UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

DAIICHI SANKYO COMPANY, LIMITED and DAIICHI SANKYO, INC., **Plaintiffs and Counterclaim Defendants,** **v.** **MYLAN PHARMACEUTICALS INC., MYLAN LABORATORIES INC., MATRIX LABORATORIES, LTD., and MYLAN, INC.** **Defendants and Counterclaim Plaintiffs.**	Civ. Nos. 06-3462, 07-3039, and 08-2752 **OPINION** **HON. WILLIAM J. MARTINI**

MARTINI, U.S.D.J.

Plaintiffs Daiichi Sankyo Company, Limited and Daiichi Sankyo, Inc. (collectively "Daiichi Sankyo") are the inventors and producers of olmesartan medoxomil, the active ingredient in the hypertension medications Benicar, Benicar HCT, and Azor. Defendants Mylan Pharmaceuticals Inc., Mylan Laboratories Inc., Matrix Laboratories, LTD., and Mylan, Inc. (collectively "Mylan") are drug manufacturers seeking to market a generic version of olmesartan medoxomil. Daiichi Sankyo filed this suit claiming infringement of its United States Patent No. 5,616,599 ("the '599 patent"). Mylan concedes infringement of the '599 patent, but counters that the '599 is invalid due

to obviousness. Claim 13 of the '599 patent is the only claim at issue.[1]

The parties tried this case before the Court on various days from March 31, 2009 to April 20, 2009. Thereafter, they submitted proposed findings of fact and conclusions of law. The Court carefully considered the parties' submission and the record evidence. For the reasons set forth below,[2] the Court finds that Mylan has failed to prove by clear and convincing evidence that the '599 patent is obvious under 35 U.S.C. § 103(a). As a result, the '599 patent is neither invalid nor unenforceable. Mylan has infringed on the '599 patent under 35 U.S.C. § 271(e)(2).

I. BACKGROUND

Olmesartan medoxomil is the active ingredient in several medications produced by Daiichi Sankyo used for the treatment of hypertension. (Stipulation of Fact ("SF") ¶ 13.) Hypertension, or high blood pressure, is one of the world's leading causes of death. (Brown 4/2/09 Tr. JA 282:20-22.) Approximately seventy-three million people in the United States age twenty and older suffer from high blood pressure, with roughly sixty-two percent of this group receiving treatment. (Boghigian 4/8/09 Tr. JA 873:9-18; JA 5275.) Hypertension contributes to stroke, myocardial infarction, and other life-threatening conditions. (Brown 4/2/09 Tr. JA 282:6-10; Carey 4/14/09 Tr. JA 1009:5-9.)

[1] Initially, Daiichi Sankyo claimed that Mylan infringed on Claim 9 and Claim 13 of the '599 Patent. Claim 9 covered the chemical compound olmesartan. (SF ¶ 9.) Daiichi Sankyo has withdrawn any claim that Mylan infringes Claim 9 and has executed a covenant not to sue Mylan on Claim 9 for future products.

[2] This Opinion shall constitute the Court's findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

A. The Renin-Angiotensin System and Early Angiotensin Receptor Blockers

Starting in the 1970s, scientists began to understand the role of the renin-angiotensin system ("RAS") in controlling hypertension. (Brown 4/2/09 Tr. JA 279:1-JA 281:21; DTX 356-B, at JA 5175-81, 5171 & 5197-200.) Angiotensin II, a peptide produced by the RAS, binds to AT_1 receptors, which are found on the surfaces of a variety of cell types including blood vessels and renal tubules. (*Id*.) The constriction caused by the binding of the angiotensin II to the AT_1 receptors leads to increased blood pressure. (*Id.*)

By the late 1970s, scientists developed angiotensin converting enzyme inhibitors ("ACE" inhibitors), which directly interfered with the production of angiotensin II. (Brown 4/2/09 Tr. JA 282:22-284:5.) While ACE inhibitors proved effective, these compounds resulted in certain unwanted side-effects. (Cohn 4/7/09 Tr. JA 784:11-JA 785:23.)

In 1982, a Japanese pharmaceutical company, Takeda Chemical Industries Ltd. ("Takeda"), developed the first non-peptide compounds, which blocked the binding of angiotensin II to AT_1 receptors. (Brown 4/2/09 Tr. JA 284:10-285:16; Weinstock 3/31/09 Tr. JA 96:14-97:10.) Termed angiotensin II receptor blockers ("ARBs"), these Takeda compounds contained an imidazole ring—a five membered ring having two nitrogen atoms. (Weinstock 3/31/09 Tr. JA 101:4-102:7; DTX 125, at JA 4164.) One early Takeda compound, known as S-8307, employed a single six-membered phenyl ring

through a methylene linkage (CH_2) at the 1-position of the imidazole ring, a butyl group at the 2-position, a chlorine atom (Cl) at the 4-position, and an acetic acid (CH_2COOH) at the 5-position. (Weinstock 3/31/09 Tr. JA 102:10-20, 104:10-106:3; DTX 356-A, at JA 5127, 5130-32.)

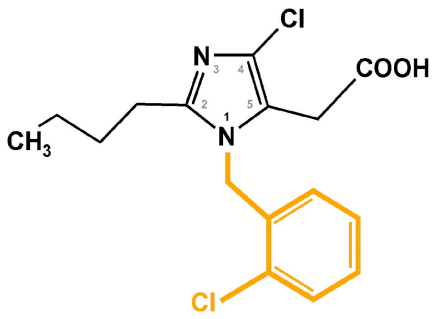

Figure 1 Chemical Structure of S-8307. (DTX 356-A, at JA 5132.)

Although the first of its kind, the Takeda compounds exhibited limited therapeutic value due to a lack of oral activity. (Weinstock 3/31/09 Tr. JA 100:7-8.)

B. Losartan

Using Takeda's work as lead, E.I. du Pont de Nemours Company, Inc. ("DuPont") embarked on its own ARB development program in 1982. (*Id.* at JA 95:23-96:1.) Several years later, in 1989, DuPont announced that it had selected one of its compounds, DuP 753, also known as losartan, for clinical trials. (*Id.* at JA 111:5-9.)

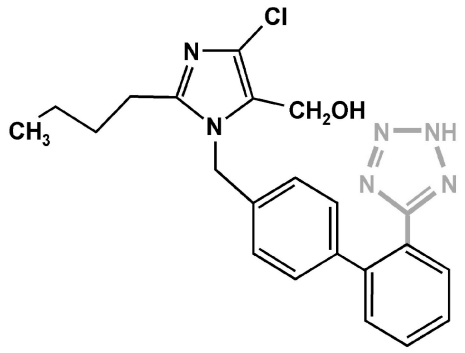

Figure 2 Chemical Structure of Losartan. (DTX 356-A, at JA 5138.)

Losartan resembled Takeda S-8307 in the sense that it retained the imidazole ring and the chlorine atom at the 4-position of the imidazole ring. The compound, however, differed through the addition of a biphenyl tetrazole—a six membered phenyl and a tetrazole—at the 1-position of the imidazole ring, as well as a hydroxymethyl at the 5-position. (DTX 356-A, at JA 5132, 5138.)

As a result of these changes, losartan exhibited a ten-fold greater binding affinity[3] and twenty-fold greater oral activity over the Takeda compounds. (Weinstock 03/31/09 Tr. JA 112:19-JA 113:8.) Losartan represented a "milestone," becoming the first non-peptide ARB clinical candidate. (*Id.* at JA 111:5-9; PTX 190, at JA 10028.) DuPont disclosed losartan and several hundred structurally related ARB compounds in United States Patent No. 5,138,069 ("the '069 patent"). (Weinstock 3/31/09 Tr. JA 119:11-23; DTX 195, at JA 3602-746.)

[3] Binding affinity is measured as an IC_{50}, which is the concentration of a compound that inhibits 50% of the binding of angiotensin II to the receptor. (Weinstock 3/31/09 Tr. JA 98:11-18.)

C. Development of Olmesartan Medoxomil

Following DuPont's success with losartan, more than twenty pharmaceutical companies established ARB research programs. (Lipinski 4/20/09 Tr. JA 1558:19-20.) Daiichi Sankyo started its own program, in late 1989, using losartan as a reference. (Yanagisawa 4/17/09 Tr. JA 1424:10-12, 1457:1-5.) The company employed a team of scientists lead by Dr. Hiroaki Yanagisawa "to come up with a drug that had ten times the activity of losartan" with "long enough duration so as to be dosed once-a-day." (*Id.* at JA 1422:10-20.)

After testing several hundred compounds, Daiichi Sankyo discovered the chemical compound olmesartan. (*Id.* at JA 1447:5-6; PTX 202-A, at JA 10499, 10256-498.) Dissatisfied with the compound's oral absorption, Daiichi Sankyo attempted to improve olmesartan's properties by attaching various ester promoieties to the chemical, converting olmesartan into the prodrug olmesartan medoxomil. (Yanagisawa 4/17/09 Tr. JA 1442:25-1446:1; PTX 26, at JA 9548-63.) The company discovered that a medoxomil ester at the 5-position of the imidazole ring led to a compound with 100 times the potency of losartan on oral administration. The medoxomil ester also crystallized, an "important factor in [a drug's] manufacturing, its formulation and in quality assurance." (Yanagisawa 4/17/09 Tr. JA 1445:20-23.)

Based on this research, on April 26, 1991, Daiichi Sankyo filed a patent application in Japan, and subsequently in the United States, claiming olmesartan and

olmesartan medoxomil. (SF ¶ 8; PTX 1, at JA 5611.) This led to the issuance the '599 patent by the United States Patent and Trademark Office ("PTO") on April 1, 1997, with Claim 13 specifically covering olmesartan medoxomil.[4] (SF ¶¶ 6, 11; PTX 1, at JA 5610.)

Like losartan and the early Takeda compounds, olmesartan medoxomil retained an imidazole backbone and possessed a biphenyl tetrazole at the 1-position of the imidazole ring. (PTX 1, JA 5610-11.)

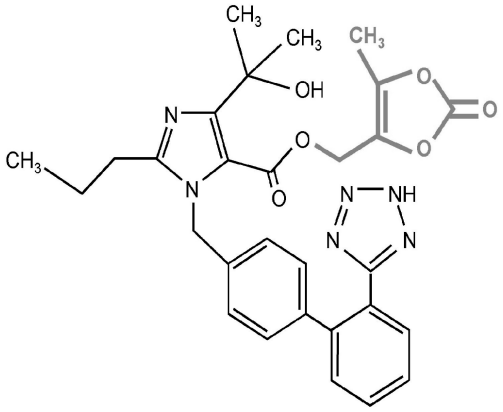

Figure 3 Chemical Structure of Olmesartan Medoxomil. (DTX 356-A, at JA 5145.)

However, olmesartan medoxomil differed from losartan in two major respects. First, at the 4-position of the imidazole ring, olmesartan medoxomil employed a hydroxyisopropyl ($C(CH_3)_2OH$) instead of a chlorine atom. (Weinstock 3/31/09 Tr. JA 121:11-17, 125:6-127:1 & 129:3-5; DTX 356-A, at JA 5143, 5146.) Second, the

[4] The '599 Patent is entitled "Angiotensin II Antagonist 1-Biphenylmethylimidazole Compounds And Their Therapeutic Use." (SF ¶ 6.) The chemical name of olmesartan medoxomil is (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(tetrazole-5-yl)phenyl]phenyl}methylimidazole-5-carboxylate. (SF ¶ 12.)

compound contained a medoxomil ester linked to a carboxylic acid at the 5-position.[5] (Weinstock 3/31/09 Tr. JA 121:1-10; DTX 356-A, at JA 5143, 5146.)

D. DuPont's '902 Patent Compounds and DuP 532

DuPont itself continued to look for improvements to losartan prior to Daiichi Sankyo's April 26, 1991 patent application in Japan. (Hieble 4/7/09 Tr. JA 711:17-23.) This additional research led to the disclosure of the '902 patent compounds, as well as DuP 532.

Following the disclosure of the '069 patent compounds, DuPont revealed six additional compounds in United States Patent No. 5,137,902 ("the '902 patent") with a February 4, 1991 priority date. (DTX 96, at JA 3747-52.) A "culmination of DuPont's ARB research," the '902 patent compounds utilized losartan's biphenyl-tetrazole-imidazole structure and contained a straight-chain propyl at the 2-position of the imidazole ring. (Weinstock 3/31/09 Tr. JA 119:24-120:12; DTX 96, at JA 3748.) Examples 1, 2, and 6 of the '902 patent compounds use a carboxylic acid at the 5-position, while Examples 3, 4, and 5 employ an aldehyde (CHO). (Lipinski 4/20/09 Tr. JA 1616:1-2.) At the 4-position of the imidazole ring, the '902 patent compounds contain various branched alkyls, including an ethyl, methyl, t-butyl, and isopropyl. (DTX 356-A, at JA 5143.)

[5] *In vivo*, enzymes cleave medoxomil from olmesartan medoxomil, liberating olmesartan. (Weinstock 3/31/09 Tr. JA 123:3-17; DTX 356-A, at JA 5145.) Instead of medoxomil at the 5-position, olmesartan possesses a carboxylic acid (COOH). (*Id.*)

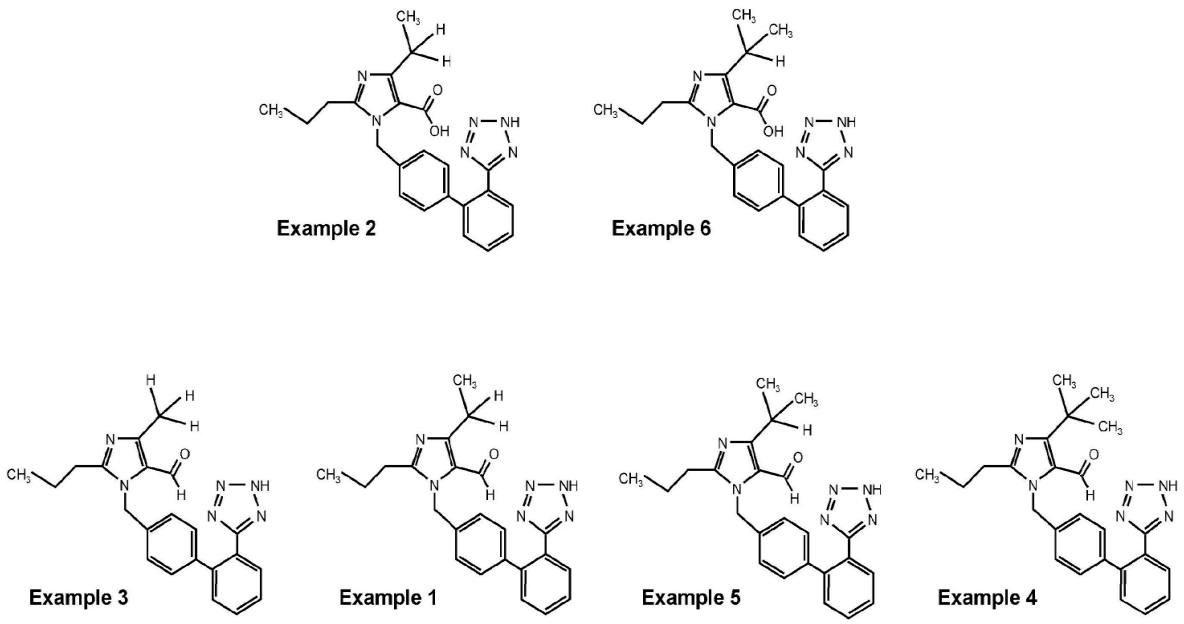

Figure 4 Chemical Structures of the '902 patent compounds. (DTX 356-A, at JA 5143.)

Although DuPont ultimately chose not to commercialize the '902 patent compounds, the most preferred '902 patent compounds exhibited oral activity "approximately 2 to 4 fold higher than most active compound specifically disclosed [in the '069 patent] which have been tested." (Brown 4/2/09 Tr. JA 405:14-16; DTX 96, at JA 3748.)

In mid-April 1991, DuPont also reported DuP 532, as part of its "new series of 4-perfluoro-alkylimidazole." (PTX 244, at JA 10761-762; PTX 246, at JA 10765-766; Weinstock 4/6/09 Tr. JA 517:3-22; Timmermans 4/16/09 Tr. JA 1383:13-1384:16; Lipinski 4/20/09 Tr. JA 1573:24-1575:3, 1576:24-1577:15.) DuPont used losartan's biphenyl-tetrazole-imidazole structure for DuP 532, but changed the 4-position of losartan from a chlorine atom to a substituent containing multiple fluorine atoms

(CF_2CF_3). (Weinstock 4/1/09 Tr. JA 213:3-6; 4/6/09 Tr. JA 517:19-22.) Unlike losartan's hydroxymethyl at the 5-position, DuP 532 employed a carboxylic acid (COOH). (Weinstock 3/31/09 Tr. JA 115:2-14; DTX 356-A at JA 5138, 5140.)

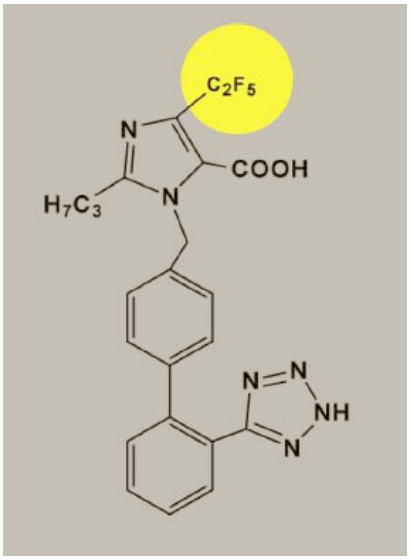

Figure 5 Chemical Structure of DuP 532. (PTX 175, at JA 9907.)

Through these changes, DuPont improved upon the oral activity of losartan. DuP 532 exhibited a three-fold increase in oral activity when compared to the company's breakthrough drug. (Timmermans 4/16/09 Tr. JA 1391:12-16; Lipinski 4/20/09 Tr. JA 1577:11-15.)

E. Other "Second Generation" ARBs

Daiichi Sankyo and DuPont were not alone in their respective quests to develop compounds superior to losartan. By April 1991, several other large pharmaceutical companies contemporaneously developed their own "second generation" ARBs. Merck & Co. ("Merck") revealed L-158,809. Ciba-Geigy, Ltd. ("Ciba-Geigy") developed

valsartan. Eisai Co. Ltd. ("Eisai") released information about a series of compounds, including E-4177 and Takeda disclosed candesartan cilexetil. (Weinstock 3/31/09 Tr. JA 48:6-9, 50:21-51:10, 62:2-5 & 63:1.)

The structure of these "second generation" ARBs differed from the early Takeda compounds, losartan, and olmesartan medoxomil. Several of these drugs did not utilize an imidazole ring: L-158,809 and E-4177 used an imidazopyridine ring, candesartan cilexetil employed a benzimidazole ring, and valsartan lacked any ring whatsoever. (PTX 248, at JA 10769-770, PTX 250, at JA 10773-813.) These compounds also differed at the position corresponding to the 2-position of the imidazole ring: E-4177 utilized a hydrocarbon ring, while cyclopropyl and candesartan cilexetil contained a non-hydrocarbon carbon chain ethyoxy. (DTX 99, at JA 3753-94; PTX 250, at JA 10773-813.)

F. Commercialization of Olmesartan Medoxomil and Other ARBs

As a result of this extensive pharmaceutical research, seven ARBs have been released for public consumption. (Boghigian 4/8/09 Tr. JA 873:25-874:2.) Daiichi Sankyo commercialized olmesartan medoxomil in three products, specifically Benicar and two combination drugs Benicar HCT and Azor.[6] (SF ¶¶ 17-19.) At the time of

[6] On April 25, 2002, the FDA approved the sale of Benicar tablets (5mg, 20mg, and 40mg), which contain the active ingredient olmesartan medoxomil, for the treatment of hypertension. (SF ¶¶ 17.) Daiichi Sankyo also received New Drug Applications ("NDA") for the sale of Benicar HCT and Azor tablets on June 5, 2003 and September 26, 2007 respectively. (*Id.* ¶¶ 18-19.) Benicar HCT is a drug containing the active pharmaceutical ingredients olmesartan medoxomil and hydrochlorothiazide (HCTZ) and Azor is a drug containing the active

Benicar's launch in 2002, six other ARBs in the drug's class had hit the market. (Boghigian 04/8/09 Tr. JA 874:11-12.) The oldest drug, Cozaar (losartan), manufactured by DuPont and then Merck, had been available for seven years, while the newest drug Teveten, manufactured by Abbott Laboratories, had been on the market for roughly two years. (PTX 584, at JA 25089.)

In its first year, Benicar enjoyed $22.5 million in gross sales. (PTX 590-1, at JA 25092.) By 2008, the combined gross sales of Benicar, Benicar HCT, and Azor reached $1.3 billion. (*Id*.) During the same time, Benicar's market share grew to 16.6%, making it the third largest ARB on the market. (PTX 583, at JA 25088.)

G. Mylan's Abbreviated New Drug Applications and the Current Litigation

Following Daiichi Sankyo's success with Benicar and the combination drugs, Mylan submitted several Abbreviated New Drug Applications ("ANDA"), seeking approval to manufacture and sell generic versions of Benicar, Benicar HCT, and Azor. (SF ¶¶ 21-23.) In conjunction with each ANDA, Mylan filed a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV), commonly referred to as a "Paragraph IV certification." (*Id.* ¶ 24.) These certifications stated that, in Mylan's "opinion and to the best of [their] knowledge, [the '599 patent is] invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of [Mylan's ANDA products]." (*Id.*)

After filing each Paragraph IV certification, Mylan sent a Paragraph IV Notice

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phamaceutical ingredients olmesartan medoxomil and amlodipine besylate. (*Id.* ¶ 18.)

Letter to Daiichi Sankyo alleging that Mylan's ANDA products will not infringe any valid claim of the '599 patent. (*Id.* ¶ 25.) Each Notice Letter affirmed that Mylan provided the factual and legal bases, known by the company at that time, that no valid claim of the '599 patent would be infringed, either literally or under the doctrine of equivalents, by the commercial manufacture, use, or sale of Mylan's ANDA products prior to the expiration of the '599 patent. (*Id.*)

After receiving Notice Letters for Benicar, Benicar HCT, and Azor, Daiichi Sankyo filed three separate actions against Mylan, each within the relevant 45-day statutory time period. (*Id.* ¶ 25.) These actions have been consolidated for all purposes under the present matter. (*Id.* ¶ 26.)

II. JURISDICTION, VENUE, AND APPLICABLE LAW

This Court has subject matter jurisdiction over Daiichi Sankyo's patent infringement claims and Mylan's counterclaims pursuant to 28 U.S.C. §§ 1331 and 1338(a). Since this action arises under the patent laws of the United States, the Court must apply the precedents of the United States Court of Appeals for the Federal Circuit, which has jurisdiction over any appeal of this judgment. *See* 28 U.S.C. § 1295(a).

III. CONCLUSIONS OF LAW

A. Standard for Obviousness

Under the United States Patent Act, an invention cannot be patented if "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(a). Since patents are presumed to be valid, *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006), the party seeking to invalidate a patent based on obviousness must demonstrate "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). Clear and convincing evidence places in the fact finder "an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984) (citation omitted).

The obviousness determination turns on underlying factual inquiries involving: (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) secondary considerations, such as commercial success and satisfaction of a long felt need. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

In cases involving chemical compounds, the patent challenger may establish a prima facie case of obviousness if the party "identif[ies] some reason that would have led a chemist to modify a known compound in a particular manner. . . ." *Takeda Chem. Indus., Ltd.* v. *Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). If a patent challenger makes a prima facie showing of obviousness, the patent owner may rebut

based on "unexpected results" by demonstrating "that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

B. Level of Ordinary Skill in the Art

The Court must first determine the level of ordinary skill in the art at the time of the filing of the '599 patent. Obviousness is judged from the perspective of a hypothetical person of ordinary skill in the art. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985). The hypothetical person must be viewed as an "inventor working in his [or her] shop with the prior art references—which he [or she] is presumed to know—hanging on the walls around him [or her]." *Union Carbide Corp. v. Am. Can Co.*, 724 F.2d 1567, 1567 (Fed. Cir. 1984). Such an individual possesses "ordinary creativity" and is not "an automaton." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420-21 (2007). In cases where the level of skill is high, courts may "assume a keener appreciation of the nuances taught by the prior art." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351 (Fed. Cir. 2001).

Here, the pertinent field of art is the design, development, synthesis, and testing of ARBs prior to the priority date of the '599 patent, April 26, 1991. (Weinstock 3/31/09 Tr. JA 124:7-125:5.) The parties agree that a person of ordinary skill is an experienced

medicinal chemist[7] with the ability to analyze structure-activity relationships ("SAR").[8] (*Id.*) Not only would a person of ordinary skill possess the ability to design, evaluate, and synthesize compounds, but such an individual would be able to evaluate pharmacological data obtained from routine screening assays. (*Id.* at JA 124:7-21.)

C. Scope and Content of the Prior Art

1. *The Prior Art at the Time of the Filing of the '599 Patent*

Under *Graham*, the Court must next define the scope and content of the prior art as of April 26, 1991. Prior art is limited to "analogous" references "from the same field or endeavor" or, if not, from the same field or endeavor art that is "reasonably pertinent to the particular problem with which the inventor is involved." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). "When the references are all in the same or analogous fields, knowledge thereof by the hypothetical person of ordinary skill is presumed . . . and the test is whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention." *In re Gorman*, 933 F.2d 982, 986 (Fed. Cir. 1991) (citation omitted).

In the instant matter, the prior art includes DuPont's '069 patent and '902 patent, as well as the thirteen scientific publications documenting DuPont's work. The prior art

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[7] Medicinal chemistry is a multi-disciplinary field concerned with the design, development, synthesis, and testing of biologically active compounds that involves aspects of organic chemistry, biological, medical, and pharmaceutical sciences. (Weinstock 3/31/09 Tr. JA 74:2-3.)

[8] A structure activity relationship is the correlation of a systematic structural change with the resulting change in the compound's activity. (*Id.* at JA 88:20-89:16.)

also incorporates the various compounds disclosed in the '069 and '902 patents, which share olmesartan medoxomil's chemical "backbone"—an imidazole ring with a biphenyl tetrazole at the 1-position and a straight chain alkyl at the 2-position. Additionally, the prior art encompasses patents related to other second generation ARB compounds published before April 26, 1991, such as Merck's L-158,809, compounds disclosed by Eisai on April 13, 1991 in patent EP 0 420 237 B1 (the "Eisai compounds"), candesartan cilexetil, and valsartan. (PTX 247, at JA 10767-768; PTX 250, at JA 10773-813; DTX 99, at JA 03753-794; PTX 204, at JA 10500-532.)

2. *Whether the Prior Art "Taught Away" From the Use of a Hydrophilic Substituent*

The parties disagree as to whether the prior art, as a whole, "taught away" from the use of a hydrophilic, as opposed to lipophilic, substituent at the 4-position of the imidazole ring.[9] Whether prior art teaches away or toward a claimed invention is a finding of fact that is a "subsidiary requirement" of the "scope and content of the prior art." *Ortho-McNeil Pharm., Inc. v. Kali Labs., Inc.*, 482 F. Supp. 2d 478, 516 (D.N.J. 2007) (citing *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006)). When the prior art "teaches away" from a particular combination of known elements, the successful combination of those elements is less likely to be obvious. *E.I. Du Pont de Nemours & Co. v. MacDermid, Inc.*, Civ. No. 06-3383, 2008 WL 4952450, at *26 (D.N.J. Nov. 19, 2008) (citing *KSR Int'l Co.*, 550 U.S. at 1740).

[9] Hydrophilicity refers to a substituent's tendency to be solvated by water, and lipophilic refers to a molecule's affinity for a fat-like environment. (Weinstock 4/1/09 Tr. JA 205:6-12.)

Under relevant Federal Circuit precedent, the prior art "teaches away" if a person having ordinary skill, "upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). For a reference to teach away, it must state more than a general preference for an alternative invention. It must "criticize, discredit, or otherwise discourage" investigation into the invention claimed. *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

In light of the above standard, the Court finds that the prior art taught away from the use of a hydrophilic group at the 4-position of the imidazole ring. The prior art evidences more than a general preference for the use of a lipophilic substituent at the 4-position, clearly discouraging a person of ordinary skill from using a hydrophilic group at this position. This clear discouragement is established by the overwhelming weight of the art, specifically language found in the '069 patent, the emphasis on lipophilicity at the 4-position in DuPont's second generation ARB compounds, DuPont SAR data from the '069 patent, and the use of lipophilic substituents at the 4-position in other second generation compounds.

a. Language Found in the '069 Patent

The '069 patent, itself, contains language which would discourage a person of ordinary skill from using a hydrophilic substituent at the 4-position of the imidazole ring. The '069 patent expresses a preference for a lipophilic group at the 4-position as

demonstrated by a regioisomer comparison.[10] The '069 patent states that: "[i]n all series examined, the more rapidly eluted isomer of a given pair has greater biological potency then the less rapidly eluted isomer." (PTX 195, at JA 10093.) The patent goes on to define the "more rapidly eluted isomer" as a compound with an imidazole ring containing a lipophilic chlorine atom at the 4-position of the imidazole ring, and the "less rapidly eluted isomer" as a compound with a hydroxymethyl (CH_2OH) at the 4-position. (*Id.*) Of the over 400 compounds released in the '069 patent, the hydroxymethyl referenced in this statement is one of the most hydrophilic. (Timmermans 4/16/09 Tr. JA 1366:24-1367:1; Weinstock 4/1/09 Tr. JA 185:17-25.) The compound containing the hydroxymethyl also has the least potency as compared to losartan. (Weinstock 4/1/09 Tr. JA 185:17-25.) Based on this statement alone, a person of ordinary skill in the art, upon reading this language, would have been discouraged from using a hydrophilic group at the 4-position. [11]

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[10] Regioisomers are two compounds that differ in the arrangement of substituents. For purposes of the '069 patent compounds, following a chemical reaction, regioisomers formed with differing 4- and 5-positions of the imidazole ring. (Timmermans 4/16/09 Tr. JA 1338:23-1339:4.)

[11] Daiichi Sankyo also points to statements found in a non-prior art reference written by the inventors of losartan David Carini et al., titled "Nonpeptide Angiotensin II Receptor Antagonists: The Discovery of a Series of N-(Biphenylylmethyl)imidazoles as Potent, Orally Active Antihypertensives" ("Carini Article"), as evidence of an explicit statement that discourages the use of a hydrophilic substituent at the 4-position of the imidazole ring. (Weinstock 4/6/09 Tr. JA 526:17-21, DTX 122 JA 4136-162.) This article was published several months after the relevant priority date. As stated above, a "reference" teaches away "when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d at 553. Under the standard for obviousness, a person of ordinary skill is presumed to have knowledge of all prior art references. *In re Gorman*, 933 F.2d

b. Lipophilicity in DuPont's Second Generation Compounds

The preference for a lipophilic substituent at the imidazole ring's 4-position is further demonstrated by DuPont's second generation ARB development. Following DuPont's success with losartan, the company engaged in additional research to create an improved antihypertensive. (Lipinski 4/20/09 Tr. JA 1559:8-13; Weinstock 4/6/09 Tr. JA 517:3-22.) As a result of this research, DuPont developed two second generation ARBs—DuP 532 and the '902 patent compounds. These second generation compounds not only shared losartan's structural backbone, but also enhanced losartan's antihypertensive properties by increasing lipophilicity at the 4-position of the imidazole ring. (Lipinski 4/20/09 Tr. JA 1559:2-7, 1677:18-20.)

DuP 532 and the '902 patent compounds modified the chlorine atom at the 4-position of the imidazole ring in favor of more lipophilic compounds. (Weinstock 4/1/09 Tr. JA 213:3-6, 216:8-10.) DuP 532 employed a more lipophilic substituent containing multiple fluorine atoms (CF_2CF_3), while the '902 patent compounds contained a series of more lipophilic alkyl substituents, including methyl, ethyl, isopropyl, and t-butyl. (*Id.*)

Based on these changes, DuP 532 and the '902 patent compounds exhibited better

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at 986. A reference qualifies as prior art if it was published before the priority date. *See* 35 U.S.C. 102(a). Turning to the facts at hand, the Carini Article fails to qualify as a prior art reference. The relevant priority date is April 26, 1991. The article was published in August 1991, several months after this date. Even though the Carini Article explicitly states that, in the biphenyl tetrazole series, disclosed in the '069 patent, "[a] large lipophilic and electron-withdrawing substituent seems to be favored" and "[t]he 4-position best tolerates a large, electronegative, lipophilic substituent," the Court cannot and need not consider this publication for purposes of its teaching away analysis. (DTX 122, at JA 4144, 4150.)

antihypertensive activity than losartan. (Lipinski 4/20/09 Tr. JA 1577:11-15.) By making the 4-position more lipophilic, DuP 532 generated a three-fold increase in oral activity over losartan. (Timmermans 4/16/09 Tr. JA 1391:12-16; Lipinski 4/20/09 Tr. JA 1577:11-15.) The most preferred compounds in the '902 patent—Examples 1, 2, and 4—exhibited "oral antihypertensive activity approximately 2 to 4 fold higher than the most active compounds specifically disclosed [in the '069 patent] which have been tested." (DTX 96, at JA 3748.)

At trial, both parties' medicinal chemistry experts emphasized the importance of lipophilic type binding forces in the '902 patent compounds. Mylan's medicinal chemistry expert, Dr. Joseph Weinstock, acknowledged that "lipophilicity is . . . an important part of this patent." (Weinstock 4/1/09 Tr. JA 218:19.) He further agreed that:

> the '902 patent teaches that a lipophilic but not an electron-withdrawing group, at the 4-position of the imidazole gives compounds with potent binding activity and are orally active . . . [which] . . . emphasizes the importance of lipophilic-type binding forces between the surface of the antagonist and the receptor.

(*Id.* at JA 218:12-15, 220:1-3.) Likewise Daiichi Sankyo's expert in medicinal chemistry, Dr. Christopher Lipinski, opined that "the '902 patent confirms the preference for lipophilic groups at the 4-position." (Lipinski 4/20/09 Tr. JA 1559:14-16.)

b. DuPont's SAR from the '069 Patent

DuPont's SAR from the '069 patent also evidences a preference for lipophilic substituents at the 4-position of the imidazole ring. This data confirms that lipophilic

substituents at the 4-position exhibited the best binding affinity. The '069 patent disclosed the specific binding affinity data for over 200 compounds. (Weinstock 3/31/09 Tr. JA 119:19-20; PTX 195, at JA 10213-215.) The vast majority of the '069 patent compounds contains lipophilic substituents at the 4-position. (Lipinski 4/20/09 Tr. JA 1555:8-10.) Of the forty-two compounds tested with a biphenyl tetrazole structure, thirty-six have lipophilic substituents at the 4-position, four use hydrophilic substituents, and two contain a neutral substituent. (*Id.* at JA 1649:7-1650:21.)

A subseries analysis of lipophilic and non-lipophilic compounds from the '069 patent illustrates a preference for lipophilicity. By looking at compounds with identical 1-, 2-, and 5-positions and varied 4-positions, Dr. Lipinski and Daiichi Sankyo's second medicinal chemistry expert Dr. Pieter Timmermans concluded that the advantage of lipophilicity is evidenced across all subseries, including non-biphenyl tetrazole series. (Timmermans 4/16/09 Tr. JA 1376:9-22, 4/17/09 JA 1530:3-6; Lipinski 4/20/09 Tr. JA 1556:18-21.) As stated by Dr. Timmermans, a comparison amongst subseries taught that a medicinal chemist could "make very potent molecules if you put a large lipophilic group on the 4-position compared to neutral, perhaps or more importantly, hydrophilic groups." (Timmermans 4/16/09 Tr. JA 1376:9-22.)

In rebuttal, Mylan points to six compounds in the '069 patent with high binding affinities and neutral or hydrophilic groups at the 4-position. (Weinstock 4/1/09 Tr. JA 233:13-17.) Mylan argues that these compounds, which equal roughly 1% of the

disclosed compounds in the '069 patent, suggest the use of a hydrophilic group at the 4-position, because two of these compounds exhibited binding affinities that exceeded losartan.[12] (Lipinski 4/20/09 Tr. JA 1651:2-9; DTX 256-A at JA 5157, 415-C at JA 5298.)

However, a placement of these six compounds in their respective subseries confirms the importance of lipophilicity for best binding activity. For each non-lipophilic compound highlighted by Mylan, the '069 patent provides a comparable compound with identical 1-, 2-, and 5-positions but with a lipophilic group at the 4-position. (PTX 628-2, at JA 25115.) In each instance, the compound containing a lipophilic 4-position exhibited better binding activity. (Weinstock 4/1/09 Tr. JA 260:13-19.)

This same emphasis is highlighted by a comparison of regioisomer pairs in the '069 patent. As both parties' experts agreed, an analysis of paired compounds, or "regioisomer" pairs, with two positions switched gives helpful information about the SAR at these positions. (Weinstock 4/6/09 Tr. JA 510:24-511:6; Lipinski 4/20/09 Tr. JA 1557:10-13.) The '069 patent contains several sets of regioisomer pairs with swapped 4- and 5-positions of the imidazole ring—the 7711 Series and the Tetrazole Series. (Timmermans 4/16/09 Tr. JA 1338:13-17.)

[12] Mylan also emphasizes language in a May 1990 article titled "The Discovery of Potent Nonpeptide Angiotensin II Receptor Antagonists" by Duncia et al., which noted that the 4-position may be substituted with either a lipophilic chlorine atom or a neutral hydrogen atom "to yield compounds of essentially equivalent binding affinity." (DTX 125, at JA 4169 n.17.) At most, this statement can be construed to indicate that a neutral—and not hydrophilic—substituent could lead to compounds with "equivalent binding affinity."

The Tetrazole Series contains the data and structure of two regioisomer pairs that use a biphenyl tetrazole at the 1-position, including losartan and its regioisomer Example 118.

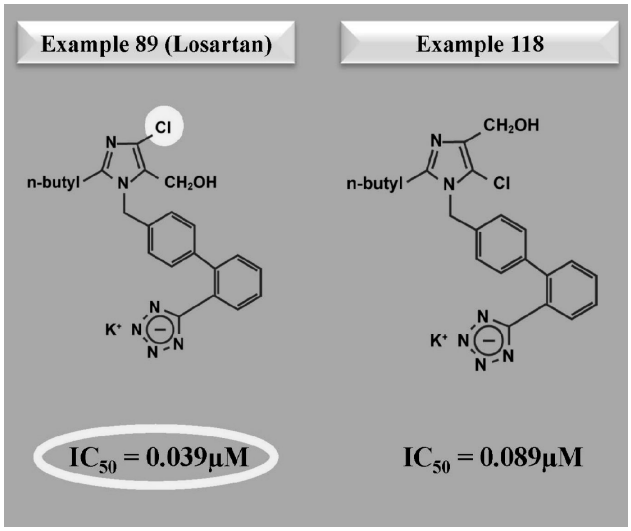

Figure 6 The Tetrazole Series. (PTX 627, at JA 25113.)

In this set, losartan exhibited better in vitro activity than Example 118, as demonstrated by lower IC_{50} values. (*Id.*) Losartan exhibited a binding affinity of 0.039 mg/kg, while the hydrophilic Example 118 showed a binding affinity of 0.089 mg/kg. (*Id.*) Likewise, in the 7711 Series, Example 94 and Example 102 both contained lipophilic substituents at the 4-position and hydrophilic substituents at the 5-position. Conversely, Examples 95 and 105 both have hydrophilic substituents at the 4-position and lipophilic substituents at the 5-position. (*Id.*) In both sets, the compound with the lipophilic substituent at the 4-position had a lower IC_{50} value, and thus better activity.

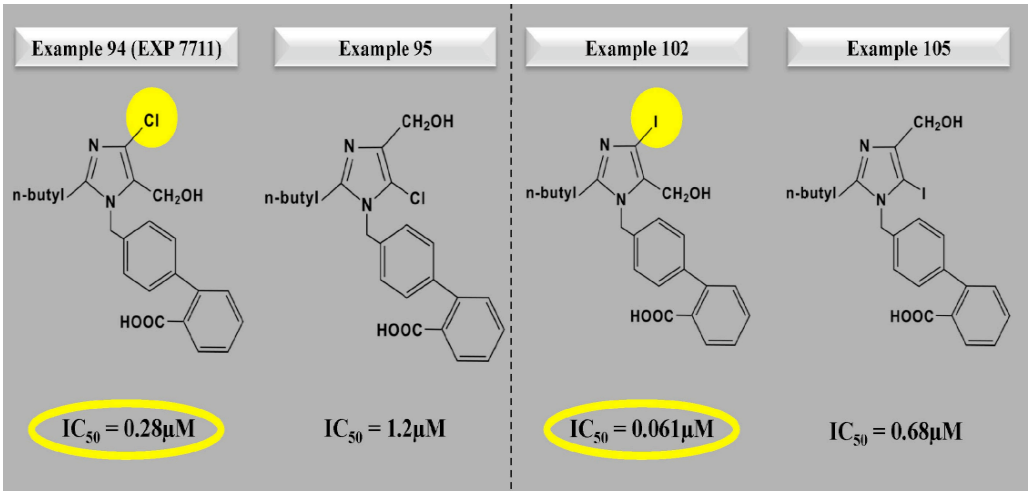

Figure 7 The 7711 Series. (PTX 626, at JA 25112.)

Example 94 exhibited a binding affinity of 0.28 mg/kg, while its regioisomer, Example 95, had a binding affinity of 1.2 mg/kg. Example 102 possessed a binding affinity of 0.061 mg/kg, while its regioisomer, Example 105, had a binding affinity of 0.68 mg/kg. (*Id.*)

Mylan refutes Daiichi Sankyo's regioisomeric analysis by reference to a July 1990 article titled "Nonpeptide Angiotensin II Receptor Antagonists" by Johnson et al. ("Johnson Article"). (PTX 224, at JA 10708.) The Johnson Article concluded that the "electron withdrawing" substituent at the 4-position would be useful in increasing oral activity, while the substituent at the 5-position may be "capable of hydrogen bonding." (*Id.*) Mylan maintains that in each regioisomeric pair cited above, the compounds with the greater binding affinity possessed an electron withdrawing substituent at the 4-position and a substituent capable of hydrogen bonding at the 5-position. (PTX 624-25, at JA 25110-111; DTX 132, at JA 4255.) After swapping the substituents at the 4- and 5-

positions, Mylan claims that the substituent at the 4-position was not electron withdrawing and the substituent at the 5-position was not capable of hydrogen bonding, thereby lowering binding affinities. Mylan's interpretation, however, is contradicted by express language of the '069 patent discussed above. The '069 patent states: "In all series examined, the more rapidly eluted [more lipophilic] isomer of a given pair has a greater biological potency than the less rapidly eluted [less lipophilic] isomer." (PTX 195, at 10093.)

c. Other Second Generation ARB Compounds

Beyond DuPont's extensive ARB work, research related to other second generation compounds evidenced the advantage of a lipophilic group at the 4-position of the imidazole ring. L-158,809, the Eisai compounds, candesartan cilexetil, and valsartan all used losartan as a lead and contain a lipophilic substituent at the 4-position or the 4-position's equivalent. (Lipinski 4/20/09 Tr. JA 1562:21-1563:3.) Dr. Weinstock even admitted that researchers, working prior to olmesartan medoxomil's priority date, "followed the teaching of lipophilicity at the 4-position" to discover irbesartan with a lipophilic 4-position. (Weinstock 4/6/09 Tr. JA 533:6-534:4.)

Mylan points to other second generation compounds as described in an October 1992 non-prior art patent review titled "Angiotensin-II Antagonists: Patent Activity since the Discovery of DuP 753" by Peter Bühlmayer, as evidence that second generation compounds used hydrophilic substituents at the 4-position. (PTX 167, at JA 9848-879.)

However, for purposes of the teaching away doctrine, only publications which qualify as prior art references may be considered. *See In re Gurley*, 27 F.3d at 553 (stating that a "reference" teaches away "when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.") Even assuming that this article qualifies as prior art, the majority of the compounds in this paper contain a lipophilic group at the 4-position. (PTX 167, at JA 9848-879.) The publication identifies "best known" compounds, which list prior art compounds containing lipophilic groups. (*Id.*; Lipinski 4/20/09 Tr. JA 1585:15-1586:7.) The one exception is eprosartan, which employs a neutral substituent hydrogen (H) at the 4-position. (Lipinski 4/20/09 Tr. JA 1586:8-1587:4; PTX 712, at JA 25191.)

When viewed in total, the express language of the '069 patent, DuPont's development of its second generation ARB compounds, DuPont's SAR, and the structure of other second generation compounds indicate that the prior art showed more than a general preference for lipophilic groups at the 4-position. Based on this prior art, the Court finds that a person of ordinary skill would have been discouraged from using a hydrophilic substituent at this position.

D. Differences between the Claimed Subject Matter and Prior Art

Turning to the third *Graham* factor, the Court must examine the differences between the claimed subject matter and prior art. When the patent at issue involves a

chemical compound, the differences between the claimed invention and the prior art often "turn[] on the structural similarities and differences between the claimed compound and the prior art." *Eisai Co. Ltd. v. Dr. Reddv's Labs., Ltd.*, 533 F.3d 1353, 1356-57 (Fed. Cir. 2008). "[S]tructural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Takeda*, 492 F.3d at 1356. "[I]t remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Id.* at 1357 (citation omitted); *see also Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009); *Eisai Co.*, 533 F.3d at 1357.

The requisite motivation can come from any number of sources and need not necessarily be explicit in the art. *Eisai Co.*, 533 F.3d at 1357 (citing *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007)). Instead, "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Id.* at 1357 (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)).

1. *Selection of Lead Compound*

An obviousness argument based on structural similarity between claimed and prior art compounds "depends on a preliminary finding that one of ordinary skill in the art

would have selected [the prior art compound] as a lead compound." *Takeda*, 492 F.3d at 1357; *see also Eisai Co.*, 533 F.3d at 1359 (stating that "post- *KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound" in the prior art). The prior art may point to more than a "single lead compound for development efforts." *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009). Even so, a compound will be found non-obvious if "the prior art disclose[s] a broad selection of compounds any one of which could have been selected as a lead for further investigation." *Takeda*, 492 F.3d at 1359-60.

A lead compound is defined as a compound with known properties that a medicinal chemist uses as a starting point for drug development. (Weinstock 3/31/09 Tr. JA 84:5-85:12.) When selecting a lead point for development, a medicinal chemist of ordinary skill considers a multitude of factors, including the lead compound's potency. (Lipinski 4/20/09 Tr. JA 1582:12-19; Weinstock 3/31/09 Tr. JA 87:25-88:4.) In addition, a medicinal chemist looks for compounds with robust packages of real data, such as binding activity, intravenous activity, oral activity, specificity, and multiple species testing. (Lipinski 4/20/09 Tr. JA 1561:10-1562:10; PTX 703-1, at JA 25172.)

Turning to the instant matter, Mylan maintains that a person of ordinary skill in the art would have selected the six compounds from the '902 patent as leads. (Weinstock 3/31/09 Tr. JA 127:2-21.) The company contends the '902 patent represented a

continuation of DuPont's work on losartan and other '069 patent compounds, as evidenced by the fact that the '902 patent explicitly stated that the most preferred compounds "exhibit[ed] remarkable and unexpected potency as antihypertensives" with "oral antihypertensive activity approximately 2 to 4 fold higher than the most active compounds [of the '069 patent] which have been tested." (DTX 96, at JA 3748.) Mylan asserts that a person of ordinary skill in the art would have selected the '902 patent compounds to take advantage of the "wealth" of SAR data from structurally similar '069 patent compounds and would have been confident in the safety of the '902 patent compounds since losartan was in clinical trials. (Lipinski 4/20/09 Tr. JA 1686:23-24; Weinstock 3/31/09 Tr. JA 127:2-21.)

Even accepting these arguments as true, Mylan has not established by clear and convincing evidence that a person of ordinary skill would have selected the '902 patent compounds out of the numerous other second generation ARBs disclosed in the prior art.[13] At the time of olmesartan medoxomil's priority date, the public had access to substantial data related to L-158,809, DuP 532, the Eisai compounds, and valsartan. Merck and DuPont released data related to the binding affinity, intravenous activity, oral activity, and selectivity of L-158,809 and DuP 532. (Lipinski 4/20/09 Tr. JA 1570-77.)

[13] Although irrelevant in light of the legal standard for obviousness, the Court notes that Daiichi Sankyo did not and could not have used the '902 patent compounds as potential lead compounds because the '902 patent's priority date of February 1, 1991 pre-dated the '599 patent, which covered olmesartan medoxomil, by a mere two months. When developing olmesartan medoxomil, Daiichi Sankyo selected losartan as a lead compound, and not the '902 patent compounds.

Eisai disclosed data relating to the Eisai compounds' binding affinity and intravenous activity, and Ciba-Geigy revealed information about valsartan's binding affinity, intravenous activity, and oral activity. (*Id.* at JA 1577-81.) In contrast, DuPont failed to report any additional data related to the '902 patent compounds. (*Id.* at JA 1566-69.)

Moreover, even if the '902 patent compounds exhibited "antihypertensive activity approximately 2 to 4 fold higher than the most active compounds" of the '069 patent, this improvement is at most comparable to other second generation ARBs. In terms of binding affinity, L-158,809 had 180 times, Example 7 of the Eisai compounds had 100 times, DuP 532 had seven times, and valsartan had two times the potency of losartan. (Lipinski 4/20/09 Tr. JA 1571:7-11, 1580:18-21.) DuP 532 even evidenced three times the oral activity of losartan and L-158,809 expressed almost perfect bioavailability. (*Id.* at JA 1576:24-1577:2.) Based on this data, Dr. Weinstock admitted on cross-examination that L-158,809 and DuP 532 were significantly more potent than losartan. (Weinstock 4/6/09 Tr. JA 529:10-531:9.)

The '902 patent compounds were not the only second generation ARBs that could rely on the "wealth" of DuPont's SAR data. Just like the '902 patent compounds, DuP 532 shared losartan's imidazole-biphenyl-tetrazole backbone. (*Id.* at JA 1677:12-14.) A person of ordinary skill who chose DuP 532 or the '902 patent compounds as leads would have had access to this data when developing an antihypertensive equivalent to olmesartan medoxomil. (*Id.* at JA 1686:23-24.)

In light of the foregoing, Mylan has failed to prove by clear and convincing evidence that a person of ordinary skill in the art would have selected the '902 patent compounds over other second generation ARBs. Since a person of ordinary skill in the art could have selected a lead compound from a "broad selection of compounds," Mylan has failed to establish its prima facie case of obviousness.

2. *Structural Differences between Lead Compound and Olmesartan Medoxomil*

Even assuming that Mylan established by clear and convincing evidence that a medicinal chemist of ordinary skill would have selected the '902 patent compounds as leads, these compounds differ structurally from olmesartan medoxomil in several respects.

At the 4-position of the imidazole ring, the '902 patent compounds employ various branched alkyls, including an ethyl, methyl, t-butyl, and isopropyl. Olmesartan medoxomil uses a hydroxyisopropyl. (DTX 356-A, at JA 5143.) The various alkyls in the '902 patent compounds belong to the alkane class of compounds and enjoy lipophilic properties. (Lipinski 4/20/09 Tr. JA 1589:22-25, 1626:5-1627:3.) Hydroxyisopropyl, found in olmesartan medoxomil, is formed by adding a hydroxyl (OH) to an isopropyl, transforming the lipophilic alkane isopropyl into a hydrophilic alcohol.[14] (*Id.* at JA

[14] Mylan seeks to rely upon Daiichi Sankyo's second supplemental interrogatory response to argue that the hydroxyisopropyl at the 4-position of olmesartan medoxomil is lipophilic. Daiichi Sankyo's interrogatory response outlines that it would not be obvious to modify the examples of the '902 patent to get to olmesartan medoxomil because:

1625:24-1626:9.)

This change results in opposing chemical properties. The lipophilic alkanes found in the '902 patent compound possess low solubility in water and lack the ability to form hydrogen bonds. (PTX 719, at JA 25196.) Conversely, the hydrophilic hydroxyisopropyl used in olmesartan medoxomil forms hydrogen bonds and exhibits high solubility in water. (*Id.*) The character of the alkyl and alcohol groups remain constant in both small and large compounds. (Lipinski 4/20/09 Tr. JA 1627:5-9.) As recognized by the patent examiner of olmesartan medoxomil, the addition of the hydroxyl was a "critical" structural difference, which distinguished olmesartan medoxomil from the '902 patent compounds. (PTX-4, at JA 8846.)

Mylan maintains that the '902 patent compounds and olmesartan medoxomil were structurally similar at the 4-position by virtue of intramolecular hydrogen bonding.[15]

> [T]here was no reason in the art to substitute the alkyl group on the 4-position of the imidazole ring in Example 6 of the '902 patent with a tertiary alcohol group as used on Olmesartan Medoxomil. Alkyl and alcohol groups are different families of substituents with entirely different properties. The prior art taught away from using a group like a tertiary alcohol at the 4-position of the imidazole ring. Preferred groups for the imidazole 4-position were lipophilic and electron-withdrawing. Changing an alkyl group at the 4-position of the imidazole ring to the tertiary alcohol group changes the properties of the resulting compounds. For example, olmesartan's tertiary alcohol group at the 4-position of the imidazole ring is capable of hydrogen bonding with the angiotensin II receptor, and is *weakly lipophilic*.

(DTX 340, at JA 5111) (citations omitted) (emphasis added). The Court finds that the phrase suggesting that the hydroxyisopropyl group itself is "weakly lipophilic" is a mistake, as evidenced from the rest of the interrogatory response.

[15] Intramolecular hydrogen bonding refers to a situation where a hydrogen bond forms within the molecule. (Lipinski 4/20/09 Tr. 1608:17-18.)

(Weinstock 4/6/09 Tr. JA 534:13-20.) This bonding caused the hydroxyisopropyl to act like a lipophilic alkane, creating a structure similar to the '902 patent compounds. Even assuming that such intramolecular bonding occurred, Dr. Weinstock admitted that the '902 patent compounds and olmesartan medoxomil would differ under such circumstances. Intramolecular hydrogen bonding would transform olmesartan at the 4- and 5-positions of the imidazole ring. (Weinstock 4/6/09 Tr. 52:25-53:3; Yanagisawa 4/17/09 Tr. 84:8-19.) This bonding would create a new ring structure that "would certainly differ in structure from losartan . . . and the '902 compounds." (Weinstock 4/6/09 Tr. 53:4-10; Lipinski 4/20/09 Tr. 66:20-67:1; PTX 725.)

Moreover, at the time of olmesartan medoxomil invention, a person of ordinary skill in the art would not have conceived of this type of bonding. Dr. Yanagisawa's post-priority date paper titled "Nonpeptide Angiotensin II Receptor Antagonists: Synthesis, Biological Activities, and Structure-Activity Relationships of Imidazole-5-carboxylic Acids Bearing Alkyl, Alkenyl, and Hydroxyalkyl Substituents at the 4-Position and Their Related Compounds" was the first paper in the ARB art to mention intramolecular hydrogen bonding. Dr. Yanagisawa speculated that this type of bonding "might account for the potent activities of and the compounds having a hydroxyalkyl group at the 4-position." (PTX 26, at JA 9555.) If a person of ordinary skill used a hydrophilic group to act as a lipophilic group, such a decision would not have been obvious to a person skilled

in the art. Instead, such a decision would have been "pretty inventive." (Lipinski 4/20/09 Tr. JA 1613:15-20.)

Turning to the 5-position of the imidazole ring, olmesartan medoxomil and the '902 patent compounds also differ. Olmesartan medoxomil is a prodrug that contains a carboxylic acid linked to a medoxomil ester at this position. (Lipinski 4/20/09 Tr. JA 1616:1-2.) Unlike olmesartan medoxomil, Examples 1, 2, and 6 of the '902 patent compounds use a carboxylic acid at the 5-position, while Examples 3, 4, and 5 employ an aldehyde (CHO). (*Id.* at JA 1616:1-2.) Notably, in 1994, DuPont attempted to create a medoxomil prodrug for Example 2 of the '902 patent compounds, resulting in a three-fold decrease in oral activity. (Hieble 4/7/09 Tr. JA 765:14-766:25; Timmermans 4/16/09 Tr. JA 1397:16-1398:1.) DuPont's failed attempt at transforming Example 2 into a prodrug highlights the significant difference in overall structure between olmesartan medoxomil and the '902 patent compounds.

3. *Reason or Motivation to Make the Specific Modifications Necessary to Achieve Olmesartan Medoxomil*

Assuming that the '902 patent compounds would have been selected as lead compounds and that a structural similarity existed between the '902 patent compounds and olmesartan medoxomil, Mylan still fails to prove by clear and convincing evidence that a person of ordinary skill in the art would have been motivated to modify the 4- and 5-positions of the '902 patent compounds to derive the invention at issue.

a. Motivation to Make a Specific Modification to the 4-position of the Imidazole Ring

Mylan argues that a medicinal chemist of ordinary skill would have been motivated to modify the lipophilic alkyls found at the 4-position of the '902 patent compounds based on a compound revealed in the '069 patent, Example 118. Besides being the regioisomer of losartan, Example 118 was one of the "more potent" compounds in the '069 patent. (Timmermans 4/17/09 Tr. JA 1532:10-14.) Example 118 employed a hydrophilic hydroxymethyl substituent at the 4-position of the imidazole ring and a chlorine at the 5-position. (DTX 356-A, at JA 5151.)

According to Mylan, a person of ordinary skill would have changed the 4-position of the '902 patent compounds, because the '902 patent taught that the 4-position did not require electron-withdrawing substituents by virtue of the fact that these compound employed non-electron withdrawing branched alkyls. (Weinstock 4/1/09 Tr. JA 216:11-17; Yanagisawa 4/17/09 Tr. JA 1467:17-1468:4.) This contradicted the Johnson Article's teaching, which stated that an electron withdrawing substituent at the 4-position *may* improve oral absorption. (DTX 132, at JA 4255.) Based on this contradiction, Mylan argues that a person of ordinary skill would have scanned DuPont's SAR from the '069 patent and deduced that a non-electron withdrawing substituent such as olmesartan medoxomil's hydroxyisopropyl was needed at the 4-position. This medicinal chemist of ordinary skill then would have utilized bioisosterism or the "principal of minor modifications" to transform the alkyls of the '902 patent compounds into a

hydroxyisopropyl.[16]

This argument fails for several reasons. First, as discussed above, the prior art taught away from the use of a hydrophilic substituent, such as a hydroxyisopropyl, at the 4-position. When the prior art teaches a preference for substituents with opposite properties, the invention at issue is not obvious. *See Eisai Co.*, 533 F.3d at 1355-57 (finding a chemical compound non-obvious where the invention at issue replaced a more lipophilic substituent with a less lipophilic substituent in contravention of the prior art's teaching that lipophilicity at a particular position on a ring structure conferred beneficial results). Since the prior art taught away from the use of a hydrophilic substituent at the 4-position, a person of ordinary skill would not have been motivated to change the lipophilic alkyls in the '902 patent compounds to the hydrophilic hydroxyisopropyl found in olmesartan medoxomil.

Second, a person of ordinary skill in the art would not select the '902 patent compounds as leads only to disregard one of their distinguishing characteristics, specifically their increased lipophilicity at the 4-position. The Federal Circuit has found that a chemical compound is not obvious when the "record . . . shows no discernible reason for a skilled artisan to begin with [a lead] only to drop the very feature . . . that

[16] Since Mylan asserts in its post-trial brief that Dr. Weinstock's testimony related to the "principal of minor modification" and bioisosterism "was not intended to substitute for the explicit motivation provided by Example 118, the Court will not address arguments raised by Daiichi Sankyo involving whether the "principal of minor modification" or bioisosterism provided an independent motivation to modify the 4-position of the imidazole ring. (Def. Post-Tr. Br. 21.)

gave this advantageous property [for which the lead was selected.]" *Id.* at 1358. As described above, Mylan contends that a person of ordinary skill in the art would have selected the '902 patent compounds over other second generation compounds, since these compounds exhibited "oral antihypertensive activity approximately 2 to 4 fold higher than the most active compounds [of the '069 patent] which have been tested." (DTX 96, at JA 3748.) Both parties acknowledge that the branched alkyls at the 4-position of the '902 compounds were more lipophilic than the chlorine found at the 4-position of losartan and Dr. Weinstock emphasized the importance of lipophilic type binding forces in the '902 patent compounds. (Weinstock 4/1/09 Tr. JA 219:19-220:17.) He explicitly stated that "lipophilicity is . . . an important part of this patent." (Weinstock 4/1/09 Tr. JA 218:17-19.) If a person of ordinary skill would have selected the '902 patent compounds over other potential leads because of their increased potency, the Court finds it illogical to conclude that the same hypothetical person would then quickly turn around and modify the 4-position to achieve the patent at issue. A person of ordinary skill would not alter an "advantageous part" of the '902 patent compounds for a hydrophilic substituent with opposing chemical properties. Such a decision would lack an obvious basis to one skilled and the art, and only could be considered non-obvious in light of the record presented at trial.[17]

[17] Even if a person of ordinary skill looked to modify the 4-position, it would have likely been to form other alkanes, alkenes, or alkynes. As admitted by Dr. Weinstock, if a lead has an alkyl group, a reasonable medicinal chemist would attempt to lengthen, shorten, branch, or make more rigid the alkyl group to derive compounds with improved properties. (Weinstock 4/6/09

b. Motivation to Make a Specific Modification to the 5-position of the Imidazole Ring

There is also scant evidence that a person of ordinary skill would be motivated to modify the 5-position of the '902 patent compounds to a carboxylic acid linked to a medoxomil acid. While Examples 2 and 6 of the '902 patent compounds contain a carboxylic acid, Examples 1, 3, 4, and 5 contain an aldehyde. (PTX 701, at JA 25170; DTX 96, at JA 3751.)

The '902 patent compounds exhibited a preference for an aldehyde at the 5-position. Two out of the three most preferred compounds in the '902 patent compounds use an aldehyde and not a carboxylic acid, suggesting to a person of ordinary skill that "there was something good" about this substituent. (Lipinski 4/20/09 Tr. JA 1615:17-21.) Dr. Lipinski opined that "based on first principals" you would expect better oral activity with the aldehyde, as opposed to the carboxylic acid. (*Id.* at JA 1615:22-25.)

Even if a person of ordinary skill focused on Examples 2 and 6, which contained a carboxylic acid at the 5-position, Mylan does not establish by clear and convincing evidence that such a person would have been motivated to transform the '902 patent compounds into a prodrug. When designing prodrugs, medicinal chemists overcome a whole series of "hurdles." (PTX 718, at JA 25195.) Pharmaceutical companies "avoid prodrugs" because "there are problems in . . . determining whether the prodrug itself has pharmacology" and "whether the conversion of the prodrug to [the] active [form] is

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Tr. JA 542:13-21.)

reproducible." (Hieble 4/7/09 Tr. JA 761:21-763:1.) As of April 26, 1991, medicinal chemists approached the creation of a prodrug as a "last resort," "a desperation, last-ditch approach," which was unpredictable. (Lipinski 4/20/09 Tr. JA 1623:2-5.)

Moreover, if a person of ordinary skill would have employed a prodrug, there is little evidence that such a person would have selected the promoiety medoxomil. As acknowledged by Mylan's expert Dr. J. Paul Heible, medicinal chemists infrequently use medoxomil. (Hieble 4/7/09 Tr. JA 761:10-12.) While Daiichi Sankyo employed medoxomil in various other antihypertensives and antibiotics, there is no evidence in the prior art that medicinal chemists successfully applied medoxomil in the ARB context prior to olmesartan medoxomil. Indeed, in 1994, DuPont attempted to make a medoxomil prodrug for Example 2 of the '902 patent, and failed. Adding the medoxomil ester to Example 2 resulted in a compound three times less potent than Example 2 itself. (*Id.* at JA 765:14-766:25; Timmermans 4/16/09 JA 1397:16-1398:1; PTX 175, at JA 9910.)

4. *Reasonable Expectation of Obtaining Olmesartan Medoxomil's Properties*

Additionally, Mylan has not proven by clear and convincing evidence that a person of ordinary skill in the art would have had a "reasonable expectation of success" in obtaining olmesartan medoxomil's properties. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); *Proctor & Gamble*, 566 F.3d at 996. In *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 402 (2007), the Supreme Court stated

that when an obvious modification "leads to the anticipated success," the invention is likely the product of ordinary skill and is obvious. "[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364 (citing *In re Corkill*, 771 F.2d 1496, 1500 (Fed. Cir. 1985)).

Here, a person of ordinary skill in the art would not have "reasonably expected" that modifying the 4-position of the imidazole ring from a lipophilic to a hydrophilic substituent would have lead to increased oral activity and binding affinity. The prior art taught that a lipophilic alkyl group at the 4-position provided better potency than a hydrophilic hydroxyalkyl group at the same position. (Lipinski 4/20/2009 Tr. JA 1625:12-15.) Based on this teaching, a person of ordinary skill would have expected olmesartan medoxomil to exhibit decreased binding activity and decreased oral activity even when compared to first generation ARBs like losartan. Instead, olmesartan medoxomil displayed high activity in binding affinity tests when administered intravenously and orally. In terms binding affinity, olmesartan medoxomil exhibited 470 times the potency of losartan. For oral and intravenous activity, olmesartan medoxomil showed 40 times the potency intravenously and 100 times the potency orally when compared to losartan. (PTX 26, at JA 9556, PTX 63, at JA 9676, PTX 676, at JA25164; Hieble 4/7/09 Tr. JA 672:8-19; Fink 4/16/09 Tr. JA 1238:9-1239:16.) Since the '902 patent compounds "exhibit[ed] remarkable and unexpected potency as antihypertensives"

when compared to losartan, a person of ordinary skill would have also expected reduced activity from compounds with a hydrophilic group at the 4-position of the '902 patent compounds. (DTX 96, at JA 3748; Lipinski 4/20/2009 Tr. JA 1628:7-11.)

In total, Mylan has failed to establish a prima facie case of obviousness. Mylan has not proven by clear and convincing evidence that a person of ordinary skill would have selected the '902 patent compounds as lead, that the '902 patent compounds are structurally similar to olmesartan medoxomil, that a person of ordinary skill would have been motivated to modify the 4- and 5-positions of the imidazole ring, or that a person of ordinary skill would have reasonably expected to obtain olmesartan medoxomil's properties. As such, Claim 13 of the '599 patent, which covers olmesartan medoxomil, is not invalid for obviousness.

E. Secondary Considerations of Non-Obviousness

Assuming *arguendo* that Mylan established a prima facie case of obviousness, secondary considerations further mitigate against a finding of obviousness. Objective indicia of non-obviousness include: (1) unexpected results; (2) commercial success; (3) long felt, unmet need; (4) copying; and (5) industry praise and recognition for the inventions. *Graham*, 383 U.S. at 17. Secondary considerations extend beyond what was known at the time of the invention and may include later discovered unexpected properties of the invention. *Knoll Pharm. Co., Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004).

When reaching the ultimate conclusion of obviousness, courts rely on secondary considerations as part of the "totality of the evidence." *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997). These considerations often represent "the most probative and cogent" evidence in the record. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Even so, "they do not control the obviousness conclusion." *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). As demonstrated by Daiichi Sankyo, several secondary considerations weigh against a finding of obviousness, specifically unexpected results and commercial success.

1. ***Unexpected Results***

Evidence of "unexpected results" allows a patent-holder to rebut a prima facie case of obviousness by showing that the "claimed invention exhibits 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 at 750. The reasoning behind this secondary consideration is straightforward: "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997). To qualify as unexpected, the claimed properties or results must be different in "kind and not merely in degree" from the results of the prior art. *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996). "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected

compared with the closest prior art."[18] *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

Daiichi Sankyo contends that olmesartan medoxomil exhibited unexpected blood pressure lowering ability as compared to the '902 patent compounds. More precisely, the patent holder argues that olmesartan medoxomil showed an unexpected result by lowering blood pressure one to two millimeters of mercury (mm Hg) more than the other ARBs on the market. Whether or not olmesartan medoxomil lowers blood pressure unexpectedly more is subject to some dispute between the parties. The Court need not address this issue, however, since it finds that olmesartan medoxomil exhibits unexpected results as compared to the '902 patent compounds in terms of potency, drug-drug interactions, insurmountable antagonism, inverse agonism, and other rehabilitative properties.

With regards to potency, a medicinal chemist of ordinary skill would have considered a two to four fold increase in intravenous and oral potency over the '902 patent compounds as unexpected. (Fink 4/16/09 Tr. JA 1237:14-21.) The '902 patent explicitly states that the most preferred compounds "exhibit[ed] *remarkable and unexpected potency* as antihypertensives" and have "oral antihypertensive activity approximately 2 to 4 fold higher than the most active compounds [of the '069 patent]

[18] As discussed above, Mylan has not established by clear and convincing evidence that the '902 patent compounds would have been selected by a person of ordinary skill as "lead compounds." Even so, for purposes of this section, the Court will consider the '902 patent compounds as the closest prior art.

which have been tested." (DTX 96, at JA 3748) (emphasis added). If the '902 patent compound exhibited "remarkable and unexpected" potency in relation to compounds from '069 patent with a two to four fold increase, then the same baseline applies to a comparison between olmesartan medoxomil and the '902 patent compounds. (Weinstock 3/31/09 Tr. JA 119:24-120:12.)

As demonstrated at trial, olmesartan medoxomil exhibited roughly 2 to 2.5 the *in vivo* activity of Examples 2 and 6 of the '902 patent compounds respectively. (Fink 4/16/09 Tr. JA 1239:5-10; PTX 26, at JA 9552.) Orally, the claimed compound showed a three-fold increase in potency over Examples 2 and 6 of the '902 patent.[19] (Hieble 4/7/09 Tr. JA 752:24-753:4.)

When compared to the '902 patent compounds, olmesartan medoxomil possessed

[19] Mylan challenges these findings by arguing that these differences in *in vivo* activity and oral potency are irrelevant because Daiichi Sankyo neglected to submit data related to Examples 1, 3, 4, and 5 of the '902 patent compounds. However, Daiichi Sankyo need "need not test compounds taught in each and every reference" to rebut a prima facie case of obviousness. Rather, there must be sufficient evidence "to permit a conclusion respecting the relative effectiveness of applicant's claimed compounds and the compounds of the closest prior art." *In re Johnson*, 747 F.2d 1456, 1461 (Fed. Cir. 1984) (citing *In re Payne*, 606 F.2d 303, 316 (CCPA 1979)). In the instant matter, there is sufficient evidence to conclude that Examples 2 and 6 represent the relative effectiveness of all the '902 patent compounds. First, although not structurally similar, Examples 2 and 6 are the closest in terms of chemical structure to olmesartan medoxomil. (PTX 701, at JA 25170.) While neither compound is a prodrug, both compounds employ a carboxylic acid at the 5-position of the imidazole ring. Example 6 of the '902 patent compound only differs from olmesartan, the active metabolite of olmesartan medoxomil, by one oxygen atom at the 4 position. (Lipinski 4/20/09 Tr. JA 1626:2-4.) Second, DuPont singled out Example 2 as one of three preferred compounds in the '902 patent. Even though the other two preferred '902 patent compounds contain an aldehyde at the 5-position, which Daiichi Sankyo acknowledged would be expected to exhibit better oral activity, the '902 patent explicitly states that Example 2, as a preferred compound, exhibited "remarkable and unexpected" oral antihypertensive properties over the '069 patent compounds. (*Id.* at JA 1615:12-16; PTX 530, at JA 24999.)

a substantially lower likelihood of drug-drug interactions. Drug-drug interactions constitute a "serious event," which may cause the removal of a commercial drug from the market. (Hieble 4/7/09 Tr. JA 699:20-23; Fink 4/16/09 Tr. JA 1264:2-7). Daiichi Sankyo presented evidence that the compound was found to be four to seven times less likely to inhibit the cytochrome P450 family of enzymes found in the liver than Examples 2 and 6 of the '902 patent compounds. (Fink 4/16/09 Tr. JA 1268:6-17.) This lack of inhibition reduced the risk of potentially deadly drug-drug interactions.

Olmesartan medoxomil also qualifies as an insurmountable antagonist. The patented compound has been shown to bind to the AII receptor in such a manner that "it cannot be displaced by angiotensin no matter how high the concentration of angiotensin." (Hieble 4/7/09 Tr. JA 693:5-15.) At "a given concentration of 0.3 nanomolar, olmesartan suppresses the response at 100 nanomolar [of angiotensin II] greater than example 6" of the '902 patent. (Hieble 4/7/09 Tr. JA 696:17-20.) At this concentration, olmesartan is completely insurmountable, while Example 6 of the '902 patent lacks this ability. (Hieble 4/7/09 Tr. 697:6-15.)

Not only does olmesartan medoxomil exhibit insurmountable antagonism, but the active metabolite olmesartan possesses higher inverse agonist activity than Example 6 of the '902 patent compounds. (Fink 4/16/09 Tr. JA 1260:19-1261:1.) Inverse agonism refers to the property of an ARB to reduce or eliminate the baseline activity of the AT_1 receptor. (Hieble 4/7/09 Tr. JA 690:9-13.) Inverse agonism represents "a potentially

very important property of ARBs [] [b]ecause of a conundrum"— hypertensive patients generally "do not have higher levels of the renin angiontensin system activity" compared to "normal patients." (Fink 4/16/09 Tr. JA 1257:7-1258:4). ARBs qualifying as inverse agonists might "work more effectively in the patients who have low levels of [] renin angiotensin system activity." (Fink 4/16/09 Tr. 1258:2-4.) As admitted by Dr. Hieble, "olmesartan had statistically-significant inverse agonism activity in the wild type receptor, and example 6 of the '902 patent had no significant effect." (Hieble 4/7/09 Tr. JA 691:13-18.)

As compared to other second generation ARBs and the '902 patent compounds, olmesartan medoxomil displayed other rehabilitative properties. In particular, olmesartan medoxomil increases renin secretion, providing the highly desirable effect of stimulating the AT_2 receptor. The drug reduces atherosclerotic plaque volume, which helps to lower plaque volume toward normal levels in hypertensive patients. (Carey 4/14/09 Tr. JA 1049:23-1053:15, 1053:24-1055:13.) Olmesartan medoxomil shows an ability to reverse damage to kidney tissue, as well as damage to vascular walls, and causes a "highly significant reduction in wall-to-lumen ratio," bringing this ratio "back to the level of [a] healthy normal control." (*Id.* at JA 1057:18-1061:24.)

2. ***Commercial Success***

Besides unexpected results, evidence of an invention's commercial success may present strong evidence of non-obviousness. *See, e.g.*, *Demaco Corp. v. F. Von*

Langsdorff Licensing, Ltd., 851 F.2d 1387, 1391 (Fed. Cir. 1988). Commercial success is "usually shown by significant sales in a relevant market." *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000). However, evidence showing sale of a large number of goods supposedly embodying the claimed invention does not necessarily demonstrate non-obviousness. The success must be due to the claimed features of the invention, rather than factors such as advertising, superior workmanship, or other features within the commercialized technology. *Pfizer Inc. v. Teva Pharms. USA, Inc.*, 461 F. Supp. 2d 271, 274 (D.N.J. 2006) (citing Roger Schechter & John Thomas, *Principles of Patent Law* 164).

Here, the record indicates that olmesartan medoxomil, as commercialized in Benicar and the two combination products Benicar HCT and Azor ("Benicar products"), is a commercial success. Since its introduction in 2002, Benicar products have enjoyed total net sales of over $3.1 billion and total gross sales over $4 billion. Benicar products have grown from yearly net sales of $18.9 million in 2002 to $909 million in 2008. (PTX 590-1, at JA 25092.) Doctors have written over 58 million prescriptions for the Benicar products, steadily growing from 378,426 in 2002 to 14,856,487 in 2008. (PTX 593, at JA 25096.) Benicar and Benicar HCT rank in the top 5% of U.S. prescription drugs in terms of sales. (PTX 652, at JA 25153.)

Although the seventh ARB in its class to hit the market, Benicar products gained market share at the expense of its competitors. Benicar's market share has grown to over

16.6%, making it the third largest available ARB. (PTX 583, at JA 25088.) Mylan's marketing expert, Harry Boghigian, opined at trial that Benicar's growth curve is "similar" to the "extremely nice growth curve" for Diovan, the market leader, as demonstrated by the dotted lines below:

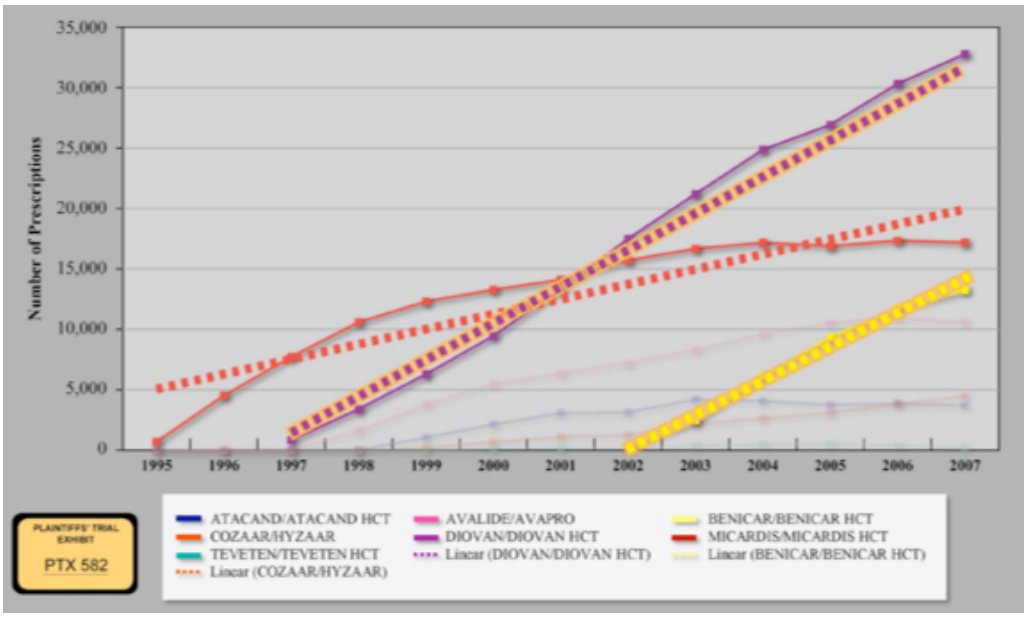

Figure 8 Linear Growth of Benicar/Benicar HCT in Comparison to Diovan/Diovan HCT and Cozaar/Hyzaar 1995-2007. (PTX 582, at JA 25087; Boghigian 4/8/09 Tr. JA 935:5-9.)

This growth is telling especially when compared to Tevetan, the last ARB to hit the market prior to Benicar. In the approximate two years prior to Benicar's launch, Tevetan gained little traction, managing to capture a mere 0.29% of the ARB market. (PTX 583, at JA 25088.)

The Benicar products not only gained market share, they vastly exceeded the internal pre-launch forecasts of Daiichi Sankyo. The cumulative net sales of the Benicar family nearly double Daiichi Sankyo's predictions. In 2005, Daiichi Sankyo expected

$265 million in net sales, while earning $447.2 million. (PTX 591, at JA 25093.) By 2008, the projections of Daiichi Sankyo differed by over $500 million. For 2008, Daiichi Sankyo estimated net sales of $345 million and earned $909.5 million. (*Id*.)

The Benicar products success was also recognized by major managed care organizations. These drugs have achieved "preferred" status on formularies of at least seven of the fourteen major managed care organizations. (Smith 4/14/09 Tr. JA 1144:8-20; PTX 662, at JA 25160.) By contrast, Avapro, which has been on the market for eight years, achieved "preferred" status on only six of fourteen major formularies, and Cozaar, the first commercialized ARB, achieved "preferred" status on nine of fourteen major formularies. (PTX 662, at JA 25160.)

Mylan argues that Benicar's success stems not from its properties, but from Daiichi Sankyo's marketing and advertising efforts. However, Daiichi Sankyo spent roughly the same amount in marketing the Benicar products as its competitors. (PTX 579-1, at JA 25083.) Daiichi Sankyo utilized a smaller sales force than other pharmaceutical companies to sell the Benicar family of drugs and Daiichi Sankyo's ratio of brand marketing expenses to sales for olmesartan medoxomil fails to illustrate pervasive marketing. (Boghigian 4/8/09 Tr. JA 951:16-952:8.) For example, in 2007, Daiichi Sankyo's ratio of brand marketing expenses to net sales for Benicar products was 39%, consistent with industry practice. (*Id.* at JA 952:7-8.) Moreover, there is no evidence that Daiichi Sankyo offered excessive discounts or rebates to managed care

organizations or Medicare and Medicaid programs or that Daiichi Sankyo priced Benicar products out of line with other ARBs on the market. (*Id.* at JA 954:4-6; PTX 264, at JA 10989.)

Mylan also asserts that certain "false or misleading" promotional materials led to Benicar's commercial success. In January 2006, the FDA sent a warning letter to Daiichi Sankyo regarding certain promotional materials for Benicar, based on material excerpted from published studies comparing the efficacy of ARBs at starting doses. (DTX 310, at JA 5053-77.) After Daiichi Sankyo ceased using this material and sent corrective letters to physicians, the sales from Benicar products continued to increase. (Boghigian 4/8/09 Tr. JA 970:2-973:3, 985:12-15.) Even after the FDA letter, physicians rated Benicar as the best, or among the best, ARBs in the market. (Smith 4/14/09, at JA 1156:13-1160:13; PTX 284, at JA 11579.)

Finally, Mylan contends that olmesartan medoxomil cannot be considered a commercial success because Daiichi Sankyo did not earn a profit from the sale of Benicar products. Mylan asserts "it's highly unlikely" that the Benicar products demonstrated profitability, based on Daiichi Sankyo's profit and loss statements. (Boghigian 4/8/09 JA 888:23-889:17.) As an initial matter, "profitability analysis has a number of issues with it . . . it's subject to a lot of internal accounting conventions that are unique to a particular company." (Smith 4/14/09 Tr. JA 1116:17-22.) A comparison of profits with competing products is difficult, since "[m]ost companies report profitability at a company level."

(*Id.* at JA 1117:13-14.)

After considering the evidence in the record, the Court finds that Daiichi Sankyo profited from sale of Benicar products. There is sufficient evidence that the Benicar products earned between $250 and $300 million a year in "direct controllable profit," after accounting for sales forces expenses and the profit sharing relationship with its co-promoter, Forest Pharmaceuticals Inc. ("Forest Laboratories.") (Smith 4/14/09 Tr. JA 1146:1-8.) This range is supported by the Benicar products reported net income for 2008 of $270 million. (PTX 650, at JA 25132-151; Smith 4/14/09 Tr. 1151:21-1152:4, 1204:13-17.)

Profitability is also demonstrated by the payments made to Forest Laboratories under the parties' co-promotion agreement. Under this arrangement, Daiichi Sankyo provided Forest Laboratories a 45% profit-split in exchange for the co-promotion of Benicar. (Boghigian 4/8/09 JA 881:25-883:6, JA 955:22-956:2.) In profit and loss statements, Daiichi Sankyo reported payments to Forest Laboratories as "co-promotion expenses," which increased as sales of the Benicar products increased. (Boghigian 4/8/09 JA 954:22-956:19.) A review of Forest Laboratories' annual reports confirms that Daiichi Sankyo made payments to its co-promoter. Daiichi Sankyo began paying Forest Laboratories when the product reached cumulative profitability in 2005. (Boghigian 4/8/09 Tr. JA 905:12-16; Smith 4/14/09 Tr. JA 1147:19-1148:1.)

Accordingly, even if Mylan established a prima facie case of obviousness, the

commercial success of the Benicar family and the unexpected results exhibited by olmesartan medoxomil over the '902 patent compounds and other second generation ARBs weigh towards a finding of non-obviousness.[20]

III. CONCLUSIONS OF LAW

For the foregoing reasons, the Court find that Mylan has failed to prove by clear and convincing evidence that the '599 patent is obvious under 35 U.S.C. § 103(a). As a result, the '599 patent is neither invalid nor unenforceable. Mylan has infringed on the '599 patent under 35 U.S.C. § 271(e)(2). An appropriate Order accompanies this Opinion.

s/William J. Martini
William J. Martini, U.S.D.J.

[20] Daiichi Sankyo also argues that other secondary considerations weigh towards a finding of non-obviousness, such as long-felt, unmet need, industry praise and recognition, and copying. At trial, Daiichi Sankyo neglected to present sufficient evidence indicating that olmesartan medoxomil addressed a real, commercial demand for purposes of establishing a long-felt, unmet need. Similarly, Daiichi Sankyo has not presented evidence of copying, except to claim that Mylan's filing of its ANDA constitutes copying and has offered no credible evidence of industry acclaim. Although Dr. Yanagisawa briefly referenced an award from the Pharmaceutical Society of Japan, it is not clear whether the award was for Benicar or for Dr. Yanagisawa's contributions to medicinal chemistry during the course of his long career. (Yanagisawa 4/17/09 Tr. JA 1455:15-1457:7.)