clopidogrel is "described" in EP 099 802, the European counterpart to the '596 patent. Two factors militate against giving that statement any credence. First, the application for the European '802 patent was filed in July 1983, well before Sanofi's separation of PCR 4099 into its enantiomers or the formulation of the

dextrorotatory enantiomer of PCR 4099 – clopidogrel – as a bisulfate salt, as described below. (Maffrand Tr. 1672-73.) Second, a named inventor of the '578 patent – Dr. Pierre Savi – testified that the statement in that patent that clopidogrel is described by the European '802 patent is "incorrect," and that he had not personally read the European patent until his deposition relating to this action. (Savi 8/21/03 Dep. 164-65, 314-17.) Dr. Savi also testified that other named inventors listed on the '578 patent are biologists, not chemists. (Id. at 317.) Accordingly, the Court does not credit the alleged disclosure in the '578 patent and does credit Dr. Savi's unequivocal later statement that clopidogrel is not described by the '802 patent.

IV. The Development of PCR 4099 and Its Enantiomers

Sanofi's decision to further develop PCR 4099 required clinical testing, which in turn required Sanofi to synthesize large quantities of the drug in tablet form. From 1980 until 1987, PCR 4099 was the subject of more than fifty different types of tests in animals and humans, and Sanofi spent "tens of millions of dollars" on those tests. (Maffrand PI Tr. 144.) Sanofi also performed additional pharmacological and toxicological studies, as well as metabolic and pharmacokinetic studies. (Maffrand PI Tr. 143.) Between 1983 and 1987, Sanofi conducted acute and long-term chronic toxicity tests on PCR 4099 in rats, mice, and baboons. In each test and in each species, convulsions were observed at certain dose ranges. (Lecheretz Tr. 2362-70; Rodricks Tr. 2481-83.) A one-year chronic toxicity study in baboons in 1987 showed convulsions at all doses, including the lowest dose tested, 25 mg/kg, and demonstrated that more convulsions were observed at higher doses. (Rodricks Tr. 2481-82.)

During 1985, Sanofi representatives, including Dr. Maffrand, made poster presentations and distributed corresponding abstracts concerning their work on thienopyridines – and, in particular, PCR 4099 – at conferences of the International Society for Thrombosis and Hemostasis held in San Diego and Jerusalem. (Maffrand Tr. 1680; see also Def. Exs. 183, 184, 185, 186, 188, 224, 308, 418, 427.) The abstract prepared for the San Diego conference regarding PCR 4099 stated that the compound "exhibits the same broad spectrum of antiaggregating effect as ticlopidine in animals but is 40 times more potent in rats and 10 times in baboons." (Def. Ex. 184.) According to Sanofi's expert Dr. Hanson, the abstracts prepared for both conferences informed a person of ordinary skill in the art that "PCR 4099 exhibits activity in both humans and animals against platelet aggregation, and specifically the activity seems to be specially active toward the ADP pathway of platelet aggregation." (Hanson Tr. 2219-20.) Dr. Maffrand testified that Sanofi's "main goal was to inform the scientific community of the potent antiplatelet and antithrombotic activities of PCR 4099" and "to show that the compound was much more effective than ticlopidine." (Maffrand Tr. 1680.)

PCR 4099 was the only compound covered by the '596 patent that was publicized at the San Diego and Jerusalem conferences. (Maffrand Tr. 1736, 1748-49.) The posters and abstracts did not, however, discuss in any way the stereoselectivity of platelet inhibition by the enantiomers of PCR 4099 or, for that matter, make any reference at all to the enantiomers of PCR 4099. (Maffrand Tr. 1681-86; Hanson Tr. 2220.) Accordingly, a person of ordinary skill in the art would not have drawn any inference from those materials concerning the stereoselectivity of platelet inhibition by the enantiomers of PCR 4099. (Maffrand Tr. 1681-86; Hanson Tr. 2220.) To the contrary,

based on the posters and abstracts, a person of ordinary skill in the art would have concluded that PCR 4099 was under development as a promising racemic drug with several positive qualities and no significant reported negative qualities. (Snyder Tr. 290-91.)

Dr. Maffrand, however, also was aware as of 1985 that testing had showed that PCR 4099 had potential negative side effects in humans. (Maffrand Tr. 1651.) Various studies – including acute toxicity, dose-range finding, and chronic oral toxicity studies – conducted in 1983 and 1985 had demonstrated the tendency of PCR 4099 to cause convulsions in animals at particular dose levels. (See Plaintiff's Exhibits ("Pl. Exs.") 114, 115, 116, 117; Rodricks Tr. 2481-82.) For example, the report of a four week oral toxicity study of PCR 4099 conducted in baboons in 1983 included the observation that "[d]eath was preceded by convulsions and was most likely not accidental." (Pl. Ex. 113.) Furthermore, as a general matter, Sanofi was aware of the possibility that drugs that appeared safe in pre-clinical and clinical development might nonetheless show rare but serious side effects after launch – as had recently been the case with ticlopidine. (Maffrand PI Tr. 144; Maffrand Tr. 1651.) With the goal of finding a compound with a better profile than PCR 4099, Dr. Maffrand decided in November 1985 to have the enantiomers of PCR 4099 separated and tested. (Maffrand Tr. 1651.)

A. Predicting the Biological Properties of the Enantiomers of PCR 4099

Whether it was possible for Sanofi to predict the biological properties of the enantiomers of PCR 4099 – and whether one could predict that the properties of a single enantiomer would be superior to those of its opposite enantiomer – is hotly contested by

the parties to this litigation. However, in view of the prior art and the testimony given in this action, the following facts are clear.

A person of ordinary skill in the art in the mid-1980s would have known that the enantiomers of a racemate could exhibit different biological activity – including different levels of both therapeutic activity and toxicity. (Snyder Tr. 169.) As of 1984, for example, Ariëns taught that "[o]ften, only one isomer is therapeutically active, but this does not mean that the other is really inactive. It may very well contribute to the side-effects." E.J. Ariëns, "Stereochemistry, a Basis for Sophisticated Nonsense in Pharmocokinetics and Clinical Pharmacology," Eur. J. Clin. Pharm. 663 (1984) (Def. Ex. 138); see also id. at 664. Similarly, Williams & Lee taught that:

> Basic pharmacological data on the differences in activity between enantiomers suggest that there are many other drugs for which an increase in therapeutic index might be obtained by using the appropriate enantiomer rather than the racemic drug.

Kenneth Williams & Edmund Lee, "Importance of Drug Enantiomers in Clinical Pharmacology," Drugs 333, 348 (1985) (Def. Ex. 164); see also Goldstein, et al., Principles of Drug Action (2d Ed.) 754 (1974) (Def. Ex. 1305).

Dr. Maffrand testified at the preliminary injunction hearing that literature in the late 1970s taught that the therapeutic properties of stereoisomers could "show no obvious difference" or "could have different affinity and different activity for their known receptor." (Maffrand PI Tr. 170-71.) Where there is variation, the extent of that variation is not predictable and can be weak, moderate, or strong – a view confirmed by experts from both parties and credited by this Court. (Harden Tr. 2295-96.) Dr. Robert Snyder, an expert for Apotex, testified that without separating and testing the enantiomers of a particular racemate, a person of ordinary skill in the art could not know what the

degree of difference – if any – between the properties of the enantiomers of a racemic compound would be. (Snyder Tr. 556.) The prior art, in fact, suggested that "weak" stereoselectivity – i.e., a difference in activity of ten-fold or less between two stereoisomers – was fairly common and that strong stereoselectivity – i.e., a difference in activity of 100-fold or more between stereoisomers– was less prevalent. (Harden Tr. 2295-99; Hanson Tr. 2215-16; Snyder Tr. 557-58.) In particular, the following prior art reference from Lehmann is relevant:

> When the biological activities of stereoisomers (enantiomeric and diastereomeric …) are compared, it is sometimes found that only one member of each pair is very active, rarely that both members are equally active. Very frequently though, both members exhibit the same type of activity but to a different degree. Several thousand such cases have been recorded . . . . The differences in activity for the members of any one pair . . . vary enormously, viz. from ca. 1 up to nearly 10^6.

P.A. Lehmann, et al., "Stereoselectivity and Affinity in Molecular Pharmacology," Prog. Drug. Res. 101, 104 (1976) (Def. Ex. 268).

The Court finds, furthermore, that a person of ordinary skill in the art would have known that absolute stereoselectivity – meaning the presence of a particular kind of activity exclusively in one stereoisomer and its total absence in the other – was uncommon. (Harden Tr. 2299-2300; Lehmann (1976) at 122.) It was also rare, moreover, if both enantiomers exhibited precisely the same levels of activity. (Snyder Tr. 172, 556-58; Lehmann (1976) at 104.) Experts from both parties agreed that even today, no scientific principles afford a basis for predicting to what degree, if any, a pair of stereoisomers will exhibit different levels of therapeutic activity and different levels of toxicity. (Snyder Tr. 563-65; Davies Tr. 2018-19; Hanson Tr. 2214.) As Dr. Davies testified, "Anything is possible . . . . You can't predict anything unless you do the

experiments." (Davies Tr. 2019.) The prior art confirms this testimony – as least as it relates to the separation of enantiomers as of the mid-1980s. See Lehmann (Def. Ex. 268) at 104 ("In spite of extended efforts . . . it has so far not been possible to explain these ratios; every biological system, sometimes every individual pair, seems to constitute a casus sui generis."); W. Soudjin, "Advantages and Disadvantages in the Application of Bioactive Racemates or Specific Isomers as Drugs," in Stereochemistry and Biological Activity of Drugs 87, 100 (1983) (Def. Ex. 495) (noting the need for "extensive pharmacological , toxicological and clinical pharmacological research" to determine "whether it is advantageous to use racemates or enantiomers in clinical practice").

There are numerous drugs marketed as racemates in which there is no clear difference between the activities of stereoisomers, or where even though one enantiomer shows a greater level of activity, the drug is nonetheless marketed as a racemate. Dr. Thomas K. Harden, an expert for Sanofi, described fluoxetine, gatifloxacin, amphetamine, and sotalol as drugs in the latter category. (Harden Tr. 2306, 2310-15.) At the time that Sanofi decided to investigate the enantiomers of PCR 4099, Dr. Maffrand was aware that in some cases, the stereoisomers of a drug have greatly different activities (e.g., ibuprofen, thalidomide), but their metabolism in vivo – as opposed to in vitro – leads to racemization or interconversion to a different enantiomeric or achiral compound. (Maffrand PI Tr. 171-72.) Racemization is a process whereby a compound consisting of a single enantiomer is converted to a one-to-one mixture of that enantiomer and its opposite (i.e., the racemate) by the cleavage and reformation of a chemical bond at the chiral center of the molecule. (Davies Tr. 1956.) The Court finds that a person of

ordinary skill in the art would also have been aware of these cases, and would have known that the risk of racemization in the body potentially eliminates any pharmacological advantage derived from preparing the individual enantiomers. (Maffrand Tr. 1656-57.)

In addition, Sanofi's work on thienopyridines heightened Dr. Maffrand's uncertainty regarding the pharmacological potential of PCR 4099's enantiomers. Dr. Maffrand knew, for example, that thienopyridines were active only after administration to live animals, but were not active after in vitro exposure to isolated platelets. (Maffrand Tr. 1684-85; Harden Tr. 2325-26.) On that basis, Dr. Maffrand and his colleagues inferred that PCR 4099 required metabolic conversion – which takes place in vivo – to an active metabolite. (Maffrand Tr. 1684-85; Harden Tr. 2325-26; Snyder Tr. 586.) That active metabolite might not be chiral, and, even if chiral, its mechanism might not show stereoselectivity. (Maffrand Tr. 1685-86; Hanson Tr. 2213-14; Harden Tr. 2325-26; Snyder Tr. 585-86.) If so, this would mean that pursuing the enantiomers of PCR 4099 might have no benefit. This, in turn, would suggest that development efforts focus on the racemate instead of the enantiomers.

Furthermore, Sanofi's prior work on the enantiomers of racemic thienopyridine compounds did not suggest that the separated enantiomers would exhibit different types or levels of activity. (Maffrand Tr. 1696-1700). Although Sanofi had previously observed that only one of the enantiomers of PCR 1033 exhibited antiplatelet activity, the enantiomers of PCR 3549, by contrast, had exhibited equivalent levels of activity. (Maffrand 1598-99, 1604-05.) Furthermore, the Court credits Dr. Davies' testimony that a medicinal chemist would not expect PCR 1033 and PCR 4099 to behave in the same

manner in the body on the basis of any structural similarity; PCR 4099 has an ester group, which allows for significant hydrogen bonding, whereas PCR 1033 does not. (Davies Tr. 2009-14.) In sum – as experts from both parties agree – it was not possible to predict whether either enantiomer would be more or less therapeutically active – and more or less toxic – than the other. (Snyder Tr. 591-92; Davies Tr. 2014-16; McClelland PI Tr. 505-06.)

B. Predicting Whether the Enantiomers of PCR 4099 Could Be Prepared

In addition, Dr. Maffrand and his colleagues could not predict with any reasonable degree of certainty that they would be able to obtain the enantiomers of PCR 4099. Up until the decision to attempt the resolution of PCR 4099, Sanofi had only twice attempted – albeit successfully – to obtain the enantiomers of racemic thienopyridines, even though Sanofi had synthesized approximately 1500 thienopyridines, of which roughly 600 were racemates with chiral carbon atoms. (Maffrand Tr. 1618-19.) As of 1987, there were at least ten different methods by which a chemist could try to obtain the individual enantiomers of a chiral compound. (Davies Tr. 1921-22.) After choosing a particular technique, a chemist would also have to make numerous decisions: the choice of solvents, of reagents, of concentrations, of temperature, and of time. (Davies Tr. 1939-43.) Sanofi's expert Dr. Davies testified on direct examination that there is no way to predict which method or methods will succeed if no prior art deals with the compound at hand; practitioners will begin with a method with which they are familiar or a method for which the necessary reagents are readily available.[5] (Davies Tr. 1939.)

[5] On cross-examination Davies did concede that at least five of the methods available would have been identified as inappropriate in the case of PCR 4099. (Davies Tr. 2023-24.)

As noted above, Sanofi had used diastereomeric salt formation to separate the enantiomers of PCR 1033, but had failed when trying to use that method to separate the enantiomers of PCR 3549. As of 1987, the prior art – including standard textbooks of organic chemistry – was replete with discussions of how to resolve enantiomers by diastereomeric salt formation, which was first identified by Louis Pasteur in 1853 and is sometimes referred to as "the classical method." (Davies Tr. 1925; Snyder Tr. 149-51, 155-56). The Feiser, Karrer, and Jacques references make clear that diastereomeric salt formation was a method of enantiomeric resolution that was well known in the art at the time that Sanofi chemists faced the task of obtaining the enantiomers of PCR 4099. See Louis F. Feiser & Mary Feiser, Advanced Organic Chemistry 85-89 (1961) (Def. Ex. 1322); Paul Karrer, Organic Chemistry 98-99 (1946) (Def. Ex. 162); Jean Jacques, et al., Enantiomers, Racemates, and Resolutions, 378-88 (1981) (Def. Ex. 492).

However, Dr. Davies explained that although that method is "one of the oldest methods," that does not mean that it is the best method, the easiest method to apply, or "the first one you should try." (Davies Tr. 1925-26.) As a general matter, obtaining the first crystals of any new compound through separation of diastereomeric salts is difficult. Jacques, for example, teaches that "[n]o infallible recipe exists for overcoming the resistance of a diastereomer to crystallize for the first time." (Jacques (Def. Ex. 492) at 386.) The Eliel reference confirms this point:

> Unfortunately, resolution is, in this respect, still very much a matter of trial and error, and even in the papers of experienced investigators one is apt to find, from time to time, a statement that a certain compound resisted resolution by any one of a large number of combinations of resolving agents and solvents that were tried.

Ernest L. Eliel, Stereochemistry of Carbon Compounds 50 (1962) (Def. Ex. 1930). See also McClelland Tr. 1117-21; Davies Tr. 1945-48. Although screening techniques would have allowed a person of ordinary skill in the art to improve the odds of a successful separation, diastereomeric salt separation was – and remains even today – a "paradigm of trial and error." Ton Vries, et al., "The Family Approach to the Resolution Of Racemates, J. Angewandte Chemie 2349 (1998) (Pl. Ex. 852); see also Jacques, Def. Ex. 492 at 380; McClelland Tr. 1137-39. Experts from both parties agreed that although a chemist can search the prior art for useful examples of prior resolutions of similar compounds, the precedents afford absolutely no assurance that the same configuration will succeed with a different compound. (McClelland Tr. 1118; Davies Tr. 1975; see also Eliel (Def. Ex. 1930) at 50.) Furthermore, the literature tends not to report failed resolution attempts. (McClelland Tr. 1135.) In the particular case of PCR 4099, the prior art offered no examples of the resolutions of chiral thienopyridines, and Apotex's expert Dr. McClelland – in preparing for his testimony – did not find any reference that contained the set of conditions that Sanofi ultimately used to obtain the enantiomers of PCR 4099. (McClelland Tr. 1071.) In fact, Dr. McClelland did not find any relevant instances of the resolution of thienopyridines in the prior art. (McClelland Tr. 1127; 1230-32.)

In addition, a person of ordinary skill in the art would have recognized the possibility that it would be more difficult to prepare the enantiomers of PCR 4099 than it had been to prepare the enantiomers of PCR 1033 and PCR 3549. First, the meythl ester group attached to the chiral center in PCR 4099 made that molecule more susceptible than PCR 3549 to racemization. (Hendrickson Tr. 1498; Maffrand Tr. 1656, 1700;

Badorc Tr. 1832-33.) Indeed, a person of ordinary skill in the art would have known that phenylglycine and its derivatives – of which PCR 4099 is one – are susceptible to racemization. (Badorc Tr. 1832; Davies Tr. 1956-60.) Second, because of the presence of the ester substituent on PCR 4099, the hydrogen atom located on the chiral carbon could easily be removed through the action of a base or an acid (which would be required in the course of resolution of the enantiomers). A free hydrogen in solution could then reform a bond to the same carbon atom, but it would bond on either side of that atom with equal likelihood, thereby yielding a racemate. (Davies Tr. 1958-61; 2002-04.) Third, the enantiomers of PCR 4099 would be susceptible to racemization in the acidic environment of the stomach by the same mechanism. (Davies Tr. 2004; Hendrickson Tr. 1463.)

Accordingly, neither the chemists at Sanofi nor a person of ordinary skill in the art could have reasonably expected that the separate enantiomers of PCR 4099 could be obtained at the time that Sanofi was contemplating whether to investigate them and, if obtained, they could not have predicted by what method and configuration.

C. Resolution of the Enantiomers of PCR 4099

In November 1985, Alain Badorc and Dr. Daniel Fréhel were asked to attempt to obtain the enantiomers of PCR 4099 in order to test whether either enantiomer would make a better drug than the racemate. (Maffrand Tr. 1650-51.) As the outset, Badorc and Dr. Fréhel decided not to attempt resolution through the formation of diastereomeric salts. The Court credits Badorc's testimony that that decision was influenced by the fact that PCR 4099 was "only barely basic and, therefore, only barely capable of carrying out a separation using diastereomeric salts." (Badorc Tr. 1829.) In addition, Badorc believed

that there were few commercially available acids that were likely to form diastereomeric salts in sufficient quantities to permit resolution. (Badorc Tr. 1830.) Instead of attempting diastereomeric salt separation, Badorc decided to attempt chemical asymmetric synthesis, the method that he had successfully used to prepare the enantiomers of PCR 3549. This choice was facilitated by the commercial availability of the required starting materials. (Badorc Tr. 1829-31.)

Badorc's lab notebook and a June 12, 1986 report show that Badorc reacted the starting materials to form the enantiomers of an intermediate compound – referred to as "OCBATH." (Pl. Ex. 50.) He then used the same "reaction sequence" that he had used in the synthesis of the enantiomers of PCR 3549. (Hendrickson 1497-98; Badorc 1836-37; Pl. Ex. 50 at S 03977-78; Pl. Ex. 51 at S 58990-91.) With PCR 4099, however, the sequence failed because the second reaction in the sequence, a condensation, yielded a racemic form of the desired product, not a pure enantiomer. (Badorc Tr. 1836-37; Pl. Ex. 50 at S 03978; Pl. Ex. 51 at S 58991.)

Badorc then tried a different approach. Starting from the racemic OCBATH, he attempted to separate that intermediate's enantiomers through the formation of diastereomeric salts with tartaric acid in isopropanol. After several crystallizations, Badorc obtained enantiomers with the same melting point and equivalent levels of optical rotation. (Badorc Tr. 1837-38; Pl. Ex. 50 at S 0379-80; Pl. Ex. 51 at S 58992-93.) Badorc then attempted to convert the enantiomers of OCBATH into those of PCR 4099 using the same cyclization reaction conditions used to prepare the enantiomers of PCR 3549. That product, however, also racemized. (Badorc Tr. 1838; Pl. Ex. 50 at S 03980; Pl. Ex. 51 at S 58993.)

Badorc also tried using diastereomeric salts to resolve the enantiomers of the acid precursor of PCR 4099, a compound designated as PCR 3068. To that end, he attempted resolution with several different chiral bases, but those efforts failed because no crystals formed. (Badorc Tr. 1839-42; Pl. Ex. 50 at S 03891.) When Badorc attempted to form diastereomeric salts of PCR 3068 with chirally pure d-camphorsulfonic acid in ethanol, crystals did form, but that effort failed because the crystals contained salts of both enantiomers, rather than just of one. (Badorc Tr. 1841-42.)

At that point – in January 1986 – Badorc revisited the technique that he had originally been reluctant to use and attempted to resolve the enantiomers of PCR 4099 directly by diastereomeric salt formation. (Badorc Tr. 1842.) To determine what combination of acid, solvent, and concentration would yield crystals, Badorc set up a "screening" experiment with approximately thirty test tubes containing various combinations of a chiral acid (e.g., camphorsulfonic, toluoyltartaric, dibenzoyl tartaric, mandelic, and tartaric) with PCR 4099 in various concentrations and in various solvents. (Badorc Tr. 1842-43.) Badorc obtained a solid material in only one of the test tubes – a gummy substance at the bottom of the tube containing a 1:1 ratio of camphorsulfonic acid and PCR 4099 in acetone. (Badorc Tr. 1844.) No crystals were obtained in any test tube. (Badorc Tr. 1844.)

In mid-February, Badorc began an additional screening test of several test tubes with different combinations of acid, solvent, and concentration. (Badorc Tr. 1844-45.) Badorc checked the test tubes each day for crystals, the presence of which would indicate the formation of a potentially separable diastereomeric salt. (Badorc Tr. 1846.) Approximately one month after beginning the experiment, Badorc detected crystals in

only one tube – the tube that contained (+) camphorsulfonic acid and PCR 4099 in a 4:10 ratio, dissolved in acetone.[6] (Badorc Tr. 1846-47.) As noted above, that same combination using the acid and PCR 4099 in a 1:1 ratio had not yielded crystals. (Badorc Tr. 1843-44.)

Because the small test tube reaction had not yielded a sufficient quantity of crystals for further testing, Badorc carried out a larger version of the experiment on March 18, 1986. (Badorc Tr. 1847-48; Pl. Ex. 72 at S 02014.) Risking the loss of the crystals that he had obtained, Badorc used those crystals to seed the larger version, which – after several trials – yielded a significant quantity of crystals of the levorotatory enantiomer of PCR 4099 in the camphorsulfanate form. (Badorc Tr. 1848-49; Pl. Ex. 72 at S 02014.) Using the same conditions – but substituting chirally pure 10-camphorsulfonic acid of opposite rotation – Badorc also resolved the dextrorotatory enantiomer (i.e., clopidogrel). (Badorc Tr. 1850-51; Pl. Ex. 50 at S 03986; Pl. Ex. 74 at S 02019.) Finally, to form the free base of both resolved enantiomers, Badorc reacted the camphorsulfonate salt forms with sodium bicarbonate, a base. (Badorc Tr. 1852.) Badorc verified the optical purity of the free base compounds to confirm that he had resolved the enantiomers and that they had not racemized at any stage. (Badorc Tr. 1852-53.) Nothing in the prior art – and nothing in his own experience with PCR 1033 and PCR 3549 – directed Badorc to employ the precise configuration of acid, solvent, and concentration that was ultimately successful with PCR 4099.

[6] Dr. Robert A. McClelland, an expert for Apotex, testified that each recrystallization takes from four hours to "perhaps overnight," and that a person of ordinary skill in the art would generally wait only that long, or "maybe for a few days," to see if crystals will form. (McClelland Tr. 880, 1131.) However, in the case of Badorc's second test tube screening experiment, it took approximately one month for crystals to form. (Badorc Tr. 1846.) The disparity between Dr. McClelland's testimony and the factual record undermines the proposition advanced by Apotex that the resolution of the enantiomers of PCR 4099 was a simple, routine procedure.

D. Preparation of Clopidogrel as a Pharmaceutically Acceptable Salt

To permit the testing and comparison of the properties of the enantiomers of PCR 4099 to those of the racemate, which had only been tested as a hydrochloride salt, Badorc prepared the hydrochloride salts of each enantiomer. (Badorc Tr. 1852-53.) As described below, pharmacological and toxicological testing showed that clopidogrel hydrochloride exhibited more antiplatelet activity than PCR 4099 and was better tolerated than the l-enantiomer, but – as a hydrochloride salt – the compound was hygroscopic (i.e., it had a tendency to absorb water from the atmosphere) and lacked stability. (Badorc Tr. 1853; Banker Tr. 1338; Pl. Ex. 48 at S 03781.) This made it a poor candidate for commercial tablet manufacture. For that reason, during May and June of 1987, Badorc searched for a salt form of clopidogrel that would be more suitable for use in commercial tablets. (Badorc Tr. 1854.)

Salts are formed by mixing an acid with a base. (Banker 1274, 1299-1300.) A basic rule of salt formation is that a weak base – such as PCR 4099 – generally requires a strong acid to form a salt.[7] (Banker 1274, 1300.) A measure of the strength of an acid or a base is its "pKa": a low pKa signifies a strong acid and a high pKa signifies a weak acid. (Banker 1274; Byrn Tr. 2111-12.) In 1977 and 1986, the scientific literature listed eighty acids as candidates for forming salts with basic drug compounds and twenty-one bases as candidates for forming salts with acidic compounds. On this point, the Court credits the Berge reference and the Gould reference. See Stephen M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1, 2-3 (1977) (Pl. Ex. 152); Philip L. Gould, "Salt Selection for Basic Dugs," 33 Int'l J. Pharm. 201, 202, 214-16 (1986) (Pl. Ex. 153); Byrn

[7] In addition to selecting the acid, the chemist must also choose a solvent and co-solvent in which to attempt to precipitate the crystals, and must also consider temperature and cooling rates. (Byrn Tr. 2127-29.)

Tr. 2126. Of the eighty acids listed by Berge, fifty-three were used in FDA-approved drugs as of 1974; the remaining twenty-seven were commercially marketed in other countries. (Berge (Pl. Ex. 152) at 2-3; Byrn Tr. 2126.) The Berge reference also taught the pKa of each of those acids. (Berge (Pl. Ex. 152) at 2-3.)

If the difference in pKa of an acid and base is greater than two, the "delta pKa rule" is a guideline that suggests that the amount of salt present in solution – as compared to that of the unreacted acid and base – will be greater than if the difference in pKa is less than two. (Byrn Tr. 2112-15.) However, even if the pKa difference between an acid and a base is only one or zero, their reaction will still yield a 10:1 or 1:1 ratio, respectively, of protonated to unprotonated base in solution. (Davies Tr. 2064-65; Byrn Tr. 2114-16.) The presence of protonated base will, in turn, permit salt formation in solution, from which crystals of the salt might precipitate. (Davies Tr. 2064-65; Byrn Tr. 2114-16.) For that reason, a person of ordinary skill in the art would not necessarily have excluded from consideration those acids whose pKa values differed from that of the relevant base by less than two. (Davies Tr. 2065; Byrn Tr. 2115-16.) Weak acids – where the resulting pKa difference is less than two – might even be preferable where there is the risk of acid-catalyzed racemization or hydrolysis of the base. (Byrn Tr. 2119.) Therefore, a person of ordinary skill in the art would not be able to predict from the list provided by Berge which acids would form useful salts for drug purposes. (McClelland PI Tr. 503-04.)

Depending on their properties, salts of pharmaceutical compounds can be characterized according to three general types, or "tiers." (Byrn Tr. 2109-11.) A Tier 1 salt results from the simple reaction of an acid and a base in solution, without regard to its properties. (Byrn Tr. 2109-10.) A Tier 2 salt is a solid salt that facilitates testing, but

may be hygroscopic or unstable over the long term and, for either of those reasons, may not be suitable for use in tablets. (Byrn Tr. 2110.) A Tier 3 salt – the type of salt that is generally desirable for use in a drug tablet – is crystalline, non-hygroscopic, stable as a tablet, soluble in bodily fluids, dissolved fast enough to allow absorption in the body, not sticky, and without a static charge. (Byrn Tr. 2110-11, 2120-21; McClelland Tr. 1173-74.)

Formation of a crystalline salt is important for an orally administered drug such as clopidogrel, and the salt form of a drug can affect a drug's pharmacological properties because of its effect on solubility, which influences absorption in the body and bioavailability. However, the prior art teaches – and both parties' experts agreed and the Court finds – that whether a crystalline material will form in a particular reaction of acid and base, the type of crystalline material that will form, and the properties that the crystalline material will have, are all unpredictable. (McClelland PI Tr. 503-04; McClelland Tr. 1101-02; Snyder Tr. 544-45; Byrn Tr. 2122-23.) In particular, Berge taught that:

> Choosing the appropriate salt . . . can be a very difficult task, since each salt imparts unique properties to the parent compound . . . . Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound.

Berge (Pl. Ex. 152) at 1. Making reference to Berge, the Gould publication provided similar teaching nearly a decade later:

> The importance of choosing the 'correct' salt form of a drug is well outlined in a published review (Berge et al., 1977) but, although salt form can have a dramatic influence on the overall properties of a drug, the selection of the salt form that exhibits the desired combination of properties remains a difficult semi-empirical choice.

Gould (Pl. Ex. 153) at 201. In addition to this high level of general unpredictability, a person of ordinary skill in the art would have recognized that there is no correlation between a racemate and its corresponding enantiomers when it comes to making a crystalline salt. (Banker Tr. 1322-24; Davies Tr. 1955-56; Byrn Tr. 2123-25.) The physical properties of racemates and their enantiomers, as well as of their respective salts, differ because the molecules pack differently, leading to different crystal structures. (Snyder Tr. 543-45; Banker Tr. 1321-23, 1327; Davies Tr. 1955; Byrn Tr. 2123-2125.) In other words, the salt form of a racemate may produce a very different crystalline structure than the same salt forms of the enantiomers of that racemate. For that reason, even if a person of ordinary skill in the art looking at the '596 patent had concluded that PCR 4099 should be reformulated as a bisulfate salt, that would not imply that the enantiomers of PCR 4099 – if obtained – should also be prepared as bisulfate salts. (Davies Tr. 1914-15; Byrn Tr. 2136-38.) Accordingly, there would have been no way for a person of ordinary skill in the art to deduce from the examples of the '596 patent that clopidogrel would form a bisulfate salt and that it would be a Tier 3 crystalline salt. (Davies Tr. 1915; Byrn Tr. 2136.)

Tasked with identifying a suitable crystalline, non-hydrochloride salt of a drug, a person of ordinary skill in the art would look to the approximately fifty pharmaceutically acceptable (i.e. FDA-approved) acids identified by the prior art. (McClelland PI Tr. 490-91; Byrn Tr. 2126.) This was essentially the approach taken at Sanofi, where Badorc and his colleagues reacted clopidogrel with an array of approximately twenty-one different acids – only about ten of which were strong acids – in different solvents. (Badorc Tr. 1854-55; Maffrand 1773-74; Pl. Ex. 73 at S 02245, S 02248-60, S 02276; Pl. Ex. 74 at S

02054.) Badorc used both strong and weak acids because it was not possible to predict which acid would yield a crystalline salt meeting all of the criteria for a suitable pharmaceutical tablet. (Badorc Tr. 1854-55; Byrn Tr. 2140-46.) When Badorc attempted to create the sulfate form of clopidogrel, the reaction instead resulted in its bisulfate salt. (Badorc Tr. 1797-98.) Although sulfuric acid was one of the first acids that he tried, Badorc continued to test other acids. (Badorc Tr. 1854-55; McClelland Tr. 2565.) This was not unreasonable. On the contrary, it would have been reasonable for a person of ordinary skill in the art to try a variety of weak acids and strong acids so as not to overlook potential Tier 3 salts. (Badorc Tr. 1854-55; Davies Tr. 1969-70; Byrn Tr. 2144-46.)

The bisulfate salt proved to be the only salt with the optimal properties: a high melting point, long-term stability, non-hygroscopicity, and good solubility. (Badorc Tr. 1855; Banker Tr. 1357.) Although a person of ordinary skill in the art would have known that hydrochloric acid, hydrobromic acid, and sulfuric acid were the three strongest acids used in pharmaceutical salts, a person of ordinary skill in the art would not have reasonably expected the bisulfate salt of clopidogrel to have the highly favorable combination of properties that it turned out to possess. (Byrn Tr. 2164.) First, the highly acidic nature of the bisulfate posed a significant risk of racemization, which made it unattractive for use with an enantiomeric compound. (Byrn Tr. 2158; Davies Tr. 1970-72.) Second, the Court credits the testimony from Dr. Stephen R. Byrn, an expert for Sanofi in the area of solid state chemistry, that the relevant prior art not only provided no positive indication that sulfuric acid would lead to a successful crystalline salt, but the prior art in fact would have led a person of ordinary skill in the art away from sulfuric

acid in the case of clopidogrel. (Byrn Tr. 2160-63.) Specifically, the Gould publication taught that to avoid hygroscopicity – the problem posed by the hydrochloride salt of clopidogrel – one should avoid polar salts, which would include the bisulfate. (Gould (Pl. Ex. 153) at 210-13; Byrn Tr. 2158-59, 2162.) Instead, Gould pointed to the use of carboxylic acids, which, in the case of clopidogrel, proved unsuccessful. (Gould (Pl. Ex. 153) at 210-13; Byrn Tr. 2160-63.) Third, another prior art reference – the Berge publication – did not even list the bisulfate salt in its list of FDA-approved commercially marketed salts; the bisulfate appears only on the list of non-FDA approved salts, making it all the more surprising that the bisulfate salt of clopidogrel, in fact, proved to be a highly suitable pharmaceutical formulation. (Berge (Pl. Ex. 152) at 2-3; McClelland PI Tr. 491.) For all of these reasons, a person of ordinary skill in the art could not have reasonably expected that the bisulfate salt of clopidogrel would be the optimal pharmaceutical salt form of the compound.

V. The Biological Properties of Clopidogrel

A. The Pharmacological Properties of the Enantiomers of PCR 4099

Testing demonstrated that the dextrorotatory enantiomer – clopidogrel – exhibited good platelet inhibition activity. (Maffrand Tr. 1659.) By contrast, the levorotatory enantiomer was "completely ineffective"; it showed no statistically significant activity in any assay. (Maffrand Tr. 1659; Snyder Tr. 2526-29.) This absolute stereoselectivity of platelet inhibition for the enantiomers of PCR 4099 was unexpected in light of the prior art. (Davies Tr. 2014-15, 2018-19; Hanson Tr. 2214, 2216, 2250-51; Harden Tr. 2338.)

A finding that the absolute stereoselectivity of the enantiomers of PCR 4099 was unexpected was not undermined by the prior art regarding ADP platelet receptors,

including the work of Dr. Robert Colman, a platelet physiologist. Apotex has failed to persuade the Court that Colman's work – in particular, a 1984 article co-authored by Colman – would have made Sanofi's results unsurprising to a person of ordinary skill in the art. See Robert W. Colman & William R. Figures, "Characteristics of an ADP receptor mediating platelet activation," Molecular & Cellular Biochem. 101 (1984) (Def. Ex. 519). As of 1987, platelet physiologists suspected the existence of one or more platelet receptors for ADP, and they knew that the suspected receptors were stereoselective for the naturally occurring stereoisomer of ADP. (Hanson Tr. 2216-17; Harden Tr. 2321-22.) Based on that phenomenon, however, a person of ordinary skill in the art would not have drawn the inference that chiral antagonists would inhibit platelet activation stereoselectively. (Hanson Tr. 2217-18; Harden Tr. 2322-23.) In the early 1980s, Dr. Colman identified a protein on the surface of platelets – aggregin – that he posited was a receptor for ADP. (Colman Tr. 1015-20.) Dr. Colman's work did not, however, address whether thienopyridines inhibited platelet activation through interaction with aggregin or any other protein – his work in the 1980s did not involve thienopyridines. (Snyder Tr. 605-06; Colman Tr. 1024-25; Maffrand Tr. 1676-77.) Nor did Dr. Colman's work address whether aggregin interacted with any molecule in a stereoselective fashion; he did not compare the effects of different stereoisomers of the same chiral molecule on aggregin or platelet activation. (Harden Tr. 2334-35; Snyder 605.) Thus while Colman's work, including the 1984 article, relates generally to the problem of platelet aggregation that Sanofi's research also addressed, the 1984 article was of no particular significance to the properties that Sanofi discovered clopidogrel to possess.

B. The Toxicological Properties of the Enantiomers of PCR 4099

Sanofi also subjected the enantiomers of PCR 4099 to a battery of toxicological testing. In acute toxicity testing of PCR 4099 and its enantiomers in March 1987, Sanofi calculated the doses at which each of the compounds is lethal in rats. The tests – reported internally in a research memorandum dated May 18, 1987 – showed that the LD_{50} for clopidogrel (4316 mg/kg) was much higher than the LD_{50} of either PCR 4099 (1615 mg/kg) or the l-enantiomer (1702 mg/kg).[8] (Lacheretz Tr. 2377-79; Pl. Ex. 118 at 11.) This showed that the acute toxicity of the levorotary enantiomer and PCR 4099 was "very different" – i.e., significantly higher – than that of clopidogrel. (Lacheretz Tr. 2379.) The absolute lethal doses of PCR 4099 and the levorotatory enantiomer were similar (2000 mg/kg) and were also lower than the absolute lethal dose of clopidogrel (5000 mg/kg). (Maffrand Tr. 1688-89; Pl. Ex. 118 at 2.) Furthermore, convulsions were observed in animals receiving PCR 4099 and the l-enantiomer in a comparative acute toxicity study, but no convulsions were observed in animals receiving clopidogrel, including clopidogrel in any of its hydrochloride, bisulfate, or hydrobromide forms. (Lacheretz Tr. 2377; Pl Ex. 130.) In sum, the data collected from tests conducted by Sanofi – data which was later reported in the '265 patent – showed (1) that the levorotatory enantiomer is lethal at significantly lower doses than clopidogrel, and (2) that the levorotatory enantiomer is neurotoxic, but clopidogrel is not. (Graham Tr. 2423-24; Maffrand Tr. 1688-90; Lacheretz Tr. 2387.) According to Sanofi's toxicologist Dr. Lecheretz, Sanofi concluded from these results that clopidogrel was "much less toxic or,

[8] The LD_{50} is the calculated dose of a compound at which 50 percent of the test animals administered the compound die. Similarly, the LD_{10} indicates the single dose at which 10 percent of the animals tested die. (Lecheretz Tr. 2358.)

in other terms, much better tolerated" than both the levorotatory enantiomer and PCR 4099. (Lacheretz Tr. 2380.)

That conclusion was amply supported at trial. Dr. Joseph V. Rodricks, an expert for Sanofi, explained that a drug's therapeutic index is a measure of a drug's safety and is calculated based on the ratio of its toxic dose to the dose that "reflects efficacy," i.e., the dose that has a therapeutic effect. (Rodricks Tr. 2488.) A higher therapeutic index indicates a safer drug. (Rodricks Tr. 2488-90.) Based on data from short-term studies, Dr. Rodricks testified that clopidogrel has a much higher therapeutic index than PCR 4099, which indicates clopidogrel's safety advantage over the racemate. (Rodricks Tr. 2494-95.) Based on data derived from longer-term studies, Dr. Rodricks determined that PCR 4099's low therapeutic index demonstrates a valid safety concern. (Rodricks Tr. 2496-99.) In contrast, serious toxic effects were not observed in response to any dose of clopidogrel in the longer-term studies. (Rodricks Tr. 2495-98.)

Based on the documentary evidence and testimony relating to both the pharmacological and toxicological properties of clopidogrel, the Court finds that the prior art offered no basis to reasonably expect that the resolution of PCR 4099 would yield an inactive enantiomer that was also less well-tolerated than the active enantiomer. (McClelland PI Tr. 505-06; Snyder Tr. 591-92; Harden Tr. 2250-51.) Accordingly – and most importantly – the fact that clopidogrel was both the more active enantiomer of PCR 4099 and was better tolerated than the levorotatory enantiomer would have been unexpected to a person of ordinary skill in the art prior to obtaining the separate enantiomers and testing them.

C. Sanofi's Decision to Discontinue Development of PCR 4099

In March 1987, Pierre Simon, then the head of research and development at Sanofi, reviewed the pharmacological and toxicological studies of PCR 4099 and its enantiomers. At that time, Dr. Maffrand was reluctant to discontinue the development of PCR 4099 in favor of clopidogrel. (Maffrand PI Tr. 154.) In an internal memorandum dated March 31, 1987, Dr. Maffrand noted that tests had shown PCR 4099 to be "consistently active in healthy volunteers," but that it had been "consistently ineffective in patients" for reasons yet unknown. (Def. Ex. 622.) Maffrand further noted that the active enantiomer of PCR 4099 showed less acute toxicity in rats and mice than the inactive enantiomer, but that there was not yet data available on subacute toxicity. (Id.) Nonetheless, Dr. Maffrand expressed doubts about abandoning Sanofi's work on PCR 4099 in favor of the active enantiomer, noting that "[i]t isn't the inactive enantiomer that is causing the problems with PCR 4099 we are encountering today." (Id.) At the preliminary injunction hearing, Dr. Maffrand testified that by that time, Sanofi had performed more than fifty tests on PCR 4099 from 1980 to 1987, including phase I human trials, at a cost of "tens of millions of dollars." (Maffrand PI Tr. 143-44, 152-53.) To develop clopidogrel, Sanofi would not have been able to rely on the data from tests that related to PCR 4099. As a result, Dr. Maffrand at that time viewed switching to the development of the active enantiomer instead of the racemate as a four year setback. (Maffrand PI Tr. 155.)

Nonetheless, Simon decided to terminate the development of PCR 4099 in favor of focusing on clopidogrel. (Maffrand Tr. 1666.) In an April 16, 1987 internal memorandum setting forth his decision, Simon wrote the following:

> These studies have demonstrated that only the D form is active and that, moreover, the L form was more toxic and was specifically responsible for convulsions observed in animals at high doses. Under these conditions, it appears clear to me that we cannot envision development of the [racemate], and I have decided to stop this development. Our efforts therefore are turning to the D form and we are taking all possible steps to reduce lost time to a minimum.

(Pl. Ex. 57t.) Accordingly, the development of PCR 4099 was stopped.

On November 6, 1987, Sanofi held a meeting in Japan with its partners in a joint venture. That meeting included discussion of the decision to abandon PCR 4099. A memorandum describing the meeting suggests that the reason for discontinuing the development of PCR 4099 in favor of clopidogrel was based on Sanofi's discovery that the therapeutic activity was located only in the dextrorotatory enantiomer and that "the [l-enantiomer] is more toxic than the [d-enantiomer] qualitatively and quantitatively." (Def. Ex. 13.) Moreover, the memorandum also notes the following:

> The trend in regulatory requirements would have made it difficult to get the NDA approval with the racemic either in France or in Europe or in the United States. It is the reason why SANOFI stopped the development of PCR 4099. In any case, our decision was not due to problem[s] in preclinical or in clinical studies, particularly no problem of G.I. intolerance was noted in volunteers, showing an advantage over Ticlopidine. For Japan, it also seems that it would not have been possible to apply for a NDA with the racemic in such a case.

(Id.) Nonetheless, because the November 7, 1987 meeting took place several months after Simon's April 16, 1987 memorandum – which focused specifically on the neurotoxicity problems associated with PCR 4099 – and, more generally, well after Sanofi had decided to split the enantiomers of PCR 4099, the Court credits the extensive trial testimony and documentary evidence that the decision to discontinue the development of PCR 4099 in favor of clopidogrel was based on the sub-optimal side effect profile of PCR 4099, not because of any specific concern raised by Sanofi's joint

venture partner or any nascent regulatory trend mandating the investigation of enantiomers where a racemic drug was proposed.

VI. The '265 Patent

A. The French Patent

As described above, Sanofi applied for a French patent claiming clopidogrel and its salts on February 17, 1987 – at a time when Sanofi was still actively engaged in developing PCR 4099. Prior to filing the application, Fréhel put together an initial draft of that application, which he circulated on December 1, 1986. That draft included the following statement in the specification: "In an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive. Moreover, the inactive levo-rotatory enantiomer I_l is the less well tolerated of the two enantiomers." (Def. Exs. 8 at S 91129, 425 at S 91129.) That statement was based on observations made by Sanofi scientists in the course of pharmacological testing of the enantiomers of PCR 4099. (Maffrand Tr. 1659-64.) That statement remained in the version of the application that was submitted to the French regulator, and, eventually, to the PTO in the United States.

On December 30, 1986, after Fréhel's initial draft had been circulated internally, Michel de Haas, head of Sanofi's legal department, circulated a memo with the heading "Patentability of the two enantiomers of PCR 4099." In that memo, Haas wrote:

> [I]f we ever develop the active isomer [i.e., clopidogrel], it would be very useful to have a patent for this isomer (prolonging our monopoly, prohibiting its use by third parties in countries where [PCR] 4099 is not patented as a product . . .). Issuing such a patent will only be effective, at least in countries with an examination process, if we make mention of an 'unexpected' advantage (whether this is the reason for developing the product or not).

(Def. Ex. 628.) Haas also noted that Sanofi would not develop the active enantiomer if it showed "no major therapeutic advantage" over PCR 4099 considering the cost of manufacture, either "by stereospecific synthesis or by separation from the racemic." (Id.) In the alternative, Haas noted that they might find the active enantiomer "very attractive" if, for example, "it does not have . . . some of the objectionable side effects of PCR 4099 (bleeding . . .)." (Id.)

In late January 1987, Jacqueline LaForest, an in-house French patent attorney at Sanofi, reviewed Fréhel's draft application for the French patent. (Maffrand Tr. 1673.) Although LaForest had studied chemical engineering as an undergraduate student, she did not have training in pharmacology or toxicology. (Maffrand Tr. 1673.) In comments dated January 26, 2007 to the draft application, LaForest wrote: "[t]he pharmacology study does not lead to surprising activity; we will not pass the examiner's hurdles without other results." (Def. Ex. 304.) Laforest also wrote: "If I understood the text [of the application] correctly, PRP aggregation results [i.e., results of testing of the compounds' ability to inhibit platelet aggregation] are missing . . . ." (Id.) However, those very results in fact appeared prominently in the application that Laforest was reviewing. (Snyder Tr. 645-46; Maffrand Tr. 1674; Def. Ex. 304.) Furthermore, LaForest's written comment on the lack of "surprising activity" was made before the results of subsequent March 1987 toxicology studies were known. (Maffrand PI Tr. 152.)

B. The U.S. Patent

On February 12, 1988, Sanofi filed an application in the United States for a patent on clopidogrel and certain of its salts. The U.S. application, as had the French application, contained the statement: "In an unexpected manner only the dextro-rotatory

enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive. Moreover, the inactive levo-rotatory enantiomer I_l is the less well tolerated of the two enantiomers." (Def. Ex. 9 at CLO-DRL 51362.)

In support of that statement, Sanofi's application reported the results of three different pharmacological tests and one acute toxicity test. The acute toxicity test showed that clopidogrel was lethal at doses that were double those at which the levorotatory enantiomer and the racemate were lethal. (Id. at CLO-DRL 51379-80.) This demonstrated that clopidogrel was much less toxic than the levorotatory enantiomer. (Maffrand PI Tr. 251-53; Maffrand Tr. 1688-89; Graham Tr. 2424.) In addition, between the dates that Sanofi filed the French patent application and the U.S. patent application, Sanofi scientists had conducted additional toxicological tests, the results of which – as described above – demonstrated that the levorotatory enantiomer and PCR 4099 caused convulsions at doses which clopidogrel did not. (Maffrand PI Tr. 151-52.)

The examiner of the application for the '265 patent was Bernard L. Dentz, the same examiner who had approved the '596 patent. On November 4, 1988, Dentz initially rejected Claims 1-5 and Claims 10-11 as unpatentable because he believed the disclosure of PCR 4099 in the '596 patent anticipated them. (Fact Stmt. ¶ 21.) In the rejection, however, Dentz stated that Sanofi could correct its application by adding the limitation "substantially pure" as a means of distinguishing the claims of the '265 patent from the claims of the '596 patent. (Id.) Dentz also noted that if Sanofi made that amendment, a basis for the invention's patentability was Sanofi's reported data showing that the "toxicity" of the l-enantiomer "is markedly higher" than that of the d-enantiomer. (Id.)

On January 9, 1989, Sanofi amended claims 1-5 by inserting the phrase "substantially separated from the levo-rotatory isomer." (Id. ¶ 23.) On January 30, 1989, the PTO issued a Notice of Allowability for the amended claims. (Id. ¶ 26.) The '265 patent issued on July 11, 1989. (Id.)

C. The Clinical Application of Clopidogrel Bisulfate

Prior to the introduction of Plavix®, physicians prescribed aspirin and/or ticlopidine to prevent cardiovascular conditions believed to be caused or exacerbated by platelet aggregation. (Schneller Tr. 738-41.) The long-term use of aspirin is associated with certain side effects, such as ulcers and gastrointestinal bleeding, and ticlopidine, as described above, is associated with an elevated risk of neutropenia and TTP. (Maffrand Tr. 1693-94; Schneller Tr. 763, 811-16.) Following its launch in 1998, Plavix® replaced ticlopidine as a prescription oral antiplatelet medication to a nearly complete extent. (Maffrand PI Tr. 155; Schneller Tr. 762, 806-07.)

Both prior to and since the launch of Plavix® on the market, large-scale clinical studies have been conducted involving clopidogrel. The results of the CAPRIE trial, published in 1996, showed that the long-term administration of Plavix® to patients with atherosclerotic vascular disease was more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or death caused by blockage of an artery. (Schneller Tr. 821-22.) Apotex's expert Dr. Stanley J. Schneller, a cardiologist, characterized the difference in efficacy as, however, "very modest." (Schneller Tr. 822.) CAPRIE also showed that Plavix® was associated with a low rate of neutropenia and TTP: only 0.1 percent of patients taking clopidogrel experienced neutropenia, and only 0.08 percent experienced neutropenia that was severe; no patient in the CAPRIE trial

experienced TTP. (Schneller Tr. 812-817.) Dr. Schneller cautioned, however, that CAPRIE did not directly compare clopidogrel to ticlopidine; data derived from the CAPRIE study – when compared against historical data on ticlopidine – indicated a lower incidence of neutropenia and TTP with clopidogrel. (Schneller Tr. 812-13.)

Additional studies involving Plavix® included the CURE trial and the CLASSICS trial. The CURE trial, conducted between 1998 and 2000, demonstrated an 18.4% relative reduction in the risk of death, nonfatal myocardial infarction, or stroke in patients taking the combination of clopidogrel and aspirin versus patients taking aspirin alone. (Schneller Tr. 825.) Plavix® is also widely prescribed for patients who have received stents, the thin wire coils used to prop open arteries narrowed by arteriosclerotic plaque, to prevent thromboses that may form on the stents after their insertion. (Schneller Tr. 807-08, 811.) The CLASSICS trial demonstrated the superior safety of Plavix® compared to ticlopidine for stenting.

CONCLUSIONS OF LAW

I. Infringement

The parties have stipulated that Apotex's generic clopidogrel bisulfate product infringes Claim 3 of the '265 patent. That patent claims the "[h]ydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl)(2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer," also known as clopidogrel bisulfate. ('265 patent at col. 12, ll. 37-41; see also Fact Stmt. at ¶¶ 18-19; May 7, 2004 Stipulation and Order.)

II. Invalidity

Having conceded infringement, Apotex bears the burden of proof because "[a] patent shall be presumed valid," and "[t]he burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." 35 U.S.C. § 282. To overcome this presumption of validity at trial, "the party challenging a patent must prove facts supporting a determination of invalidity by clear and convincing evidence." Schumer v. Lab. Computer Sys., 308 F.3d 1304, 1315 (Fed. Cir. 2002) (citing Apotex USA, Inc. v. Merck & Co., 254 F.3d 1031, 1036, (Fed. Cir. 2001), cert. denied, 534 U.S. 1172, 122 S. Ct. 1196, 152 L. Ed. 2d 136 (2002)). As noted above, Apotex challenges the validity of the '265 patent on the grounds of anticipation, obviousness, and obviousness-type double patenting and challenges the enforceability of the '265 patent on the grounds that Sanofi engaged in inequitable conduct before the PTO. At trial, Apotex bore the burden of proving each of these defenses by clear and convincing evidence. See Oney v. Ratliff, 182 F.3d 893, 895 (Fed. Cir. 1999) (invalidity); Elk Corp. v. GAF Bldg. Materials Corp., 168 F.3d 28, 30 (Fed. Cir. 1999) (unenforceability), cert. denied, 528 U.S. 873, 120 S. Ct. 178, 145 L. Ed. 2d 150 (1999). This is a "heavy burden," Am. Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350, 1359 (Fed. Cir. 1984) (quoting Radio Corp. of Am. v. Radio Eng'g Labs., 293 U.S. 1, 8, 54 S. Ct. 752, 79 L. Ed. 163 (1934)), 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) (quoting Colorado v. New Mexico, 467 U.S. 310, 316, 104 S. Ct. 2433, 81 L. Ed. 2d 247 (1984)).

A. Anticipation

1. Legal standard

An invention may receive a patent unless "the invention was patented or described in a printed publication in this or a foreign country or in public use or sale in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102. See Hoover Group, Inc. v. Custom Metalcraft, Inc., 66 F.3d 299, 302 (Fed. Cir. 1995) ("Invalidity based upon lack of novelty (often called 'anticipation') requires that the same invention . . . was known or used by others before it was invented by the patentee.") The application for the '265 patent was filed with the PTO on February 12, 1988, but claims priority from two French patent applications filed on February 17, 1987 and November 27, 1987, respectively. (Fact Stmt. at ¶ 9.) A patent is invalid due to anticipation when "each and every limitation is found either expressly or inherently in a single prior art reference." See Celeritas Techs. Ltd. v. Rockwell Int'l Corp., 150 F.3d 1354, 1361 (Fed. Cir. 1998); see also Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006); Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1379 (Fed. Cir. 2003).

In addition, the prior art reference must be "an enabling disclosure," rather than mere "vague intimations of general ideas that may or may not be workable." Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366 (Fed. Cir. 1997) (citing Brenner v. Manson, 383 U.S. 519, 536, 86 S. Ct. 1033, 16 L. Ed. 2d 69 (1966)). "Accordingly, invalidity by anticipation requires that the four corners of a single, prior art reference describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue

experimentation." Advanced Display Sys., Inc. v. Kent State Univ., 212 F. 3d 1272, 1282 (Fed. Cir. 2000). However, a disclosure is an "enabling disclosure" if a person of ordinary skill in the art "could have combined the publication's description of the invention with his own knowledge to make the claimed invention," Impax Labs., Inc. v. Aventis Pharms., Inc., 468 F.3d 1366, 1381 (Fed. Cir. 2006) (quoting In re Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985), and the fact "[t]hat some experimentation is required to practice the claimed invention is permissible, so long as it is not undue." Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1321 (Fed. Cir. 2003).

2. Discussion

As a preliminary matter, the burden of showing invalidity is "especially difficult" when "the infringer attempts to rely on prior art that was before the patent examiner during prosecution." See Glaxo Group Ltd. v. Apotex, Inc., 376 F.3d 1339, 1348 (Fed. Cir. 2004) (citing Al-Site Corp v. VSI Int'l Inc., 174 F.3d 1308, 1323 (Fed. Cir. 1999)). Here, not only was the prior art patent – the '596 patent – before the patent examiner during the prosecution of the '265 patent, but also the very same patent examiner, Bernard Dentz, approved both the '596 patent and the '265 patent.

a. The '596 Patent Does Not Explicitly or Inherently Describe Clopidogrel Bisulfate

Apotex relies on the '596 patent or its Canadian counterpart – the '875 patent – for its anticipation defense. The Court finds that Apotex has not proved by clear and convincing evidence that either patent describes clopidogrel bisulfate.

Claim 3 of the '265 patent, which claims clopidogrel bisulfate, reads as follows:

> Hydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5 (4,5,6,7-tetrahydro (3,2-c) thienopyridl) (2-

> chlorophenyl) – acetate substantially separated from the levo-rotatory isomer.

'265 patent at col. 12. ll. 37-40. Thus, the claim consists of the following key limitations: (1) the bisulfate salt of (2) the dextrorotatory enantiomer of (3) the compound MATTPCA (4) substantially separated from the levorotatory enantiomer. (See Order dated May 7, 2004.)

Claim 2 of the '596 patent, in contrast, reads as follows:

> Methyl α-(4,5,6,7-tetrahydro-thieno(3,2,c)-5-pyridyl)-o.chlorophenyl-acetate.

'596 patent at col. 13, ll. 19-20. In the '596 patent specification, Claim 2 is exemplified as Example 1, which describes the hydrochloride salt of PCR 4099. '596 patent at col. 3, ll. 36-57.

In its decision affirming this Court's grant of a preliminary injunction in favor of Sanofi, the Federal Circuit found that "the plain language of claim 2 [of the '596 patent] only recites the free base, MATTPCA, and does not expressly describe the dextrorotatory or levorotatory enantiomers or any salt. Because claim 2 [of the '596 patent] fails to describe each and every limitation of claim 3 [of the '265 patent] on its face, claim 2 does not anticipate claim 3." Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1376 (Fed. Cir. 2006), reh'g denied, 2007 U.S. App. LEXIS 2807 (Fed. Cir. Jan. 19, 2007). Nothing in the trial record changes the plain language of the patents, and this Court therefore reaches the same conclusion on a complete record as this Court and the Federal Circuit reached on a more limited record: Claim 2 of the '596 patent does not expressly describe clopidogrel or its bisulfate salt.[9] The Court also finds that Example 1 does not expressly

[9] That conclusion is supported by the absence from Claim 2 of the limitation which appears in Claim 1 – that the compounds within the genus "[include] both enantiomeric forms or their mixture." Because that

describe clopidogrel bisulfate – there is no explicit reference to the enantiomers of PCR 4099 in that example and the particular salt described is the hydrocholoride, not the bisulfate.

The more difficult question is whether the additional limitations – namely the dextrorotatory enantiomer and its bisulfate salt – are inherently described elsewhere in the '596 patent. "Inherent anticipation requires that the 'missing characteristic is necessarily present, or inherent, in the single anticipating reference.'" Glaxo Group, 376 F.3d at 1348-49 (quoting Schering Corp., 339 F.3d at 1377); see also In re Cruciferous Sprout Litig., 301 F.3d 1343, 1349 (Fed. Cir. 2002) (quoting MEHL/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1365 (Fed. Cir. 1999)) ("Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates.").

Claim 1 of the '596 patent claims a general formula and specifies that the compounds covered by that formula include:

> their addition salts with pharmaceutically acceptable mineral or organic acids . . . including both enantiomeric forms or their mixture.

'596 patent at col. 13, ll. 8-19. The parties have stipulated that clopidogrel bisulfate is a compound within the genus of Claim 1 of the '596 patent. (Fact Stmt. at ¶ 32.)

Claim 8, which is also relevant, reads as follows:

> A therapeutic composition having blood-platelet aggregation inhibiting activities and anti-thrombotic activities containing an effective amount of a compound of

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language does not appear in Claim 2, it is appropriate to infer that Sanofi did not intend Claim 2 to cover the enantiomers of PCR 4099. See Seachange Int'l, Inc. v. C-COR Inc., 413 F.3d 1361, 1368 (Fed. Cir. 2005) (quoting Karlin Tech. Inc. v. Surgical Dynamics, Inc., 177 F.3d 968, 971-72 (Fed. Cir. 1999)) (applying "the common sense notion that different words or phrases used in separate claims are presumed to indicate that the claims have different meanings and scope").

> claim 1, or an addition salt thereof with a pharmaceutically acceptable mineral or organic acid or with mineral bases, or one of the two enantiomers or their mixture and a pharmaceutically acceptable carrier.

'596 patent at col. 14, ll. 5-11.

Apotex contends that importing the limitations of Claims 1 and 8 into Claim 2 or Example 1 of the specification discloses clopidogrel bisulfate to a person of ordinary skill in the art. Indeed, Claims 1 and 8 do make express reference to the claim limitations which are absent from Claim 2 – namely, that the invention disclosed by the '596 patent includes the enantiomers of each racemic mixture and their formulation as pharmaceutically acceptable salts. Furthermore, some of the examples set forth in the specification – albeit not Example 1, which discloses PCR 4099 – are formulated as bisulfate salts.

Apotex's argument, however, is ultimately unpersuausive. First, it is undisputed that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category." Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings, 370 F.3d 1354, 1367 (Fed. Cir. 2004); see also Atofina, 441 F.3d at 999. In essence, patentability is not precluded by the fact that an inventor has identified or selected a single compound with particularly desirable qualities from a large class of previously patented compounds. See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 364 F.Supp. 2d 820, 897 (S.D. Ind. 2005) ("Inventions based on the identification or selection of a specific material or compound with particularly desirable properties within a previously disclosed genus of such materials or compounds do not violate any of the substantive requirements for patentability.") Although clopidogrel bisulfate concededly falls into the broad genus disclosed by Claims 1 and 8 – a genus which includes millions

of possible compounds – a person of ordinary skill in the art would need to engage in impermissible "mechanistic dissection and recombination" of those disparate elements to arrive at the particular combination that is clopidogrel bisulfate. In re Ruschig, 343 F.2d 965, 974 (C.C.P.A. 1965); see also Zenith Goldline, 364 F. Supp. 2d at 900.

As noted above, Claim 2 describes the free base of PCR 4099 and Example 1 depicts PCR 4099 as a hydrochloride salt. However, neither of these disclosures describes the enantiomers of the racemate. See Pfizer Inc. v. Ranbaxy Labs. Ltd., 405 F. Supp. 2d 495, 519 (D. Del. 2005), aff'd in part, rev'd in part on other grounds, 457 F.3d 1284 (Fed. Cir. 2006) (noting that "courts considering issues related to racemates and their individual isomers have concluded that a prior art disclosure of a racemate does not anticipate the individual isomers of the racemate"); In re May, 574 F.2d 1082, 1090 (C.C.P.A. 1978) ("[T]he novelty of an [enantiomer] is not negated by the prior art disclosure of its racemate.").

Despite the fact that the '596 patent covers millions of possible compounds when taking into account the full range of possible addition salts, Apotex invokes In re Petering, 301 F.2d 676 (C.C.P.A. 1962), and In re Schaumann, 572 F.2d 312 (C.C.P.A. 1978) in support of the proposition that the '596 patent would be read by a person of ordinary skill in the art to describe a dramatically smaller genus of nine preferred compounds, including clopidogrel bisulfate.

In Petering, the Court of Customs and Patent Appeals upheld a Patent Board decision which had found that a claim covering several specific chemical compounds was anticipated by a prior art patent that had disclosed a class of compounds of which the specific compounds were members. 301 F.2d at 682. To reach that conclusion, the court

identified "specific preferences" in the prior art patent that narrowed the generic formula to a limited subclass of approximately twenty compounds. Id. at 681. That same court reached a similar conclusion on similar facts in Schaumann, again noting the presence of a disclosed preference in the prior art patent. 572 F.2d at 316. Petering and Schaumann thus stand for the proposition that a genus may be small enough that its disclosure is equivalent to the description of each species within it. See Petering, 301 F.2d at 681-82; Schaumann, 572 F.2d at 316-17.

Apotex's proposed "sub-genus" consists of PCR 4099 and its levorotatory and dextrorotatory enantiomers, as well as three possible addition salts – the hydrobromide, the hydrochloride, and the bisulfate. This results in a subset of nine possible combinations out of the millions of combinations otherwise covered by the general formula disclosed in Claim 1 of the '596 patent. Apotex, however, has not persuaded the Court that the specification and claims of the '596 patent would have guided a person of ordinary skill to that particular subset.

First, Apotex contends that the pharmacological testing data in the '596 patent points a person of ordinary skill in the art directly to PCR 4099 and its enantiomers. That proposition, however, is undermined by several of this Court's findings. Most importantly, the testing data relied on by Apotex is based on screening tests that do not provide precise or sophisticated data. The tests did not, for example, involve a sufficient variety of doses of each compound from which ED_{50} values could be calculated. A person of ordinary skill in the art would not use that data to rank the tested compounds against each other as a means of evaluating pharmacological activity, except where a particular compound showed virtually no platelet inhibition activity.

Furthermore, although PCR 4099 performed well in all four tests, other compounds also performed as well or, arguably, better, on one or more of the tests. Certainly, the results did not rule out the potential development of every other compound exemplified in the '596 patent apart from PCR 4099. The Court also notes that nothing in the '596 patent would have taught a person of ordinary skill in the art which of the tested compounds was the least toxic or best tolerated in animals or humans. The '596 patent specification describes all the compounds of the invention as exhibiting "an excellent tolerance and low toxicity." '596 patent at col. 8, ll. 41-49. That data, therefore, fails to support the proposition that the testing data disclosed in the '596 patent singles out PCR 4099 – and, by extension, its enantiomers – as the "specific preferences" of the inventors. Accordingly, the '596 patent would not direct a person of ordinary skill in the art to a "sub-genus" consisting of PCR 4099 and its enantiomers.[10]

Second, Apotex contends that the examples in the '596 patent specification make clear that the three most likely salts forms would have been the hydrobromide, the hydrochloride, and the bisulfate. That contention is undermined by the fact that the person of ordinary skill in the art recognizes that there is no necessary correlation between the use of a particular pharmaceutically acceptable acid to form a crystalline salt with a racemate, on one hand, and the choice of acid to be used for the formation of a crystalline salt of the corresponding enantiomer, on the other. Thus, the fact that certain acids were used to purify the compounds exemplified in the '596 patent would not lead the person of ordinary skill in the art to a limited sub-genus involving only three salts.

[10] The fact that Sanofi publicized PCR 4099 at the San Diego and Jerusalem conferences in 1985 is inapposite for purposes of Apotex's contention that a person of ordinary skill in the art would have viewed PCR 4099 and its enantiomers as a sub-genus. Anticipation requires that the claimed invention be described in a single, prior art reference; the disclosures of multiple references may not be combined. See Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc., 726 F.2d 724, 726-27 (Fed. Cir. 1984).

Although certain acids might – for a variety of reasons – be better candidates than others to use for the formulation of a pharmaceutical salt, the prior art would not have limited the choice of likely acids to only those three acids asserted by Apotex.

Accordingly, the full trial record compels the conclusion that the '596 patent does not direct a person of ordinary skill in the art exclusively to PCR 4099, its enantiomers, and three particular salt forms. In sum, the '596 patent does not inherently disclose clopidogrel bisulfate.

For largely the same reasons, the Canadian '875 patent does not describe clopidogrel bisulfate. The main distinction between the '875 patent and the '596 patent is that the former includes the language that "if desired," the enantiomers of any compound covered by the general formula may be isolated and prepared as a salt. This does nothing, however, to narrow the universe of possible compounds to the bisulfate salt of the dextrorotatory enantiomer of a particular racemate – MATTPCA. Accordingly, the '875 patent also does not describe clopidogrel bisulfate.

b. The '596 Patent Does Not Enable a Person of Ordinary Skill in the Art to Practice Clopidogrel Bisulfate Without Undue Experimentation

Because the '596 patent does not expressly or inherently describe clopidogrel bisulfate, the Court need not determine whether the prior art patent enabled its practice. Nonetheless, even if one impermissibly engaged in "mechanistic dissection and recombination" of the various claims and examples of the '596 patent to piece together the elements of clopidogrel bisulfate, see Ruschig, 343 F.2d at 974, the Court finds that that patent did not enable a person of ordinary skill in the art "to practice the invention

without undue experimentation." Advanced Display Sys., 212 F.3d at 1282. See Impax Labs, 468 F.3d at 1383 ("When a reference discloses a class of compounds, i.e., a genus, a person of ordinary skill in the art should be able to at once envisage each member of th[e] . . . class for the individual compounds, i.e. species, to be enabled.") (internal quotations omitted) (emphasis in original); Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1355 (Fed. Cir. 2003) (finding that even if a presumption of enablement arises from the fact that a claimed compound falls within the genus of a prior art patent, the patentee can adduce evidence to prove that the disclosure is not enabling).

There is no serious dispute between the parties that a person of ordinary skill in the art for these purposes has a bachelor's degree in chemistry with a specialization in organic chemistry and would have several years experience in the field involved in the synthesis, study and properties of drugs, drug candidates, and biologically active compounds. This person would have both knowledge and experience in the preparation and separation of stereoisomers.

First, the '596 patent did not disclose to a skilled person how the enantiomers of PCR 4099 could be separated. Nothing in the prior art patent suggests, for example, that diastereomeric salt formation is the preferred means of obtaining the enantiomers of the racemic mixtures covered by the general formula of Claim 1. Although there were as many as ten different methods that a chemist might use to obtain the enantiomers of a racemate in 1987, the evidence proved that even if some of those methods could be immediately eliminated from consideration, there was no way to know which particular method or methods of the remaining options would be successful with a particular racemate. A chemist cannot be certain which method of separation or synthesis – or what

configuration of variables presented by a particular method – will be effective for a given compound. Although the Canadian '875 patent states that "if desired" one can separate the enantiomers of the claimed compounds or make a salt, that statement does not demonstrate that undue experimentation would not be required to implement that suggestion. Discovering which method and what combination of variables is required is sufficiently arduous and uncertain as to require undue experimentation, even by one skilled in the relevant art. While not entirely dispositive, it is noteworthy that Sanofi – whose chemists were highly sophisticated and well-trained in the relevant art – spent a considerable amount of time trying to obtain the enantiomers of PCR 4099. If the '596 patent enabled clopidogrel, Sanofi would most certainly not have recorded numerous failed attempts using a variety of methods before attempting diastereomeric salt formation and obtaining the enantiomers.

Second, there is evidence, which is credited, that even if the enantiomers of a racemic mixture are obtained, a person of ordinary skill in the art must often experiment at length to formulate a suitable, crystalline salt when the prior art provides no guidance regarding what salt form of a particular compound will possess the required properties – the exact situation that confronted Sanofi in this case. As noted, the '596 patent provided no specific guidance that would have led a person of ordinary skill to prepare a methyl ester, or any enantiomer, as a bisulfate salt. Although the prior art – as a general matter – would have pointed a person of ordinary skill in the art to the universe of pharmaceutically acceptable acids, there are sufficient additional factors – including the risk that attempting to form a salt with certain acids will lead to racemization of the

compound – such that the Court finds that preparing the free base of clopidogrel as a bisulfate salt also would have required a level of experimentation that was undue.

3. Conclusion

In view of the evidence and the applicable law, neither of the prior art patents – the '596 patent and its Canadian counterpart, the '875 patent – explicitly or inherently described the invention disclosed by Claim 3 of the patent-in-suit. Although the benefit of hindsight permits one to pull together the various claim limitations of clopidogrel bisulfate from the '596 patent or the '875 patent, these disparate references in each patent do not as a matter of law or fact anticipate the precise combination of elements described by Claim 3 of the '265 patent. Furthermore, neither the '596 patent nor the '875 patent provides specific guidance regarding how to obtain the enantiomers of any racemate covered by Claim 1, including PCR 4099, nor how to select a particular pharmaceutically acceptable acid to create a suitable salt form of a particular enantiomer. In sum, neither the '596 patent nor the Canadian '875 patent invoked by Apotex enable a person of ordinary skill in the art to practice the invention disclosed by the patent-in-suit without undue experimentation. Accordingly, Apotex has failed to show by clear and convincing evidence that clopidogrel bisulfate is anticipated by the '596 patent.

B. Obviousness

1. Legal Standard

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 to a person having ordinary skill in the art." 35 U.S.C. § 103. "Obviousness is a question of law which is predicated upon several factual inquiries."

Ranbaxy Labs., 405 F. Supp. 2d at 516. To assess whether an invention is obvious, the Court considers: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) objective evidence, or "secondary considerations," of nonobviousness, such as "commercial success, long felt but unsolved needs, [or] failure of others." Graham v. John Deere Co., 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966). To this end, "mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole. Rather, a party alleging invalidity due to obviousness must articulate the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them." Abbott Labs. v. Andrx Pharms., Inc., 452 F.3d 1331, 1336 (Fed. Cir. 2006) (quoting In re Kahn, 441 F.3d 977, 986 (Fed. Cir. 2006)).

Moreover, it is not enough for Apotex to have shown that the combination of claim limitations found in Claim 3 of the '265 patent would have been "obvious to try." See In re Deuel, 51 F.3d 1552, 1559 (Fed. Cir. 1995) ("A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out."); Gillette Co. v. S.C. Johnson & Son, Inc., 919 F.2d 720, 725 (Fed. Cir. 1990) ("[W]e have consistently held that 'obvious to try' is not to be equated with obviousness under 35 U.S.C. § 103."). Rather, to establish obviousness, "a claimed specific compound" must be "precisely envisioned" by the prior art. Deuel, 51 F.3d at 1559 (emphasis in original). To make that determination, the Court must assess, without the benefit of hindsight, whether the prior art would have suggested to a person of ordinary skill in the art that the invention should be made and that it would have a

"reasonable likelihood of success." In re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988).

In addition, "[t]he proper approach to the obviousness issue must start with the claimed invention as a whole." Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d 1437, 1448 (Fed. Cir. 1984) (emphasis in original). Where the claimed invention is a chemical compound, the "compound and all of its properties are inseparable; they are one and the same thing." In re Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963). This principle requires the Court to determine whether clopidogrel bisulfate – including its properties – would have been obvious to a person of ordinary skill in the art as of February 17, 1987, the date on which the first French patent application for clopidogrel bisulfate was filed. Evidence that the compound exhibited unexpected or surprising properties rebuts a finding of prima facie obviousness. In re Dillon, 919 F.2d 688, 696 (Fed. Cir. 1990).

2. Discussion

According to Apotex, clopidogrel bisulfate was rendered obvious by the '596 patent because, after gaining familiarity with that patent, a person of ordinary skill in the art would have viewed as obvious the active enantiomer of PCR 4099 in the form of each of the three salts used for ester compounds in the examples of the '596 patent – namely, the hydrochloride, bisulfate and hydrobromide. Apotex also contends that a person of ordinary skill would have known that PCR 4099 held the most promise among the compounds disclosed by the '596 patent, a conclusion that would have been bolstered by Sanofi's own efforts to publicize PCR 4099 in the scientific community. A person of ordinary skill would also have known, in Apotex's view, that separating the enantiomers of PCR 4099 would elicit one active and one inactive enantiomer and that the enantiomer

that exhibited antiplatelet activity would also be better tolerated. The person of ordinary skill in the art also would have viewed as obvious the preparation of that active enantiomer of PCR 4099 as each of the disclosed salt forms. Moreover, the '596 patent expressed the purpose behind the exercise – the search for a platelet aggregation inhibitor with a better activity/toxicity ratio than other drugs currently on the market. Thus, according to Apotex, the '596 patent also provided the motivation for a person of ordinary skill to synthesize clopidogrel bisulfate. Apotex further contends that regulatory trends in the mid-1980s favoring the development of enantiomers rather than their racemic mixtures – a trend that was forecasted by the prior art – provided additional motivation.

In sum, Apotex contends that the evidence demonstrates a prima facie case of obviousness. Indeed, in the case of chemical compounds where the prior art is "close enough to the claimed invention to give one skilled in the relevant chemical art the motivation to make close relatives (homologs, analogs, isomers, etc.) of the prior art compound(s), then there arises what has been called a presumption of obviousness or a prima facie case of obviousness." Dillon, 919 F.2d at 696. "[E]ven though a patentee never must submit evidence to support a conclusion by a judge or jury that a patent remains valid, once a challenger introduces evidence that might lead to a conclusion of invalidity – what we call a prima facie case – the patentee 'would be well advised to introduce evidence sufficient to rebut that of the challenger.'" Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1360 (Fed. Cir. 2007) (quoting Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1570 (Fed. Cir. 1986)). Rebuttal evidence may consist of "a comparison of test data showing that the claimed composition[] possess[es] unexpectedly

improved properties or properties that the prior art does not have." Dillon, 919 F.2d at 692-93. An "unexpected result" includes "some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995). Obviousness can also be rebutted by showing that "the prior art teaches away from the claimed invention." In re Geisler, 116 F.3d 1465, 1471 (Fed. Cir. 1997).

The Court, therefore, must first consider whether Apotex has established a prima facie case of obviousness based on the prior art and, if so, whether Sanofi has effectively rebutted that presumption on the basis of the evidence submitted. For purposes of analysis, the Court assumes that Apotex has made a prima facie case of obviousness of the dextrorotatory enantiomer of PCR 4099 in view of the disclosure of the racemate in the '596 patent and the prior art teachings that (1) racemic compounds may be separated into their enantiomers; and (2) those enantiomers, if obtained, may exhibit different biological activity or different degrees of the same type of biological activity exhibited by the racemate. Thus, the analysis will proceed directly to whether the specific properties exhibited by clopidogrel bisulfate – the invention, as a whole – would have been unexpected to a person of ordinary skill in the art.

Because a compound and its properties are one and the same, see Papesch, 315 F.2d at 391, evidence of the fact that any property of clopidogrel bisulfate is unexpected – as compared to PCR 4099 or anything else in the prior art – rebuts the presumption that clopidogrel bisulfate is obvious in view of its racemate. See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 760-61 (N.D.W.Va. 2004); May, 574 F.2d at 1092-93. In this regard, the Court concludes that the prior art did not enable a person of

ordinary skill in the art to predict with a reasonable expectation of success whether one enantiomer of PCR 4099 would have better pharmaceutical properties than the racemate itself, whether one enantiomer would have all of the activity and none of the toxicity of the racemate as a whole, or whether a single enantiomer would have both all of the activity and all of the toxicity. Moreover, the prior art would not have made obvious whether an isolated enantiomer of PCR 4099 would racemize in the body, serving to neutralize the gains achieved by separating the enantiomers.

Apotex contends that clopidogrel's lack of neurotoxicity should not be viewed as unexpected because Sanofi – prior to filing the application for the '265 patent – had not disclosed its internal testing data which showed that PCR 4099 had a tendency to cause convulsions in animals. Moreover, Sanofi had publicized that PCR 4099 exhibited good tolerance and had even conducted human trials with the racemate. Apotex's argument, however, misapprehends the role of "unexpected properties" in the analysis of obviousness. To determine whether a given compound is obvious compared to a prior art compound, any and all properties of those compounds must be considered, even where the prior art has not disclosed the relevant properties of the prior art. See Zenith Goldline, 471 F.3d at 1378; In re Lunsford, 327 F.2d 526, 528 (C.C.P.A. 1964).

Evidence of the course of Sanofi's research prior to securing the '265 patent also weighs in favor of the conclusion that separating the enantiomers of PCR 4099 would not have been obvious to a person of ordinary skill in the art at the relevant time. See Dow Chem., 837 F.2d at 473; Rosemount, Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 1544 (Fed. Cir. 1984). Sanofi spent four years and "tens of millions of dollars" developing and extensively testing the racemate PCR 4099 before deciding to try

separating the enantiomers of the racemic mixture. (Maffrand PI Tr. 144.) The superiority of clopidogrel to PCR 4099 – which was only confirmed later – was clearly not obvious to the chemists at Sanofi. Apotex has not made a persuasive case to provide an explanation as to why the skilled chemists at Sanofi, furthermore, would have acted – as Apotex contends – so contrary to the hypothetical person of ordinary skill in the art.

Furthermore, the fact that the formulation of clopidogrel as a bisulfate salt results in a pharmaceutical compound possessing a highly favorable combination of properties would also not have been obvious to a person of ordinary skill. There is undisputed testimony from experts for both sides that the bisulfate salt of clopidogrel has a highly favorable combination of properties: a high melting point, long-term stability, non-hygroscopic, and good solubility. Furthermore, the bisulfate salt was the only salt obtained by Sanofi that demonstrated that favorable combination of properties. That result was unexpected.

Apotex contends that a very recent decision of the Federal Circuit, Pfizer, Inc. v. Apotex, 480 F.3d 1348 (Fed. Cir. 2007), reh'g denied, 2007 U.S. App. LEXIS 11886 (Fed. Cir. May 21, 2007), compels a different conclusion in this case. The Court, however, finds that Pfizer is distinguishable from this case. In Pfizer, the invention was the "besylate" salt of the antihypertensive drug amlodipine. 480 F.3d at 1352. Amlodipine had been specifically described in a prior Pfizer patent, and that prior art patent had described twelve illustrative pharmaceutically acceptable acid addition salts. Id. at 1353. The maleate was listed as the "preferred" salt and amlodipine was exemplified in that form in the prior art patent. Id. After obtaining that patent, however, Pfizer discovered that the maleate salt, for unforeseen reasons, was not suitable for the

commercial manufacture of tablets due to stickiness and tablet degradation. Id. at 1353-54. The chemists at Pfizer attributed those problems to the particular chemical structure of the maleate salt – a reactive double bond in the maleate anion – which made the salt susceptible to degradation. Id. at 1362. Based on that knowledge, Pfizer chemists compiled a list of seven salts, including besylate, which lacked the problematic double bond. Id. at 1354. After testing the various options, the besylate salt was found to be the most suitable alternative to the maleate. Id.

The Court finds, however, that Pfizer does not support the proposition that it would have been obvious to a person of ordinary skill in the art to formulate clopidogrel as a bisulfate salt. First, the chemists in Pfizer were able to identify the structural feature of the maleate salt that was causing problems, and, with that knowledge, were able to produce a short list of salts that they expected to solve the problem. In this case, importantly and by contrast to the situation in Pfizer, there were no structural features that would have guided Sanofi chemists in avoiding or selecting any specific acid.

Second, in Pfizer, the Federal Circuit noted that several prior art references, including patents, specifically suggested to a person of ordinary skill in the art that the use of the besylate salt would offer improved stability in the particular compound at issue. Id. at 1363. The Federal Circuit emphasized that the nature of the prior art in that case was such that the role of testing – after Pfizer chemists had identified the besylate salt as an option that they expected to succeed – was simply to verify the expected physicochemical characteristics of the salts identified. Id. at 1366-67. Here, there was no prior art teaching that the bisulfate salt was particularly likely to be a successful salt form of clopidogrel, and additional prior art – such as the Gould reference – might actually

have led the person of ordinary skill in the art away from sulfuric acid, at least as an initial matter.

For these reasons and based on the findings of fact with respect to preparation of clopidogrel as a bisulfate salt, this Court concludes that Pfizer – which the Federal Circuit emphasized rested on its "particularized facts," id. at 1367 – does not control under the "particularized facts" of this case. Accordingly, the unexpected success of the bisulfate salt of clopidogrel – especially taking into account the lack of prior art directing a person of ordinary skill in the art to that particular outcome – independently supports the conclusion that Claim 3 of the '265 patent is non-obvious over the prior art.

As noted above, courts must also consider objective indicia, or "secondary considerations," of nonobviousness. See Graham, 383 U.S. at 17-18; Ruiz v. A.B. Chance Co., 234 F.3d 654, 667-68 (Fed. Cir. 2000). Whether an invention fulfills a "long-felt but unsolved" need, see Graham, 383 U.S. at 17-18, 35-36, was the only secondary consideration on which the parties offered extensive evidence in this case. At trial, the parties presented conflicting evidence regarding whether a long-felt need existed in the market for a more effective and safer platelet aggregation inhibitor and, more particularly, whether Plavix® filled that need. The Court need not resolve that debate. As this Court found following the preliminary injunction hearing, Sanofi's ownership of the '596 patent precluded anyone else from bringing clopidogrel bisulfate to market throughout the duration of that patent. For that reason, evidence relating to the "failure of others," a "long-felt but unsolved need," the "commercial success" of Plavix®– a factor on which the parties expressly did not present evidence at trial – and "copying" is undermined by the fact that those phenomena – to the extent they exist in this case –

could have been derived from Sanofi's ownership of the '596 patent as much as from the nonobviousness of clopidogrel bisulfate. See, e.g., Merck & Co. v. Teva Pharms. USA, Inc., 395 F.3d 1364, 1377 (Fed. Cir. 2005) (the inference drawn from a product's commercial success fails when others are legally barred from testing or practicing the invention given the existence of another patent covering that invention.) Although the Court has considered these secondary factors of nonobviousness – to the extent they were asserted by the parties at trial or find support in the record – the Court concludes that they do not relate to obviousness in this particular case.

3. Conclusion

This Court concludes that Sanofi has effectively rebutted a prima facie case of obviousness by demonstrating that clopidogrel bisulfate – as a whole – possesses unexpected properties that could not have reasonably been viewed as a likely outcome of preparing the invention. Whether or not it may have been "obvious to try" separating the enantiomers of PCR 4099 and, secondarily, preparing its dextrorotary enantiomer as a bisulfate salt, the wide range of possible outcomes and the relative unlikelihood that the resulting compound would exhibit the maximal increase in antiplatelet aggregation activity and the absence of neurotoxicity makes clopidogrel bisulfate non-obvious. Sanofi's discovery that the bisulfate form of clopidogrel – a combination that the prior art did not predict would yield a Tier 3 salt with a highly desirable combination of properties – is an additional basis for concluding the clopidogrel bisulfate was non-obvious on the relevant date.

C. Double-Patenting

The judicial doctrine of obviousness-type double-patenting prevents a patent claim from validly issuing when it "is obvious over, or anticipated by" a claim in an earlier patent. Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 968 (Fed. Cir. 2001). It is a "judge-made criterion adopted out of necessity where the courts were faced with a situation in which claims in two applications or patents were not drawn precisely to the same invention, but were drawn to inventions so very much alike as to render one obvious in view of the other and to effectively extend the life of the patent that would have [had] the earlier of the two issue dates." Gerber Garment Tech., Inc. v. Lectra Sys., Inc., 916 F.2d 683, 686 (Fed. Cir. 1990) (emphasis in original).

The test for obviousness-type double-patenting is narrower than the statutory obviousness inquiry pursuant to 35 U.S.C. § 103. See Geneva Pharms., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1378 (Fed. Cir. 2003) ("Obviousness compares claimed subject matter to the prior art; nonstatutory double patenting compares claims in an earlier patent to claims in a later patent or application."); Affymetrix, Inc. v. Pe Corp., 01 Civ. 0634, 2002 U.S. Dist. LEXIS 24649, at *5 n.3 (S.D.N.Y. Dec. 24, 2002) ("The same type of analysis is used for an obviousness-type double patenting inquiry as for a Section 103 obviousness inquiry, except that the scope of a double patenting inquiry is limited to only the claims of the first patent, rather than the entirety of its disclosure.").

The double-patenting inquiry is subsumed by the broader statutory inquiry pursuant to 35 U.S.C. § 103 because Sanofi's entire '596 patent was prior art at the time the '265 patent issued. Because Apotex has failed to prove at trial that the '265 patent

was obvious in light of the '596 patent as a whole, it has also necessarily failed to prove that the '265 patent was obvious in light of the specific claims of the '596 patent.

III. Unenforceability Due to Inequitable Conduct Before the PTO

Apotex contends that the '265 patent is unenforceable due to inequitable conduct by Sanofi when the patent was prosecuted before the PTO.

A. Legal Standard

"To hold a patent unenforceable for inequitable conduct, a court must find, by clear and convincing evidence, that the applicant omitted or misrepresented material facts with the intention of misleading of deceiving the patent examiner." Monsanto Co. v. Bayer BioScience N.V., 363 F.3d 1235, 1239 (Fed. Cir. 2004). Both materiality and intent are questions of fact. See Life Techs., Inc. v. Clontech Labs., Inc., 224 F.3d 1320, 1324 (Fed. Cir. 2000). Pursuant to 37 C.F.R. § 1.56, as in effect in 1988, certain individuals associated with the application for a patent have a duty of candor and good faith toward the PTO, which includes the duty to disclose to the PTO "information they are aware of which is material to the examination of the application." A breach of this duty may constitute inequitable conduct rendering the patent unenforceable.

To demonstrate a failure to disclose material information, the party asserting inequitable conduct must show "(1) prior art that was material; (2) knowledge chargeable to an applicant of that prior art and of its materiality; and (3) failure of the applicant to disclose the art resulting from an intent to mislead the PTO." Elk Corp., 168 F.3d at 30. Proof of inequitable conduct can be rebutted by "a showing that (a) the prior art was not material, (b) if the prior art was material, a showing that the applicant did not know of that art; (c) if the applicant did know of the art, a showing that the applicant did not know

of its materiality; or (d) a showing that the applicant's failure to disclose the art did not result from an intent to mislead the PTO." Id. at 30.

"Information is 'material' when there is a substantial likelihood that a reasonable examiner would have considered the information important in deciding whether to allow the application to issue as a patent." Id. at 31. "[A]n otherwise material reference need not be disclosed if it is merely cumulative of or less material than other references already disclosed." Id.

With regard to intent to deceive the PTO, the Court must infer intent from the facts and circumstances surrounding Sanofi's overall conduct. See Paragon Podiatry Lab., Inc. v. KLM Labs., Inc., 984 F.2d 1182, 1190 (Fed. Cir. 1993). However, the Court will not infer intent to deceive without clear and convincing evidence. See Baxter Int'l Inc. v. McGaw, Inc., 149 F.3d 1321, 1329 (Fed. Cir. 1998) ("[T]here must be clear and convincing evidence that the applicant made a deliberate decision to withhold a known material reference."); Old Town Canoe Co. v. Confluence Holdings Corp., 448 F.3d 1309, 1322 (Fed. Cir. 2006) (affirming district court's finding of no intent to deceive when party did "little more than urge this court to draw an inference of intent to deceive, arguing that the applicant or his attorney knew, or should have known that withheld information would be material").

B. Discussion

Apotex alleges that Sanofi made materially false statements and omitted material facts in an intentional effort to deceive the PTO examiner. Apotex first claims that Sanofi falsely represented to the PTO that the therapeutic activity of the dextrorotatory enantiomer was "unexpected." Second, Apotex asserts, Sanofi falsely informed the PTO

examiner that the relative levels of tolerance between the dextrorotatory and levorotatory enantiomers were surprising. Finally, Sanofi allegedly concealed that Dr. Maffrand was a true inventor of clopidogrel. Because, Apotex contends, Sanofi failed to name Dr. Maffrand as an inventor in the '265 patent, it was able to conceal both his knowledge that there was nothing unexpected about the properties of clopidogrel as well as the 1984 journal article co-authored by Dr. Robert Colman on this topic that Maffrand knew about and that allegedly should have been submitted as relevant prior art. Taking each of these allegations in turn, the Court concludes that Apotex has failed to prove by clear and convincing evidence that Sanofi engaged in inequitable conduct when prosecuting the '265 patent before the PTO.

1. "Unexpected" Therapeutic Activity

Apotex has not proven that Sanofi misled the examiner when it stated: "In an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive. Moreover, the inactive levo-rotatory enantiomer I_l is the less well tolerated of the two enantiomers." (Def. Ex. 9 at CLO-DRL 51362.)

As the Court concluded above, the properties of the dextrorotatory enantiomer of PCR 4099 were, taken together, unexpected in light of the prior art. Apotex contends that Sanofi's characterization of the therapeutic properties of clopidogrel as "unexpected" was false in light of Sanofi's prior work on thienopyridine compounds. The Court finds, however that, Sanofi's internal, non-public test data – particularly regarding PCR 1033 and its enantiomers – was not material. First, those results were non-public and not part of the prior art, and, therefore, could not effect the examiner's determination of whether

clopidogrel bisulfate exhibited unexpected properties in light of the prior art. Even if that data had been disclosed, moreover, it did not provide any firm basis on which a person of ordinary skill in the art could reasonably have predicted the likely results of separating the enantiomers of PCR 4099 and preparing the active enantiomer as a bisulfate salt. If Sanofi had disclosed its conflicting data relating to both PCR 1033 and PCR 3549 – where the enantiomers of the former exhibited different levels of activity and the enantiomers of the latter exhibited equivalent activity – this would have confirmed that a skilled chemist would not have known ex ante whether PCR 4099's enantiomers would exhibit a significant split in therapeutic activity and toxicity.

Apotex also points to the written comments from Sanofi's French patent agent Jacqueline LaForest in 1987 as she helped to prepare the application for the French patent on clopidogrel bisulfate. Ms. LaForest replied to a draft of the French patent application with the handwritten remark, "[t]he pharmacology study does not lead to surprising activity; we will not pass the examiner's hurdles without other results." (Def. Ex. 304.) Apotex alleges that this remark can only be taken as a reply to the draft phrase, "[i]n an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive." However, LaForest's comments were made in January 1987, before the results of March 1987 toxicology studies were known. These toxicology studies revealed what was – for purposes of review by the PTO – "unexpected" about clopidogrel, and that was the complete decoupling of therapeutic activity and neurotoxicity between the two enantiomers of the racemate. In addition, Laforest commented on the pharmacological activity yet also believed – mistakenly – that the relevant test results were not part of the application. As

noted above, those very results in fact appeared in the draft application. Accordingly, the Court cannot credit Laforest's comment regarding a perceived lack of "surprising activity" in support of Apotex's allegations of inequitable conduct.

With respect to the memorandum from Michel de Haas dated December 30, 1986, the Court notes that these comments were made over a year after Dr. Maffrand first asked Badorc to pursue the isolation of the enantiomers of PCR 4099 and nearly a month after Fréhel had already circulated his first draft of the French patent application for clopidogrel bisulfate – a draft in which the phrase "[i]n an unexpected manner" already appeared. Haas' speculation that the active enantiomer might offer a "major therapeutic advantage" was subsequently confirmed by the results of toxicology testing, which demonstrated that virtually all of the neurotoxicity associated with PCR 4099 was located in the inactive levorotatory enantiomer. Accordingly, the Court finds that the Haas memorandum fails to provide convincing evidence of any intent to mislead the PTO by inserting the phrase "[i]n an unexpected manner . . ." If anything, the Haas memorandum is simply a correct statement of the principle that the patentability of the dextrorotatory enantiomer depended on its unexpected properties – and the Court finds that those properties were, in fact, unexpected and discovered by Sanofi prior to the date that the U.S. patent application for clopidogrel bisulfate was filed.

2. Tolerance

Apotex's second allegation of inequitable conduct before the PTO concerns Sanofi's statement regarding the relative levels of tolerance between the dextrorotatory and levorotatory enantiomers. Apotex asserts that Sanofi in fact had not conducted any

tolerance testing at the time of the U.S. patent application, and thus had no data to support any assertions regarding how well clopidogrel was tolerated.

However, at the time of its '265 patent application, Sanofi had evidence from pharmacological and toxicity studies that was relevant to how well clopidogrel was tolerated. Apotex primarily contends that the prior art recognizes a distinction between tolerance and toxicity. The record shows, however, that – at a minimum – the terms are closely related and are often used interchangeably, both at Sanofi and elsewhere. Furthermore, the Court finds that the patent examiner, Bernard Dentz, viewed the toxicity data included in the patent application as a sufficient basis for the statement that the levorotatory enantiomer was "less well tolerated" than clopidogrel. This strongly supports the Court's conclusion that the examiner was not misled by Sanofi's usage of the term "less well tolerated" in the patent application itself.

Apotex also relies on Hoffman-La Roche, Inc. v. Promega Corp., 323 F.3d 1354, 1363-65 (Fed. Cir. 2003), and Purdue Pharma L.P. v. Endo Pharmaceuticals Inc., 438 F.3d 1123, 1129-33 (Fed. Cir. 2006), to suggest that the accuracy of the statement depended exclusively on the existence of test data predating Fréhel's drafting of the original French patent application. But Apotex's reliance on those cases is misplaced. In those cases, unlike here, the patentees had made assertions about the properties of their inventions in the past tense – not the present – implying that they were relying exclusively on data obtained before the assertion was made. In this case, the data supporting the statement in the '265 patent application was presented in Table IV of the application, and Sanofi obtained additional data supporting the statement both before and after it applied for the U.S. patent.

In sum, there is no substantial evidence that any person with a duty of candor intended to mislead the examiner by describing the levorotatory enantiomer as less well-tolerated than clopidogrel. Indeed, there is no evidence that the examiner was misled.

3. Dr. Maffrand's Knowledge

Apotex's third inequitable conduct allegation is that Sanofi concealed that Dr. Maffrand was a true inventor of clopidogrel bisulfate, and that concealing his status facilitated Sanofi's concealment of his knowledge that there was nothing unexpected about the properties of clopidogrel, based on his prior work with PCR 1033. Withholding Dr. Maffrand's name, Apotex argues, enabled Sanofi to conceal a prior art journal article by Robert W. Colman and William R. Figures entitled "Characteristics of an ADP Receptor Mediating Platelet Activation" of which Maffrand was aware. Apotex contends that this article was "highly material" because it provided a basis for understanding the likely activity of various molecules – by describing characteristics of protein receptors relevant to platelet aggregation – which a reasonable PTO examiner would have found important.

As explained above, the Court finds that the Colman article was not material. Apotex has thus failed to prove that Sanofi had any reason to mislead the PTO as to the true inventorship of the claimed invention. There is no evidence that any person with a duty of candor to the PTO intended to mislead the PTO, either by failing to disclose the Colman article or by not including Dr. Maffrand as a named inventor on the patent application.

Accordingly, Apotex has failed to show by clear and convincing evidence that Sanofi engaged or intended to engage in any inequitable conduct in its prosecution of the '265 patent.

IV. Equitable Considerations

The Supreme Court has reiterated that there is no rule that a permanent injunction "automatically follows" a determination that a patent has been infringed. See eBay Inc v. MercExchange, L.L.C., 547 U.S. ___, 126 S. Ct. 1837, 1840, 164 L. Ed. 2d 641 (2006). When a plaintiff seeks a permanent injunction in a patent case, a court must apply a traditional four factor test. Specifically, "[a] plaintiff must demonstrate: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction." Id. at 1839. The decision to grant or deny permanent injunctive relief is "an act of equitable discretion" by the district court. Id.

In regard to the first two factors – irreparable injury and whether monetary damages are inadequate to make the patent holder whole – the Court concludes that both factors support the issuance of an injunction in this action. Sanofi has shown that it is likely to suffer irreparable price erosion, loss of goodwill, and a negative impact on the amount of research devoted to developing other medical uses for Plavix®. In regard to the third factor – i.e., whether "considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted" – the Court adheres to the analysis set forth upon issuing the preliminary injunction in this action, see Sanofi-Synthelabo v.

Apotex Inc., U.S. Dist. LEXIS 65127, at *75-78, and finds that the balance of hardships favors issuance of a permanent injunction. In regard to the fourth factor – i.e., "whether the public interest would not be disserved by a permanent injunction" – this involves essentially a balancing of the public interest in having access to generic drugs at reduced prices with the "significant public interest in encouraging the massive investment in research and development that is required before a new drug can be developed and brought to market." Id. at *80; see Pfizer Inc. v. Teva Pharms. USA, Inc., 429 F.3d 1364, 1382 (Fed. Cir. 2005). As in its analysis at the preliminary injunction phase of this action, the Court finds that the competing, important public interests in this litigation are either in equipoise or slightly favor Sanofi. In sum, utilizing the four part test set forth in eBay to guide the Court's discretion once it has concluded – as it has here – that a patent has been infringed and is valid and enforceable, this Court concludes that a permanent injunction is appropriate in this action.

V. Conclusion

Apotex has concededly infringed Sanofi's '265 patent. This Court now finds that Apotex has failed to prove by clear and convincing evidence that the '265 patent is invalid or unenforceable and Sanofi is entitled to a permanent injunction prohibiting Apotex from further infringement. 35 U.S.C. § 271(e)(4)(B). Damages will be set in an amount to be determined through future proceedings. 35 U.S.C. §§ 271(e)(4)(C).

Accordingly, judgment will be entered in favor of Sanofi. Apotex, Inc. and Apotex Corp. and their agents, servants, employees, and other representatives, and all persons acting in concert with them, are hereby permanently enjoined from engaging in

any activity that infringes U.S. Patent No. 4,847,265.

Dated: New York, New York
June 19, 2007

SO ORDERED:

Sidney H. Stein, U.S.D.J.