IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION and NOVARTIS AG, Plaintiff; v. BRECKENRIDGE PHARMACEUTICAL, INC., Defendant.	Civil Action No. 1:14-cv-1043-RGA
NOVARTIS PHARMACEUTICALS CORPORATION and NOVARTIS AG, Plaintiff; v. WEST-WARD PHARMACEUTICALS INTERNATIONAL LIMITED, Defendant.	Civil Action No. 1:14-cv-1196-RGA
NOVARTIS PHARMACEUTICALS CORPORATION and NOVARTIS AG, Plaintiff; v. PAR PHARMACEUTICAL, INC., Defendant.	Civil Action No. 1:14-cv-1289-RGA

AMENDED TRIAL OPINION

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April 3, 2017

ANDREWS, U.S. DISTRICT JUDGE:

Plaintiffs brought these patent infringement actions against Breckenridge Pharmaceutical, Inc., Roxane Laboratories, Inc.[1], and Par Pharmaceutical, Inc. in 2014. (D.I. 1).[2] Breckenridge, Roxane, and Par each filed an Abbreviated New Drug Application ("ANDA"), seeking to engage in the commercial manufacture, use, and sale of generic versions of Novartis's Zortress product. (D.I. 141-1, ¶¶44, 52, 59). Plaintiffs allege that these ANDAs infringe U.S. Patent No. 5,665,772 ("the '772 patent"). Plaintiffs further allege that by filing these ANDAs, Roxane and Breckenridge induced infringement of U.S. Patent No. 6,239,124 ("the '124 patent") and Breckenridge, Roxane, and Par induced infringement of U.S. Patent No. 6,455,518 ("the '518 patent").

At issue in these cases is the compound 40-O-(2-hydroxyethyl)-rapamycin, also referred to as everolimus, which is the active ingredient in Novartis's Zortress product. Everolimus is a derivative of the compound rapamycin and is claimed in the '772 patent. The only difference between rapamycin and everolimus is that the hydroxyl group at the C-40 position in rapamycin is replaced with a 2-hydroxyethyl group in everolimus. (Trial Transcript ("Tr.") 193:4-13).

Rapamycin has long been known to have beneficial medicinal properties, such as antifungal activity (Tr. 96:11-12), anticancer activity (Tr. 96:13-97:3), and immunosuppressive activity (Tr. 95:2-10). Rapamycin is recognized as having limited utility in pharmaceutical applications as it has low bioavailability, high toxicity, and poor solubility. ('772 patent at 1: 36-40). Rapamycin derivatives such as everolimus, however, have been shown to have better stability and bioavailability, making them more desirable for pharmaceutical preparations. (*Id.* at 1:41-45).

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[1] On February 27, 2017, after post-trial briefing was completed, Defendant Roxane Laboratories, Inc. filed an unopposed motion to substitute West-Ward Pharmaceuticals International Limited to replace Roxane Laboratories, Inc, which the Court granted. (Civ. Act. No. 14-1196, D.I. 190, 191). Defendant West-Ward is now the owner of the ANDAs at issue in this litigation and has not contested jurisdiction of this Court. (Civ. Act. No. 14-1196, D.I. 190 at ¶¶5-6). Any reference to Defendant Roxane in this opinion should, therefore, be construed as a reference to Defendant West-Ward.

[2] Unless otherwise indicated, all docket citations are to Civ. Act. No. 14-1043.

Also at issue are methods of treating or preventing transplant rejection using everolimus and one of a class of compounds known as IL-2 transcription inhibitors. The '124 patent claims the use of synergistically effective amounts of cyclosporin A and everolimus in weight ratios from 2:1 to 180:1. The proposed labels for both Roxane's and Breckenridge's generic products include instructions for co-administration of cyclosporin A and everolimus for the prevention and treatment of transplant rejection in kidney transplant patients. (D.I. 130-1, ¶¶ 51, 58). The '518 patent claims the use of synergistically effective amounts of an IL-2 transcription inhibitor and everolimus in weight ratios from 2:1 to 180:1. The proposed labels for both Roxane's and Par's generic products include instruction for co-administration of the IL-2 transcription inhibitor FK506, also known as tacrolimus, and everolimus for the prevention and treatment of transplant rejection in liver transplant patients. (*Id.* at ¶¶ 58, 66).

The Court held a bench trial on August 29-September 1, 2016. Defendants concede that their proposed products meet all limitations of the '772 patent. (D.I. 152 at 3). Defendants argue that Plaintiffs have not proven by a preponderance of evidence that Defendants induced infringement of the '124 and '518 patents. Defendants further argue that the '772, '124, and '518 patents are invalid as obvious and for obviousness-type double patenting.

I. LEGAL STANDARDS

A. Obviousness-Type Double Patenting

"Obviousness-type double patenting is a judicially created doctrine that 'prohibit[s] a party from obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent.'" *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, 518 F.3d 1353, 1363 (Fed. Cir. 2008) (internal citation omitted). There are two steps to a double-patenting analysis. First, the court construes the claims of the commonly owned patents

and identifies the differences. *See Pfizer*, 518 F.3d at 1363 (citing *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 967 (Fed. Cir. 2001)). In the second step of the double patenting analysis, the court determines whether the differences between the claims render them patentably distinct. *See Eli Lilly*, 251 F.3d at 968. A later claim that is obvious over, or anticipated by, an earlier claim is not patentably distinct from it. *See id.*

B. Obviousness

A patent claim is invalid as obvious under 35 U.S.C. § 103 "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406–07 (2007). The determination of obviousness is a question of law with underlying factual findings. *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1359-60 (Fed. Cir. 2012). "The underlying factual inquiries include (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) any relevant secondary considerations . . . ." *Western Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1370 (Fed. Cir. 2010) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.*, 676 F.3d 1063, 1078-79 (Fed. Cir. 2012). Relevant secondary considerations include commercial success, long felt but unsolved needs, failure of others, praise, unexpected results, and copying, among others. *Graham*, 383 U.S. at 17-18; *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 662–63 (Fed.

Cir. 2000); *Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). Secondary considerations of nonobviousness are important because they "serve as insurance against the insidious attraction of the siren hindsight...." *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

A patentee is not required to present evidence of secondary considerations. *See Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1101 (Fed. Cir. 2015). That said, if the patent challenger establishes a prima facie case of obviousness, "the patentee would be well advised to introduce evidence sufficient to rebut that of the challenger." *Id.* (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007)). There must be enough evidence, however, for a finding that a given secondary consideration exists by a preponderance of the evidence. *See Apple, Inc. v. Samsung Elec. Co., Ltd.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016) (en banc). If there is, then the probative value of each secondary consideration will be considered in light of the evidence produced. That does not mean, though, that the burden of persuasion on the ultimate question of obviousness transfers to the proponent of the secondary consideration. *Pfizer, Inc.*, 480 F.3d at 1359. That burden stays always with the patent challenger. *Id.* at 1359–60.

A party asserting that a patent is invalid as obvious must "show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). That "expectation of success need only be reasonable, not absolute." *Id.* at 1364. "Whether an ordinarily skilled artisan would have reasonably expected success . . . . is measured as of the date of the invention[] . . . ." *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340,

1362 (Fed. Cir. 2009).

C. Infringement

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent . . . ." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *See id.* This second step is a question of fact. *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998). "Literal infringement of a claim exists when every limitation recited in the claim is found in the accused device." *Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1477 (Fed. Cir. 1998). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). The patent owner has the burden of proving infringement by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

35 U.S.C. § 271(b) provides that "[w]hoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). "In order to prevail on an inducement claim, the patentee must establish first that there has been direct infringement, and second that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *ACCO Brands, Inc. v. ABA Locks Mfrs. Co.*, 501 F.3d 1307, 1312 (Fed. Cir. 2007) (internal quotation marks omitted). In other words, "inducement requires evidence of culpable conduct, directed to encouraging another's infringement, not merely that the inducer

had knowledge of the direct infringer's activities." *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc). "[S]pecific intent may be inferred from circumstantial evidence where a defendant has both knowledge of the patent and specific intent to cause the acts constituting infringement." *Ricoh Co. v. Quanta Computer Inc.*, 550 F.3d 1325, 1342 (Fed. Cir. 2008). "[L]iability for induced infringement can only attach if the defendant knew of the patent and knew as well that 'the induced acts constitute patent infringement.'" *Commil USA, LLC v. Cisco Sys., Inc.*, 135 S. Ct. 1920, 1926 (2015) (quoting *Global–Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2068 (2011)). The knowledge requirement may be satisfied by showing actual knowledge or willful blindness. *See Global–Tech,* 131 S. Ct. at 2068 (2011).

In Hatch-Waxman cases alleging that a proposed drug label will induce infringement by physicians, "The pertinent question is whether the proposed label instructs users to perform the patented method." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). "The label must encourage, recommend, or promote infringement." *Takeda Pharm. USA, Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015). "The mere existence of direct infringement by physicians, while necessary to find liability for induced infringement, is not sufficient for inducement." *Id.* Rather, "specific intent and action to induce infringement must be proven." *Id.* (internal quotation marks omitted). Even where a proposed label does not explicitly track the language of a claimed method, a package insert containing directives that will "inevitably lead some consumers to practice the claimed method" provides sufficient evidence for a finding of specific intent. *See AstraZeneca*, 633 F.3d at 1060; *see also Abraxis Bioscience, Inc. v. Navinta, LLC*, 630 F. Supp. 2d 553, 570 (D.N.J. 2009) ("Statements in a package insert that encourage infringing use of a drug product are alone sufficient to establish intent to encourage direct infringement."), *rev'd and vacated on other grounds*, 625 F.3d 1359 (Fed. Cir.

2010).

II. VALIDITY OF THE '772 PATENT

A. Findings of Fact

1. The '990 patent is a proper double-patenting reference for the '772 patent.
2. The '772 and '990 patents are both assigned to Novartis.
3. Each of claims 8, 9, 11-21, 25, and 27-35 of the '990 patent discloses all limitations of claims 1-3 and 10 of the '772 patent.
4. Each of claims 25 and 27-35 of the '990 patent discloses all limitations of claim 7 of the '772 patent.

B. Conclusions of Law

Prior to trial, the parties stipulated that the '990 patent discloses all limitations of claims 1-3, 7, and 10 of the '772 patent, and that the two patents are assigned to the same entity and share named inventors.[3] (D.I. 152 at 5). The parties further stipulated "that if the Court finds the '990 patent is a proper double-patenting reference to the '772 patent, then the claims of the '990 patent will render the Asserted Claims invalid for non-statutory double patenting." (*Id.* at 4). Therefore, the only issue to be decided is whether the '990 patent is a proper double-patenting reference.

The unusual facts of this case are the result of the Uruguay Round Agreements Act ("URAA"), which changed how patent terms are determined, effective as of June 8, 1995. Any patent issuing from an application filed prior to June 8, 1995, received a term of seventeen years from the date of issuance or twenty years from the earliest effective filing date, whichever was longer. 35 U.S.C. § 154(c)(1). Patents issuing from post-URAA applications receive a term of

[3] Plaintiffs originally asserted claims 1-3, 7, and 10 of the '772 patent. (D.I. 130-1, ¶¶10-12). At trial, Plaintiff withdrew claims 1-3. (Tr. 668:2-14). Defendants, however, still seek declaratory judgment of invalidity as to claims 1-3. (D.I. 162 at 11 n.1).

twenty years from the earliest effective filing date. 35 U.S.C. § 154(a)(2).

The issue in this case is that, through the operation of the URAA, the '772 patent, which issued from an earlier filed application, has a later expiration date than the later-filed '990 patent.

The application that issued as the '772 patent was filed on April 7, 1995 with an earliest effective filing date of September 24, 1993. (D.I. 152 at 6). This pre-URAA patent received a term of seventeen years from its issue date of September 9, 1997. (*Id.* at 6-7). Although the original expiration date of this patent was, therefore, September 9, 2014, it received a patent term adjustment of five years pursuant to 35 U.S.C. § 156 so that it now expires on September 9, 2019. (*Id.* at 7).

The application that issued as the '990 patent began life as a divisional of the application that issued as the '772 patent. (*Id.* at 8). This application was filed in 1997, making it a post-URAA patent. It also has an earliest effective filing date of September 24, 1993. (*Id.*). This patent, therefore, received a term of twenty years from the earliest effective filing date and expired on September 24, 2013. (*Id.*).

While the Federal Circuit has not addressed the precise issue presented in this case, the Court has addressed the issue of whether a later-filed but earlier expiring patent can serve as a double-patenting reference for an earlier-filed but later-expiring patent. *Gilead Sciences, Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1212 (Fed. Cir. 2014). The patents at issue in *Gilead* were both post-URAA patents that were not part of the same family and, therefore, had different priority dates. *Id.* at 1210. The different priority dates led to a situation where the later-filed patent expired before the earlier-filed patent. *Id.* The *Gilead* court emphasized that the "bedrock principle of our patent system" that the prohibition on double patenting seeks to protect is the idea that when a patent expires, the public is entitled to use the invention and any obvious modifications of the

invention claimed in the patent. *Id.* at 1214. According to the Federal Circuit, what matters in a double patenting analysis, at least for post-URAA patents, is the expiration dates of the patents. *Id.* at 1215. The Federal Circuit has since revisited this question and made explicit that "the doctrine of obviousness-type double patenting continues to apply where two patents that claim the same invention have different expiration dates." *AbbVie, Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust*, 764 F.3d 1366, 1374 (Fed. Cir. 2014).

Significant to the instant case is the fact that the *Gilead* decision cites to a Board of Patent Appeals and Interferences ("BPAI" or "Board") decision with substantially similar facts to the instant case. *Id.* at 1211 n.2. In that case, the Board found that a later-filed post-URAA patent with an expiration date in 2015 could serve as a double-patenting reference for an earlier-filed pre-URAA patent with an expiration date in 2019. *Ex Parte Pfizer, Inc., Patent Owner & Appellant*, 2010 WL 532133, at *16 (Bd. Pat. App. & Interf. Feb. 12, 2010). The Board found that the later-expiring pre-URAA patent would "extend Appellant's right to exclude the public from practicing" the invention. *Id.* at *21. This, the Board concluded, was "precisely what obviousness-type double patenting was intended to prevent." *Id.* This is the same reasoning applied by the *Gilead* court. *Gilead*, 753 F.3d at 1214.

Other district courts have considered cases with facts substantially identical to the instant case. In *Janssen*, the district court faced the same question and, in light of the Federal Circuit's decision in *Gilead*, reached the conclusion that a later-filed post-URAA patent with an earlier expiration date is a proper double-patenting reference for an earlier-filed pre-URAA patent with a later expiration date. *See Janssen Biotech, Inc. v. Celltrion Healthcare Co., Ltd.*, 2016 WL 5698362 (D. Mass. Sept. 28, 2016), *appeal docketed*, No. 17-1120 (Fed. Cir. Oct. 25, 2016). Other district courts have also reached the same conclusion on identical facts. *See MLC Intellectual*

Property, LLC v. Micron Technology, Inc., 2016 WL 4192009, at *3 n.4 (N.D. Cal. Aug. 9, 2016) ("The fact that the patents in *Gilead* were governed by the URAA was not relevant to the Court's reasoning."); *DDB Technologies, LLC v. Fox Sports Interactive Media, LLC*, 2014 WL 12167628, at *3-4 (W.D. Tex. May 15, 2014) (applying reasoning from *Gilead* that "expiration date of the patents should control").

Plaintiffs expend considerable effort attempting to distinguish this case from *Gilead*. Plaintiffs argue first that Defendants have misread *Gilead*. (D.I. 170 at 8). According to Plaintiffs, double-patenting is an equitable doctrine requiring Defendants to prove that the patentee has obtained an unjustified extension of patent rights. (*Id.* at 11). Plaintiffs argue strenuously that there has been no unjustified extension of patent rights in this case. (*Id.* at 15). I disagree. *Gilead* reaffirms the long-standing principle that when a patent expires, the public is entitled to make use of the claimed invention. *Gilead*, 753 F.3d at 1214. The "unjustified extension of patent rights" here is the extension on the patent holder's term of exclusivity past the expiration date of a patent that discloses the invention. The patentee in this case chose to seek two patents on the same invention. If the term of one of those patents is allowed to extend past the expiration date of the other, the patentee has obtained an unjustified extension of patent rights.

Plaintiffs next argue that *Gilead* and *AbbVie* are inapplicable because the patentees in those cases engaged in gamesmanship, acting strategically to obtain the benefit of a later expiration date. (D.I. 170 at 8-11). According to Plaintiffs, Novartis's actions here are unlike those of the patentees in *Gilead* and *Abbvie* because Novartis did not violate any of the principles of double patenting. (*Id.* at 14). Plaintiffs further argue that Novartis has not engaged in gamesmanship. (*Id.* at 21). I disagree that there is no violation of double patenting principles and I find the argument about the absence of gamesmanship irrelevant. A patentee need not engage in gamesmanship or act

strategically in order to violate the principles of double patenting. Neither *Gilead* nor *AbbVie* held that gamesmanship is required. A patentee can obtain an unjustified extension of patent rights without engaging in gamesmanship simply by seeking two patents on the same invention, as the patentee did here. The only relevant issue is the earlier expiration date of the '990 patent, as it is the extension of the period of exclusivity by virtue of the '772 patent's later expiration date that violates the principles underlying the double patenting prohibition. The patentee's motives are not relevant.

Plaintiffs next argue that expiration dates alone do not control the double patenting analysis. (D.I. 170 at 17). According to Plaintiffs, the holdings and reasoning in *Gilead* and *AbbVie* are limited to the specific factual contexts of those cases. (*Id.* at 17-18). While it may be true that *Gilead* did not establish a hard and fast rule that expiration dates control the double patenting analysis, I am not persuaded that the facts of this case require a different analysis. I think that the reasoning in *Gilead* is equally applicable to the facts of this case for the reasons I have already stated.

Plaintiffs next argue that application of *Gilead* to the facts of this case would frustrate legislative intent. (D.I. 170 at 19). Plaintiffs contend that allowing an earlier-expiring post-URAA patent to serve as a double patenting reference for a later expiring pre-URAA patent would effectively shorten the statutorily mandated terms of pre-URAA patents. (*Id.* at 19-20). Plaintiffs' argument misses the mark.[4] A patentee who chooses to seek a second patent for an obvious variant of his invention, as the patentee did here, runs this risk and cannot claim in retrospect that only the

[4] It seems to me that the only circumstance in which a pre-URAA patent would be in danger of having its statutorily mandated term shortened is if a patentee chose to seek a second patent on the same invention or an obvious modification thereof. This is exactly what happened in this case. The patentee chose to seek two patents on the same invention. The patentee must now live with the consequences of that choice, one of which is a period of exclusivity governed by the expiration date of the earlier-expiring patent.

later-expiring patent counts.

Plaintiffs next argue that there is no harm to the public because "Novartis has not enjoyed more than one patent term per invention." (*Id.* at 20). According to Plaintiffs, the '772 patent's expiration date "is the same as it would have been had the '990 patent never issued." (*Id.*). This argument also misses the mark. The patentee chose to file the application that matured into the '990 patent. The patentee knew when the '990 patent issued on August 27, 2002 that it would expire before the '772 patent, which had issued five years earlier. The harm to the public lies in the inability to make use of an invention disclosed in an expired patent. That the '772 patent's expiration date would be unchanged had the '990 patent never issued is irrelevant. The '990 patent did issue and upon its expiration the public was entitled to make use of the invention it disclosed.

Plaintiffs next argue that the post-*Gilead* district court decisions cited by Defendants are not binding precedent, and that they were incorrectly decided. (*Id.* at 22). Plaintiffs are correct that these district court decisions are not binding precedent, but I find them persuasive and I agree with the reasoning these courts used to reach their conclusions. Plaintiffs also argue that the BPAI decision in *Pfizer* is not binding precedent. (*Id.* at 24). Plaintiffs cite again to two pre-*Gilead* cases that rejected *Pfizer*'s holding. (*Id.*). I am not persuaded. The pre-*Gilead* case law Plaintiffs cite is inconsistent with *Gilead*'s reasoning. Furthermore, the *Gilead* court cited *Pfizer* and directly quoted the BPAI's reasoning regarding the importance of patent term expiration date. *Gilead*, 753 F.3d at 1211 n.2. While *Pfizer* is not binding precedent, it was cited in a Court of Appeals decision that is precedential, and I find the Board's reasoning persuasive.

After briefing was completed in this case, this Court issued a decision that Plaintiffs argue is inconsistent with *Janssen*, *MLC*, and *DDB*. *Merck Sharp & Dohme Corp. v. Teva Pharm. USA, Inc.*, 2016 WL 6804914 (D. Del. Nov. 16, 2016), *appeal docketed,* No. 17-1366 (Fed. Cir. Dec.

16, 2016). The facts of *Merck* are distinguishable from the instant case, however. In *Merck*, both patents at issue were pre-URAA patents. *Id.* at *3. As the *Gilead* court acknowledged, pre-URAA, issue date was important in the double patenting analysis because "the expiration date was inextricably intertwined with the issuance date." *Gilead*, 753 F.3d at 1215. Pre-URAA, the later-issuing patent was the one subject to the double patenting bar. *Id.* at 1214. This is precisely what *Merck* holds, rejecting the "oddity" of using a later issued pre-URAA patent as a double patenting reference for an earlier-issued pre-URAA patent. *Merck* says nothing about whether an earlier-expiring post-URAA patent can serve as a double patenting reference for a later-expiring pre-URAA patent. Furthermore, the *Merck* opinion does not analyze, or even mention, the post-*Gilead* cases that have considered this specific fact pattern. Therefore, I hold that *Merck* is not relevant to this case and is not necessarily inconsistent with *Gilead* or the other post-*Gilead* district court cases cited above.

Finally, Plaintiffs argue that a § 156 patent term extension is not an unjustified extension of patent rights. (D.I. 170 at 26). While this, in the abstract, is certainly true, it is not the § 156 extension that is at issue here. What is at issue is the disclosure of the same invention in an earlier-expiring patent. Plaintiffs appear to be arguing, without citing a single case to support their position, that a § 156 patent term extension somehow immunizes a patent from a double patenting challenge. I disagree. The patent term extension provision of the Hatch-Waxman Act was intended to restore to a patent the time lost in seeking FDA approval for the drug claimed in the patent. I see no reason why such a patent term extension would protect a patent from a double patenting challenge.

For the reasons discussed above, I find that the '990 patent is a proper double patenting reference for the '772 patent. Therefore, claims 1-3, 7, and 10 of the '772 patent are invalid for

obviousness-type double patenting over the '990 patent. Because I find that the asserted claims of the '772 patent are invalid for double patenting, there is no need to consider whether these claims are obvious.

III. VALIDITY OF THE '124 AND '518 PATENTS

Plaintiffs assert claim 7 of each of the '124 and '518 patents. The '518 patent is a continuation of the application that issued as the '124 patent. The two patents share an identical specification. The patents disclose that rapamycin had been discovered over twenty years prior to the application date, but had not been marketed due in part to difficulties in formulation, poor solubility, and poor bioavailability. ('124 patent at 1:47-51). The rapamycin derivative everolimus, on the other hand, has improved pharmacokinetic properties and is easier to formulate. (*Id.* at 1:51-53).

Claim 7 of the '124 patent teaches 1) methods for treating or preventing transplant rejection comprising 2) co-administering 3) synergistically effective amounts 4) of cyclosporin A and everolimus 5) in the weight ratio 2:1 to 180:1. Claim 7 of the '518 patent is identical with the exception of element 4, which calls for an IL-2 transcription inhibitor in place of cyclosporin A. The '518 patent identifies FK506, also known as tacrolimus, as an IL-2 transcription inhibitor. ('518 patent at 2:20-29).

Defendants argue that claim 7 of each of the '124 and '518 patents are invalid as obvious over the prior art. Defendants also argue that these claims are invalid for obviousness type double patenting over claim 11 of U.S. Patent No. 6,440,990 ("the '990 patent").

A. Findings of Fact

1. The level of ordinary skill in the art is a medical doctor with experience and expertise in using immunosuppressants and several years of experience treating conditions that require

immunosuppressants, including transplantation and autoimmune diseases, who, if necessary, collaborates with an immunologist or pharmacologist.

2. The priority date for claim 7 of both the '124 and '518 patents is July 30, 1996.

3. WO'010, Tu, Kahan, Murgia, and Schreiber are prior art.

4. WO'010, Tu, Kahan, Murgia, and Schreiber do not teach a person of ordinary skill that co-administration of everolimus and cyclosporin A or tacrolimus would be safe and effective in humans.

5. WO'010, Tu, Kahan, Murgia, and Schreiber do not teach a person of ordinary skill that co-administration of everolimus and cyclosporin A or tacrolimus would be synergistically effective.

6. WO'010, Tu, Kahan, Murgia, and Schreiber do not teach a person of ordinary skill the weight ratio of everolimus to cyclosporin A or tacrolimus claimed in the '124 and '158 patents.

7. WO'010 and Schreiber do not teach a person of ordinary skill that everolimus is an obvious substitute for rapamycin.

8. Co-administration of synergistically effective amounts of everolimus and cyclosporin A at weight ratios 12.5:1 to 200:1 would not have been obvious to one of ordinary skill in the art.

9. Co-administration of synergistically effective amounts of everolimus and tacrolimus at weight ratios 12.5:1 to 200:1 would not have been obvious to one of ordinary skill in the art.

10. The '990 patent is a proper double patenting reference for both the '124 and '518 patents.

11. The asserted claims of the '124 and '518 patents are patentably distinct from claim 11 of the '990 patent.

B. Conclusions of Law

Defendants contend that co-administration of everolimus with cyclosporin A or tacrolimus for prevention or treatment of transplant rejection would have been obvious to a person of ordinary

skill in the art. The essence of Defendants' obviousness argument is that the prior art teaches that rapamycin could be safely co-administered with cyclosporin A or tacrolimus with synergistic effectiveness and that everolimus would have been an obvious substitute for rapamycin. Therefore, according to Defendants, the invention as a whole, including all limitations, would have been obvious to a person of ordinary skill in the art.[5]

The parties agree that a person of ordinary skill to whom the '124 and '158 patents are directed is a medical doctor with experience and expertise in using immunosuppressants and several years of experience treating conditions that require immunosuppressants, including transplantation and autoimmune diseases, who, if necessary, collaborates with an immunologist or pharmacologist. (Tr. 1214:8-22).

1. Scope and Content of the Prior Art

i. WO'010

The WO'010 reference is the Patent Cooperation Treaty ("PCT") publication of PCT/EP93/02604, the PCT counterpart of the '772 patent, filed on September 24, 1993. WO'010 discloses certain novel derivatives of rapamycin, including everolimus, that "have an improved pharmacologic profile over rapamycin." (JTX-54 at p. 2; Tr. 1226:14-24). WO'010 further discloses everolimus as a preferred compound for immunosuppressive use, including treatment and prevention of transplant rejection. (JTX-54 at pp. 3, 5; Tr. 1227:3-13, 1228:12-19). WO'010 teaches the use of everolimus in treating and preventing transplant rejection by administering a "pharmaceutically effective dose." (JTX-54 at pp. 4-5, 7). WO'010 further teaches that

[5] The parties argued the obviousness of each limitation of the claims individually, so I will address these arguments in turn, keeping in mind that the ultimate question is whether the claimed invention as a whole would have been obvious as "obviousness requires a suggestion of all limitations in a claim." *See CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (*citing In re Gulack*, 703 F.2d 1381, 1385 n. 9 (Fed.Cir.1983); *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

everolimus "may be used in combination with Ciclosporin, FK-506, or their immunosuppressive derivatives." (*Id.* at p. 8). It is undisputed that WO'010 does not teach all elements of the asserted claims of the '124 and '518 patents. (D.I. 162 at 43). Specifically, WO'010 does not teach 1) co-administration of everolimus with cyclosporin A; 2) that co-administration would result in synergistic effectiveness; or 3) the appropriate weight ratios. (*Id.*).

ii. Tu

Tu describes the results of a study of co-administration of rapamycin and cyclosporin A in mice. (Tr. 1253:14-23). Tu reports that co-administration with weight ratios of 12.5:1 to 200:1 results in a "modestly synergistic effect on survival." (Tr. 1325:12-23; JTX-48 at p. 181-82). It is undisputed that Tu does not provide any information on co-administration of everolimus with cyclosporin A. (Tr. 1253:19-21). It is further undisputed that Tu does not provide any direct evidence regarding whether co-administration of rapamycin and cyclosporin A would result in synergistic effectiveness in humans. (Tr. 1258:3-9).

iii. Kahan

Kahan discusses the theoretical basis for synergistic effectiveness of combination treatment with rapamycin and cyclosporin A. (Tr. 1245:12-23; JTX-24 at p. 21). It is undisputed that Kahan does not provide information on combination treatment with everolimus and cyclosporin A. (Tr. 1328:24-1329:4). It is also undisputed that Kahan does not explicitly teach co-administration of rapamycin and cyclosporin A. (Tr. 1249:9-13). Defendants argue, however, that Kahan's silence on the relative timing of administration of the two drugs would be interpreted by a person of ordinary skill to mean co-administration. (Tr. 1249:13-16).

iv. Murgia

Murgia teaches that combination therapy with rapamycin and cyclosporin A in human

transplant patients does not result in increased toxic side effects compared to treatment with rapamycin alone. (Tr. 1251:6-1252:11). It is undisputed that Murgia does not provide information on combination treatment with everolimus and cyclosporin A. (Tr. 1326:20-22). It is also undisputed that Murgia does not explicitly teach co-administration of rapamycin and cyclosporin A. (Tr. 1252:12-15). As with Kahan, however, Defendants argue that Murgia's silence on the relative timing of administration of the two drugs would be interpreted by a person of ordinary skill to mean co-administration. (Tr. 1252:17-21).

v. Schreiber

Schreiber discloses a model that identifies binding domains and effector domains in rapamycin and tacrolimus. (Tr. 1239:12-1240:6). According to Schreiber's model, rapamycin and tacrolimus have identical binding domains but different mechanisms of immunosuppression. (Tr. 1240:15-1241:4). Specifically, Schreiber posits that the C-40 position on rapamycin, the position at which the molecule is altered by the addition of a hydroxyl group to create the rapamycin derivative everolimus, lies outside both the binding and effector domains. (Tr. 1241:18-1242:3).

2. Comparing Prior Art and Claimed Subject Matter

Defendants' expert, Dr. Tullius, opines that a person of ordinary skill in the art would have been motivated to co-administer synergistic amounts of everolimus and an IL-2 inhibitor at the ratios given in the asserted claims to treat or prevent transplant rejection. (Tr. 1223:1-9). Specifically, Dr. Tullius stated that the prior art references Tu, Kahan, and Murgia showed that rapamycin and cyclosporin A had been shown to have synergistic effectiveness when co-administered. (Tr. 1259:9-12). According to Dr. Tullius, this prior art, combined with the teachings of WO'010 and Schreiber about the similarities between everolimus and rapamycin,

would lead a person of ordinary skill to believe everolimus could be safely co-administered with cyclosporin A or tacrolimus with synergistic effectiveness. (Tr. 1259:13-22). Dr. Tullius further opined that a person of ordinary skill in the art would be able to combine the general knowledge about the relative effectiveness of everolimus compared to rapamycin with the teachings of Tu and WO'010 to arrive at the claimed weight ratios. (Tr. 1262:6-22). Therefore, according to Defendants, these references can be combined to suggest all limitations of claim 7 of each of the '124 and '518 patents.

i. Co-Administration

Defendants acknowledge that none of the references they rely on explicitly teaches co-administration of everolimus and cyclosporin A. (D.I. 162 at 43). Instead, Defendants argue that the prior art discloses co-administration of rapamycin and cyclosporin A. As discussed below, Defendants further argue that everolimus is an obvious substitute for rapamycin.

During claim construction, the parties did not identify "co-administration" as a term in need of construction. The patents explicitly define co-administration to mean administering two drugs "together or at substantially the same time." ('124 patent at 6:20-26). Plaintiffs argue that, at a minimum, the prior art did not teach co-administration. (D.I. 171 at 45). Plaintiffs further urge that the prior art, in fact, taught away from co-administration. (*Id.* at 44-45). I do not think it is necessary to decide whether the prior art taught away from co-administration as I think it is evident that co-administration is not obvious under any combination of prior art cited by Defendants.

Defendants rely on a combination of three references: Tu, which teaches co-administration of rapamycin and cyclosporin A in mice (JTX-048); Murgia, which teaches combination therapy with rapamycin and cyclosporin A in humans, but is silent on timing (DTX-079); and Kahan,

which provides a theoretical basis for synergy when rapamycin and cyclosporin A are administered as a combination therapy, but is also silent on timing (JTX-024). Defendants argue in post-trial briefing that a person of ordinary skill "would have understood [silence on timing] to mean that Cyclosporine and rapamycin were co-administered." (D.I. 162 at 39). This argument appears to be based primarily on Dr. Tullius's testimony, first, that the prior art teaches co-administration, and second, that co-administration of the two drugs would be important for ensuring patient compliance. (Tr. 1259:23-1260:5; 1260:22-1261:6).

As an initial matter, I am not persuaded that patient compliance would be sufficient motivation for a physician to co-administer the two drugs, in the absence of evidence that it would be safe for humans, in light of the known toxicity of each of these drugs. Dr. Tullius acknowledged that both cyclosporin A and tacrolimus were known as of July 30, 1996 to have toxic side effects. (Tr. 1309:14-1312:1). Everolimus and rapamycin were also known to have toxic side effects. ('124 patent at 1:53-55). Dr. Tullius admitted during his testimony that patient safety was more important than convenience and that a physician would not co-administer two drugs without evidence that doing so would be safe. (Tr. 1317:3-13).

Dr. Tullius also testified that both cyclosporin A and tacrolimus are metabolized by the CYP3A enzyme and that any drug that inhibited CYP3A enzymes would increase blood levels of, and, therefore, increase the toxicity of, cyclosporin A and tacrolimus. (Tr. 1311:12-17; 1312:2-5). One way to avoid increased toxicity is to not co-administer a CYP3A inhibitor with cyclosporin A or tacrolimus. (Tr. 1312:10-15). There was no evidence presented, however, about whether everolimus was known in 1996 to be a CYP3A inhibitor. Plaintiffs did present evidence that it was known in 1996 that over fifty percent of drugs used in humans "may be" CYP3A inhibitors. (Tr. 1312:18-23; PTX-952, p.140). While this does not represent definitive evidence that a person

of ordinary skill would have believed everolimus to be a CYP3A inhibitor, and, therefore, dangerous to co-administer with cyclosporin A or tacrolimus, it does support the argument that a physician would have exercised caution in considering co-administration of these drugs, especially when considered in conjunction with the knowledge that all of these drugs were known to have toxic side effects. Therefore, notwithstanding the desirability of co-administration from a patient compliance stand-point, I reject Defendants' argument that co-administration would be obvious to a person of ordinary skill simply because of the perceived importance of patient compliance.

I am also not persuaded that the prior art expressly teaches co-administration. Defendants presented no direct evidence that co-administration of everolimus and cyclosporin A or tacrolimus was known to be safe in humans in 1996. Defendants instead rely on Murgia, which they argue discloses that co-administration of rapamycin and cyclosporin A in humans was safe. (Tr. 1251:4-1252:11).

The problem with Defendants' reliance on Murgia is that Murgia is silent on the timing of administration of rapamycin and cyclosporin A. (Tr. 1252:12-15). Dr. Tulius testified that "in the absence of a clear characterization on the timing application, a POSA would have reasonably expected that the timing was a coadministration of both agents." (Tr. 1252:17-21). I am not convinced that silence on timing equates to co-administration, particularly in light of the known toxicities of the two drugs. Furthermore, Murgia reports a small (N=43) Phase I study lasting only fourteen days. (Tr. 1326:23-1327:22; DTX-079, p. 209). The authors report only a "preliminary characterization of the side effects of" rapamycin. (DTX-079, p.215). I am dubious that a person of ordinary skill would look at such a small Phase I trial and conclude that co-administration of rapamycin and cyclosporin A in humans was safe.

There was also evidence in 1996 that co-administration of rapamycin and cyclosporin A

was not safe. Plaintiffs' expert Dr. Fung testified that there was evidence at least as early as 1991 that "co-administration of cyclosporine and rapamycin caused worsened kidney function" in rat models. (Tr. 410:22-411:6).[6] Given the conflicting evidence in the prior art as of 1996, I find that co-administration of rapamycin and cyclosporin A in humans would not have been obvious to a person of ordinary skill in view of Murgia. Since the Kahan reference is also silent on timing, I find this reference equally unhelpful to Defendants' argument.

The only prior art reference Defendants rely on that expressly discloses co-administration is Tu, which reports on a study involving co-administration of cyclosporin A and rapamycin in mice. (JTX-048). In light of my conclusions regarding Murgia and the general knowledge about the toxicities of these drugs, I am not persuaded that a single reference disclosing co-administration in an experimental study in mice would cause a person of ordinary skill to conclude that co-administration of these two drugs in humans would be safe. Therefore, I find that co-administration of rapamycin and cyclosporin A in humans would not have been obvious to a person of ordinary skill in view of Tu in 1996.

Given the substantial evidence presented about the toxicities of the two drugs individually and the lack of evidence about safety of co-administration in humans, I find that co-administration of everolimus and cyclosporin A would not have been obvious to a person of ordinary skill in 1996.

ii. Synergistically Effective Amounts

During claim construction, I construed the term "synergistically effective amounts" to mean "amounts which are individually equal to or below their respective effective dosages for the relevant indication and which together have a more than additive effect." (D.I. 69 at 3). One way

[6] In fact, Dr. Fung also testified that this result was confirmed in human trials and that cyclosporin A and rapamycin are not co-administered today; rather, the two drugs are administered four hours apart. (Tr. 411:7-412:5).

of evaluating synergy is to calculate a value called the combination index from experimental data related to the effective doses of each drug when used individually and in combination. (Tr. 1253:24-1254:12). A combination index of less than one indicates synergism, a value of one indicates an additive effect, and a value above one indicates an antagonistic relationship. (Tr. 1256:22-1257:1).

Defendants do not contest that the prior art does not disclose synergistic effectiveness of everolimus and cyclosporin A or tacrolimus. (Tr. 1322:21-1323:1). Instead, Defendants rely on the rapamycin prior art and argue that everolimus would have been an obvious substitute for rapamycin. (Tr. 1323:2-12). Defendants again rely on Tu (JTX-048) and Kahan (JTX-024).

Tu reports an experimental study in which rapamycin and cyclosporin A were co-administered in mice. (Tr. 1253:14-21). According to Dr. Tullius, Tu discloses synergy between rapamycin and cyclosporin A. (Tr. 1253:21-23). Tu reports co-administration at a variety of weight ratios, as well as calculations of the combination index for each of those ratios, with values ranging from 0.01 to 1.5. (Tr. 1255:23-1256:22). Dr. Tullius opined that Tu would teach a person of ordinary skill to expect synergy upon co-administration of rapamycin and cyclosporin A in humans. (Tr. 1257:24-1258:9). According to Dr. Tullius, a person of ordinary skill would have considered the combination index values above one, which show antagonism instead of synergy, to be "outliers" and opined that if he were doing this research, he "would expect some variance." (Tr. 1325:3-8). I am not convinced that a person of ordinary skill would have so easily dismissed the variances in the data reported in Tu. The reference itself concludes that the combination index values indicated "modest synergism, additivity or even antagonism." (Tr. 1325:12-17; JTX-048, p. 179). Given that this is a single study, conducted in mice, I do not think that this reference unequivocally shows synergism between rapamycin and cyclosporin A. At best, Tu establishes

that co-administration of rapamycin and cyclosporin A in mice may, under some circumstances, result in modest synergism.

Dr. Tullius also opined that Kahan teaches that co-administration of rapamycin and cyclosporin A would result in synergistic effectiveness. (Tr. 1245:12-18). Kahan provides a theoretical basis for synergy and also reports the combination index values calculated in a variety of experimental studies in animal models, including the study reported in Tu. (Tr. 1246:7-1247:6; JTX-024, p. 21-22). Kahan also reports the results of Phase I clinical trials in humans showing synergistic effectiveness. (Tr. 1248:9-23). The "essence" of what Kahan reports, according to Dr. Tullius, is the "rational[e] for the application of rapamycin and cyclosporine and the expectation of synergistic effects." (Tr. 1331:9-22).

The problem with Dr. Tullius's characterization of Kahan is that it is a theoretical argument, based primarily on the understanding, in 1996, of the mechanisms by which cyclosporin A and rapamycin acted. (Tr. 1332:19-1333:2). The only experimental data reported showed, at best, modest synergism and sometimes antagonism. Most of the experimental data available was from animal models rather than humans. Based on Dr. Tullius's testimony, I understand Kahan to be an argument for further study on the possible synergistic effectiveness of rapamycin and cyclosporin A rather than a conclusive statement that one should expect synergism, particularly in human subjects. I am not convinced that synergistic effectiveness in humans of everolimus and rapamycin or tacrolimus would have been obvious in view of Tu and Kahan.

iii. Substituting Everolimus for Rapamycin

Defendants argue that a person of ordinary skill would have been motivated to use everolimus as a substitute for rapamycin in 1996. Specifically, Defendants argue that a person of ordinary skill would have expected everolimus to have the same binding properties and the same

mechanism of immunosuppression as rapamycin. (1244:14-1245:4).

Defendants rely on WO'010 in view of Schreiber to argue that everolimus is an obvious substitute for rapamycin. WO'010 discloses that everolimus is a rapamycin derivative with an improved pharmacologic profile as compared to rapamycin. (Tr. 1226:10-21). WO'010 also discloses that the structure of everolimus is very similar to that of rapamycin. (Tr. 1224:17-21). The only chemical difference between the two compounds is the substitution at the C-40 position of a 2-hydroxyethyl group in everolimus in place of the hydroxyl group in rapamycin. (Tr. 1227:21-1228:3; JTX-054).

Defendants rely on Schreiber for the proposition that a person of ordinary skill would have understood that the two molecules would have the same mechanism of immunosuppression, despite this small chemical difference. Schreiber discloses a model that identifies rapamycin's binding domain, responsible for binding to the protein FKBP-12, and its effector domain, responsible for its immunosuppressive activity. (Tr. 1239:12-1240:6). Rapamycin and tacrolimus both bind to the protein FKBP-12. (Tr. 1239:16-18). Rapamycin and tacrolimus have different immunosuppressive mechanisms, however. (Tr. 1239:22-1240:1). Schreiber infers from these properties that the portions of the rapamycin and tacrolimus molecules that are identical can be identified as the binding domain and the portions that are different can be identified as the effector domain. (Tr. 1239:18-21; 1240:2-6). Defendants' expert Dr. Tullius opined that because the C-40 position on rapamycin is outside of both the binding and effector domains identified by Schreiber, a person of ordinary skill would have concluded that everolimus would have the same binding and immunosuppressive properties as rapamycin. (Tr. 1241:18-1242:3, 1244:14-1245:4).

In rebuttal, Plaintiffs offer the Van Duyne reference, which post-dates the Schreiber

reference and includes Schreiber as a co-author. (JTX-051). Van Duyne discloses a structural study of the bound rapamycin-FKBP-12 complex. (*Id.*). Dr. Tullius admitted on cross-examination that Van Duyne reports that the C-40 hydroxyl group in rapamycin is involved in binding with the FKBP-12 protein. (Tr. 1339:9-14). Dr. Tullius stated that Van Duyne was specifically a structural study and, in his opinion, had no relevance to the integrated function and structure model disclosed by Schreiber. (Tr. 1339:20-1340:5).

I am not convinced that a person of ordinary skill would have considered Van Duyne's structural study irrelevant, particularly since Schreiber's model was based primarily on inferences about the similarities and differences between rapamycin and tacrolimus. A person of ordinary skill would have understood that if the C-40 hydroxyl group was involved in binding with the FKBP-12 protein, then the binding properties of everolimus might be different than the binding properties of rapamycin. Furthermore, WO'010 discloses that everolimus and rapamycin have different properties, including differences in bioavailability and stability. (Tr. 1226:14-21; JTX-054). It seems to me that a person of ordinary skill in the art, knowing of these differences and the equivocal evidence about the C-40 position's possible involvement in binding, would not conclude that everolimus is an obvious substitute for rapamycin. Therefore, I do not think that Defendants have proven by clear and convincing evidence that using everolimus as a substitute for rapamycin would have been obvious in 1996 under WO'010 in view of Schreiber.

iv. Weight Ratio

Defendants do not argue that any of the prior art references explicitly teaches the weight ratios in claim 7 of each of the '124 and '518 patents. (D.I. 162 at 43). Defendants rely on Tu, WO'010, and the Physicians' Desk Reference from 1995 to argue that a person of ordinary skill

could have arrived at weight ratios that fall within the claimed weight ratios. (*Id.* at 45-46).

Dr. Tullius opined that a person of ordinary skill would know, based on the teachings of WO'010, that everolimus is less effective than rapamycin by a factor of three. (Tr. 1262:9-14) This knowledge, combined with the teachings of Tu as to the appropriate weight ratios for co-administration of cyclosporin A and rapamycin in mice, would, according to Dr. Tulius, lead a person of ordinary skill to choose a weight ratio in the range of 4:1 to 67:1, which is within the range claimed in the '124 and '518 patents. (Tr. 1262:6-8, 15-22). There are at least two problems with Dr. Tullius's method, however. First, as Dr. Tullius admitted, WO'010 provides only *in vitro* data about the relative effectiveness of everolimus alone. (Tr. 1321:9-1322:20). Second, as Dr. Tullius also admitted, Tu provides weight ratios for co-administration of rapamycin and cyclosporin A from an experimental *in vivo* study in mice, but no information on appropriate doses in humans. (Tr. 1320:8-19). It seems to me that combining these two sources to arrive at a weight ratio for synergistically effective use in humans is at best contrived. I am not persuaded that a person of ordinary skill in the art would have been motivated to combine these references in this way.

Dr. Tullius also stated that a person of ordinary skill would have consulted the Physicians' Desk Reference (JTX-037) to determine an appropriate dose of cyclosporin A and would have combined that information with the teachings of WO'010 about effective doses of everolimus to obtain a weight ratio similar to that obtained from the teachings of Tu. (Tr. 1265:6-1266:19). This, according to Dr. Tullius, would lead a person of ordinary skill to use these weight ratios in treating human patients. (Tr. 1266:24-1267:4). Again, I am not persuaded. Dr. Tullius admitted that this calculation required him to extrapolate from two unrelated sources which reported only the individual effective doses of each drug. (Tr. 1319:6-1320:5). It seems to me, then, that his

calculation does not account for synergistic effectiveness and, further, seems to require substantial hindsight bias. Therefore, I find that the weight ratios in claim 7 of each of the '124 and '518 patents would not have been obvious to a person of ordinary skill in the art in 1996.

For the reasons given above, I find that Defendants have failed to prove that all limitations of claim 7 of each of the '124 and '518 would have been obvious over the prior art.

3. Obviousness-Type Double Patenting

Defendants also argue that claim 7 of each of the '124 and '518 patents are invalid for obviousness type double patenting over claim 11 of the '990 patent in view of the same prior art references cited in their obviousness argument. Plaintiffs do not contest that the '990 patent is a proper double patenting reference.

Claim 11 of the '990 patent depends from claim 10 and claims a method of treating or preventing transplant rejection by administering an effective amount of cyclosporin A and everolimus. This claim does not disclose co-administration, synergistically effective amounts, or the weight ratios claimed in the '124 and '518 patents. Defendants make the same arguments for double patenting that they made for obviousness, using the same prior art references. I reject these arguments for the same reasons I have already stated. Therefore, I find claim 7 of each of the '124 and '518 patents is not invalid for obviousness type double patenting.

IV. INFRINGEMENT OF THE '124 AND '518 PATENTS

Plaintiffs assert claim 7 of each of the '124 and '518 patents. As discussed above, claim 7 of the '124 patent teaches 1) methods for treating or preventing transplant rejection comprising 2) co-administering 3) synergistically effective amounts 4) of cyclosporin A and everolimus 5) in the weight ratio 2:1 to 180:1. Claim 7 of the '518 patent is identical with the exception of element 4, which calls for an IL-2 transcription inhibitor in place of cyclosporin A. The '518 patent identifies

FK506, also known as tacrolimus, as an IL-2 transcription inhibitor. ('518 patent at 2:20-29).

A. Findings of Fact

1. A physician would look to the indications and usage section of Defendants' proposed labels before prescribing everolimus to a transplant patient. The indications and usage section of Defendants Roxane's and Breckenridge's proposed labels states, "Everolimus is indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant." This section further states that everolimus is intended to be administered "concurrently in combination with reduced doses of cyclosporine."
2. The indications and usage section of Defendants Roxane's and Par's proposed labels states, "Everolimus is indicated for the prophylaxis of allograft rejection in adult patients receiving a liver transplant." This section further states that everolimus is intended to be administered "concurrently in combination with reduced doses of tacrolimus."
3. A physician would refer to the dosage and administration section of Defendants' proposed labels to determine the appropriate doses of everolimus and cyclosporin A or tacrolimus. In following the instructions found in the dosage and administration section of the proposed labels, a physician would prescribe doses that fall within the weight ratios claimed in claim 7 of the '124 and '518 patents.
4. Quantitative analyses using data from humans generally, and use of the Berenbaum-Chou equation on such data specifically, are not required to show synergistic effectiveness.
5. Co-administration of everolimus and cyclosporin A as directed in Defendants Roxane's and Breckenridge's labels will result in synergistic effectiveness.
6. Co-administration of everolimus and tacrolimus as directed in Defendants Roxane's and Par's labels will result in synergistic effectiveness.

7. Defendants Roxane and Breckenridge had and have knowledge of the '124 patent.
8. Defendants Roxane's and Breckenridge's proposed labels teach all elements of claim 7 of the '124 patent.
9. Defendants Breckenridge, Roxane, and Par had and have knowledge of the '518 patent.
10. Defendants Breckenridge's, Roxane's, and Par's proposed labels teach all elements of claim 7 of the '518 patent.

B. Conclusions of Law

Defendants concede that their proposed labels teach all elements of claim 7 with the exception of the synergistic effectiveness element.[7] Specifically, Defendants argue that Plaintiffs have not proven that co-administration of everolimus with cyclosporin A (for kidney transplant indication) or tacrolimus (for liver transplant indication), as indicated on the label instructions, would result in synergistic effectiveness. Plaintiffs presented substantial evidence that co-administration of these drugs results in synergistic effectiveness, including examples from the patents themselves (Tr. 1092:15-1094:8), peer-reviewed journal articles (Tr. 1095:2-1098:21), results of a clinical trial (Tr. 1099:8-1102:13), and testimony of an expert with years of experience treating transplant recipients using these and other drugs (Tr. 1102:14-21). Some of these references evaluated synergistic effectiveness quantitatively using the Berenbaum-Chou equation. (Tr. 1092:20-1094:8).

On cross-examination of Plaintiffs' expert, Dr. Henry, Defendants focused primarily on the perceived importance of the Berenbaum-Chou equation for determining synergistic effectiveness. (Tr. 1118:10-1122:13). According to Defendants, the evidence cited by Plaintiffs

[7] At trial, Defendants also argued that Plaintiffs had not proven the weight-ratio element of the asserted claims. (Tr. 1040:12-18). In post-trial briefing, however, Defendants abandoned this argument, "[i]n view of the strength of Defendants' argument that Novartis has not proven that the synergy element of the asserted claims." (D.I. 169 at 5, n.4). Therefore, this argument is deemed waived.

does not support a conclusion that co-administration results in synergistic effectiveness in humans because none of the cited references evaluated synergistic effectiveness in humans using the Berenbaum-Chou equation. (Tr. 1125:9-1129:7). I am not convinced that use of the Berenbaum-Chou equation is required for evaluating synergy as is contemplated in these patents. Defendants have not argued, now or at claim construction, that "synergistically effective" meant "synergistically effective as determined by the Berenbaum-Chou equation." Accordingly, the term, as I have construed it, consistent with the specification, does not require a specific method of evaluating synergistic effectiveness.

During claim construction, I found that the term "synergistically effective amounts" needed to be construed only because the patent defined the term to have a narrower meaning than the plain and ordinary meaning of the term. (D.I. 69 at 3). I construed the term, consistent with the definition in the specification, to mean "amounts which are individually equal to or below their respective effective dosages for the relevant indication and which together have a more than additive effect." (*Id.*) Defendants' sole non-infringement argument is that Plaintiffs have not shown that co-administration as instructed by their labels would "have a 'more than additive effect' in human transplant patient." (D.I. 169 at 4). The essence of Defendants' argument is that this "additive effect" must be proved through a quantitative analysis, which, Defendants contend, Plaintiffs have not performed. (*Id.* at 5).

It seems to me that Defendants are asking me to interpret my construction of the term "synergistically effective amounts" to implicitly require a quantitative analysis. This I will not do. I am not persuaded that the word "additive" implies a quantitative analysis. There are a number of ways of determining whether an effect is more than additive; performing a rigorous quantitative analysis is only one of them. I think it is evident that an expert in the treatment of transplant

patients could, as Dr. Henry did, examine clinical data, in light of a large body of pre-clinical data that provides quantitative evidence, and opine on whether co-administration results in a greater than additive effect. I find Dr. Henry's testimony on this matter credible.

Defendants' own expert, Dr. Rabb, admitted that the references cited by Plaintiffs confirm that co-administration of these drugs results in synergistic effectiveness, evaluated using the Berenbaum-Chou equation with animal models and in vitro data. (Tr. 1190:4-1191:3). Dr. Rabb further testified that there are no peer-reviewed publications that reach a different conclusion, even for co-administration in humans. (Tr. 1194:24-1195:14). I am satisfied that experts in the field, including Dr. Henry, have evaluated the clinical data from co-administration of everolimus and cyclosporin A or tacrolimus in humans and have reached a consensus that co-administration results in a more than additive effect, indicating synergistic effectiveness.

For these reasons, I find that Plaintiffs have met their burden of proving by a preponderance of the evidence that Defendants' proposed labels induce infringement of claim 7 of the '124 and '518 patents.

V. CONCLUSION

Defendants proved that the asserted claims of the '772 patent are invalid for obviousness-type double patenting. Defendants failed to prove by clear and convincing evidence that the asserted claims of the '124 and '518 patents are invalid. Plaintiffs proved by a preponderance of the evidence that Defendants Roxane and Breckenridge induced infringement of claim 7 of the '124 patent and Defendants Breckenridge, Roxane, and Par induced infringement of claim 7 of the '518 patent.

Plaintiffs should submit an agreed upon form of final judgment within two weeks.