

**NOT FOR PUBLICATION**

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

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OTSUKA PHARMACEUTICAL CO., LTD.,	:	
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Plaintiff,	:	<b>Consolidated Civil Action No.</b>
	:	<b>3:07-cv-01000 (MLC)</b>
v.	:	
	:	
SANDOZ, INC.,	:	
TEVA PHARMACEUTICALS USA, INC.,	:	
TEVA PHARMACEUTICAL INDUSTRIES	:	
LTD.,	:	<b>AMENDED</b>
BARR LABORATORIES, INC., BARR	:	<b>MEMORANDUM OPINION</b>
PHARMACEUTICALS, INC.,	:	
APOTEX INC., APOTEX CORP.,	:	
SUN PHARMACEUTICAL INDUSTRIES,	:	
LTD.,	:	
SYNTHON HOLDING BV, SYNTHON BV,	:	
SYNTHON PHARMACEUTICALS, INC., and	:	
SYNTHON LABORATORIES, INC.,	:	
	:	
Defendants.	:	

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**Cooper, District Judge**

Otsuka Pharmaceutical Co., Ltd. (“Plaintiff” or “Otsuka”) brought this action and a number of now-consolidated actions against generic drug manufacturers, Sandoz, Inc. (“Sandoz”); Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd. (“Teva”); Barr Laboratories, Inc., Barr Pharmaceuticals, Inc. (“Barr”); Apotex Corp., Apotex Inc. (“Apotex”); Sun Pharmaceutical Industries, Ltd. (“Sun”); Synthon Holding BV, Synthon BV, Synthon Pharmaceuticals, Inc., and Synthon Laboratories, Inc. (“Synthon”) (collectively,

“Defendants”).<sup>1</sup> Otsuka alleges infringement of U.S. Patent No. 5,006,528 (the “‘528 Patent”), which claims, inter alia, the chemical compound aripiprazole, based on Defendants’ submissions of an Abbreviated New Drug Application (“ANDA”) to the United States Food and Drug Administration (“FDA”) for approval to engage in the commercial manufacture, use, or sale in the United States of generic aripiprazole products. Infringement is not contested in this action, as Defendants concede that their ANDA filings constitute literal acts of infringement “to the extent [the asserted] claims are valid and enforceable.” (See Pl.’s Post-Trial Br. at 9.) 35 U.S.C. § 271(e)(2)(A); see also Glaxo, Inc. v. Novopharm Ltd., 110 F.3d 1562, 1569 (Fed. Cir. 1997) (noting that § 271(e)(2) provides “patentees with a defined act of infringement sufficient to create case or controversy jurisdiction to enable a court to promptly resolve any dispute concerning infringement and validity”). Defendants contend that the ‘528 Patent is invalid as obvious under 35 U.S.C. § 103; invalid due to obviousness-type double patenting over Otsuka’s prior art U.S. Patent No. 4,734,416 (the “‘416 Patent”); and unenforceable due to inequitable conduct arising from Otsuka’s failure to disclose certain information to the United States Patent and Trademark Office (“USPTO”). Because this civil action arises under the United States

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<sup>1</sup> Teva and Barr merged after these actions were filed. (Dkt. entry no. 382, Defs.’ Post-Trial Proposed Findings of Fact and Conclusions of Law (“Defs.’ Post-Trial Br.”) at 2 n.1.) Only the Teva-Barr and Apotex defendants participated in the trial of this consolidated action, with the remaining defendants agreeing to be bound by the final judgment herein. (See, e.g., dkt. entry no. 310, 5-7-10 Stipulation staying the action as to Sandoz; dkt. entry no. 285, 4-5-09 Stipulation staying the action as to Sun; dkt. entry no. 92, 1-11-08 Stipulation staying the action as to Synthon.) Similar stipulations have been executed in two related but non-consolidated cases, Otsuka Pharm. Co., Ltd. v. Zydus Pharm. USA, Inc., Civ. No. 08-2675 (dkt. entry no. 13, 7-13-10 Supp’l Stipulation) and Otsuka Pharm. Co., Ltd. v. Zydus Pharm. USA, Inc., Civ. No. 10-2857 (dkt. entry no. 5, 7-15-10 Stipulation staying the action as to Zydus and Cadila Healthcare Ltd.). (See generally dkt. entry no. 381, Plaintiff’s Post-Trial Proposed Findings of Fact and Conclusions of Law (“Pl.’s Post-Trial Br.”) at 4-8.)

patent laws, Title 35, United States Code, the Court exercises subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

The parties tried the case before the Court from August 5, 2010 through August 26, 2010. The parties thereafter submitted proposed findings of fact and conclusions of law. The Court heard closing arguments and received additional documentary evidence on October 21, 2010.<sup>2</sup> This Amended Memorandum Opinion constitutes the Court's findings of fact and conclusions of law on the issues of invalidity and unenforceability, pursuant to Fed.R.Civ.P. 52(a), and supersedes the Memorandum Opinion entered on November 15, 2010. (See dk. entry no. 390, 12-14-10 Order.) For the reasons set forth herein, the Court concludes that Defendants did not show by clear and convincing evidence that '528 Patent is invalid as obvious under either 35 U.S.C. § 103 or the judicially-created doctrine of obviousness-type double patenting, or that the '528 Patent is unenforceable due to inequitable conduct. Accordingly, the Court will enter judgment in favor of Otsuka on its claims that Defendants have infringed the '528 Patent.

## **BACKGROUND**

### **I. Abilify<sup>®</sup>**

Otsuka markets aripiprazole under the trade name Abilify<sup>®</sup>. Abilify<sup>®</sup> is approved by the FDA for the treatment of, inter alia, schizophrenia, bipolar disorder, irritability associated with autistic disorder in pediatric patients, and as an add-on treatment for depression. (Pl.'s Post-Trial Br. at 52.) The listing for Abilify<sup>®</sup> in the FDA's Approved Drug Products with Therapeutic

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<sup>2</sup> The Court advised the parties at the conclusion of the October 21, 2010 hearing that it would cite the parties' post-trial briefs containing proposed findings of fact and conclusions of law, with the understanding that those briefs contain the relevant citations to the record, and that such citations are incorporated herein for purposes of this Amended Memorandum Opinion.

Equivalence Evaluations (the “Orange Book”) contains references to both the ‘416 Patent and the ‘528 Patent as covering aripiprazole. (Defs.’ Post-Trial Br. at 1, 11; Pl.’s Post-Trial Br. at 4.) Abilify<sup>®</sup> was first marketed in the United States in 2002 and was the result of several decades of drug development by Otsuka. (See Defs.’ Post-Trial Br. at 144 (“Aripiprazole was the last episode in years of work by Otsuka.”).) It has been commercially successful. By the end of 2009, sales of Abilify<sup>®</sup> were \$3.3 billion annually, and from 2005 onward, sales of Abilify<sup>®</sup> have exceeded a billion dollars each year, qualifying it as a “blockbuster drug.” (Pl.’s Post-Trial Br. at 124-25.)

## **II. Development of Antipsychotic Drugs for the Treatment of Schizophrenia**

Schizophrenia is a serious and debilitating mental disease affecting approximately one percent of the human population. (Pl.’s Post-Trial Br. at 25.) Despite extensive research, the cause, mechanism, and etiology of schizophrenia were unknown in 1988 and remain unknown today. (Id. at 26.) Researchers believe that both genetic and environmental factors may play a role in the cause of the illness. (Id.)

Individuals with schizophrenia suffer from positive symptoms, negative symptoms, and cognitive deficits. (Id.) Positive symptoms include hallucinations and delusions, while negative symptoms include flat affect, poverty of speech, inability to experience pleasure, lack of desire to form relationships, and lack of motivation. (Defs.’ Post-Trial Br. at 6.)

The first antipsychotic drug, chlorpromazine, was discovered by accident in the early 1950s. (Pl.’s Post-Trial Br. at 27.) After chlorpromazine was discovered, researchers determined that its antipsychotic properties were due to its antagonism, or blocking, of dopamine receptors in the brain. (Id.; Defs.’ Post-Trial Br. at 6.) That key finding led to the development

of other “typical” antipsychotics, including haloperidol, thiothixene, trifluoperazine, fluphenazine, thioridazine, mesoridazine, loxapine, molindone, perphenazine, and pentoxide. (Pl.’s Post-Trial Br. at 27.) Typical antipsychotic drugs treat the positive symptoms of schizophrenia, but not the negative symptoms. (Defs.’ Post-Trial Br. at 6.) Typical antipsychotic drugs also have problematic side effects, including extrapyramidal symptoms (“EPS”), tardive dyskinesia, prolactin elevation (hyperprolactinemia), and sudden decrease in blood pressure (orthostatic hypotension). (Id.) Despite these various drawbacks, the typical antischizophrenic drugs are still used today. (Id.) Loxapine was the last of the typical antipsychotics to be approved by the FDA, in 1975. (PTX 79, Winston Shen, “A History of Antipsychotic Drug Development,” Comprehensive Psychol., Vol. 40, No. 6 (1999), at 409.)

The adverse side effects of the first-generation typical antipsychotics led researchers to seek alternatives with a better side effect profile, particularly with regard to EPS. Clozapine, discovered in the early 1960s, was the first “atypical” antipsychotic drug in that it had diminished propensity to cause EPS. (Id.) Clozapine also differed from typical antipsychotics in that it was useful in treating both positive and negative symptoms of schizophrenia. (Shen at 409-10.) Unfortunately, clozapine has several potential adverse side effects including agranulocytosis, a life-threatening decrease in white blood cells; orthostatic hypotension; and frank hypotension. (Defs.’ Post-Trial Br. at 6-7; Pl.’s Post-Trial Br. at 28-30.) Because of its side effect profile, clozapine was withdrawn from clinical trials in the 1970s and not approved by the FDA for treatment of schizophrenia until 1990, and then only for treatment-resistant or treatment-intolerant patients, subject to rigorous blood testing. (Pl.’s Post-Trial Br. at 30; dkt. entry no. 352, Roth Tr. at 1129, 1133, 1137.)

Scientists have been attempting since the early 1970s to discover an atypical antipsychotic treatment for schizophrenia that would be similar to clozapine in efficacy, but without the toxicity and significant side effects. (Pl.’s Post-Trial Br. at 30; see, e.g., PTX 116, Samuel Gershon, “Update on Drug Development,” Psychopharmacology Bull., Vol. 16, No. 3 (1980), at 32 (“Clozapine-like drugs have provided investigators with results that were sometimes promising and sometimes disappointing. . . .”).) These efforts, however, were largely unsuccessful, and the FDA approved no new antipsychotic drugs between 1976 and 1989. (Pl.’s Post-Trial Br. at 31; see also PTX 93, Leo E. Hollister, “Strategies in Clinical Psychopharmacology,” Psychopharmacology Bull., Vol. 23, No. 3 (1987), at 389 (“It is most discouraging that more effective pharmacotherapy for schizophrenia has not been developed in the more than three decades since the introduction of the first effective drugs.”).)

Risperidone was the first post-clozapine atypical antipsychotic approved by the FDA, in 1994. (Shen at 410.) While clozapine remains the “gold standard” with respect to efficacy, a total of nine atypical antipsychotics, including aripiprazole, have been approved by the FDA and are considered “at least as effective as typical antipsychotic drugs in treating the positive symptoms of schizophrenia while causing fewer EPS side effects . . . [and] also show superiority over typical antipsychotic drugs in improving the negative symptoms of schizophrenia.” (Shen at 410, 412-13; Pl.’s Post-Trial Br. at 60.) With the exception of aripiprazole, all FDA-approved atypical antipsychotics are structurally related to either clozapine or risperidone.<sup>3</sup>

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<sup>3</sup> The FDA-approved atypical antipsychotics are clozapine (1990), risperidone (approved in 1993 and first marketed in 1994), olanzapine (1996), quetiapine (1997), ziprasidone (2001), aripiprazole (2002), paliperidone (2007), asenapine (2009), and iloperidone (2009). (See dk. entry no. 356, Nichols Tr. at 1586-87.)

### III. The '416 Patent

Otsuka is the assignee of the '416 Patent covering "Pharmaceutically Useful Carbostyryl Derivatives," which issued on March 29, 1988, and expired on March 29, 2005. It teaches that "[c]arbostyryl derivatives having antihistamic action and central nervous controlling action are useful as antihistamic agents or central nervous controlling agents." ('416 Patent, Abstract.) The '416 Patent covers approximately nine trillion compounds. (Defs.' Post-Trial Br. at 132; Pl.'s Post-Trial Br. at 77.) It therefore discloses a broad genus of carbostyryl compounds that generically encompasses aripiprazole, although aripiprazole is not specifically disclosed. (Pl.'s Post-Trial Br. at 53; see also Defs.' Post-Trial Br. at 11 (noting that Claim 1 and Claim 30 of the '416 Patent cover aripiprazole).)

The inventors of the '416 Patent included Dr. Yasuo Oshiro, who is also an inventor on the '528 Patent; Dr. Kazuyuki Nakagawa; and Dr. Kazuo Banno. (Defs.' Post-Trial Br. at 11.) The '416 Patent specification disclosed that compounds of the invention "are useful for central nervous controlling agents such as central muscle relaxing agents, sleep-inducing agents, pre-operative drugs, antischizophrenia agents, sedatives, antianxiety drugs, anti-manic depressive psychosis agents, antipyretic agents, analgetic agents and depressors, without showing side-effects such as . . . parkinsonism, and/or delayed dyskinesia [sic] which exist with conventional central nervous controlling agents." ('416 Patent at col. 3, lines 13-22.) Claim 13 of the '416 Patent is directed to the compound 7-[4-(4-phenylpiperazinyl)-butoxy]-3,4-dihydrocarbostyryl, referred to at trial as the "unsubstituted butoxy" because it lacks any substituents on the phenyl ring and has a butoxy linker connecting the carbostyryl core to the piperazine ring. ('416 Patent at col. 70, lines 62-63; see also Pl.'s Post-Trial Br. at 80 (noting that the term "unsubstituted

butoxy” does not appear in the ‘416 Patent).) Claim 116 is directed to a particular use of, inter alia, the unsubstituted butoxy, by reference to Claim 50, which discloses “[a] method for producing an antihistaminic effect in a mammal.” (‘416 Patent at col. 84, lines 29-30, 36-37; col. 76, lines 1-2.)

#### **IV. The ‘528 Patent-in-Suit**

The ‘528 Patent, entitled “Carbostyryl Derivatives,” was issued in 1991, but has a foreign application priority date of October 31, 1988, pursuant to 35 U.S.C. § 119. (See Defs.’ Post-Trial Br. at 2; Pl.’s Post-Trial Br. at 31.) The exclusivity engendered by the ‘528 Patent, including a six-month pediatric exclusivity period, will expire on April 20, 2015. (Defs.’ Post-Trial Br. at 4.)<sup>4</sup>

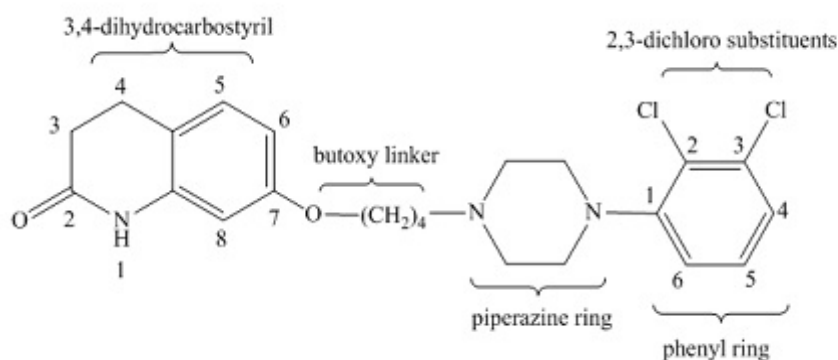
Otsuka asserts infringement of Claim 12, Claim 17, and Claim 23 of the ‘528 Patent. (Pl.’s Post-Trial Br. at 8.) Claim 12 of the ‘528 patent is directed to the compound aripiprazole, which has the chemical name 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyryl. (‘528 Patent at col. 19, lines 18-19.) Claim 17 of the ‘528 patent is directed to a pharmaceutical composition for treating schizophrenia containing, as the active ingredient, aripiprazole or a pharmaceutically acceptable salt thereof. (‘528 Patent at col. 20, lines 4-7.) Claim 23 of the ‘528 patent is directed to a method of treating schizophrenia comprising the administration of a pharmaceutical composition containing, as an active ingredient, aripiprazole or a salt thereof. (‘528 Patent at col. 20, lines 17-20.)

The structure of aripiprazole is shown below:

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<sup>4</sup> See also DTX 498, Certificate Extending Patent Term Under 35 U.S.C. § 156 (granting five-year extension of patent term based upon regulatory review of the product Abilify<sup>®</sup> (aripiprazole) by the FDA).





Aripiprazole is a carbostyryl derivative with a butoxy linker at the 7-position of the carbostyryl core. (Pl.’s Post-Trial Br. at 47.) The butoxy linker consists of four methylene ( $\text{CH}_2$ ) units, whereas a propoxy linker consists of three methylene units. Because aripiprazole has two hydrogens at positions 3 and 4 of the carbostyryl ring, it is referred to as a “dihydrocarbostyryl.” (Id.) Researchers commonly refer to both dihydrocarbostyryls and carbostyryls as “carbostyryl derivatives.” (Id.) A dihydrocarbostyryl has a single bond between positions 3 and 4 whereas a carbostyryl has a double bond. (Id.)

Aripiprazole has a piperazine ring connected to the butoxy linker. (Id.) The other side of the piperazine ring is connected to a phenyl ring. (Id.) The phenyl ring includes chlorine substituents attached at both the 2 position and 3 position of the phenyl ring. (Id. at 47-48.) This substitution of chlorine at the 2 position and the 3 position of the phenyl ring may be referred to as a “2,3 dichloro substitution” or a “2,3 dichlorophenyl substitution.” (Defs.’ Post-Trial Br. at 10-11.)

## V. Reexamination of the ‘528 Patent

Otsuka filed a Request for Ex Parte Reexamination Proceedings on August 11, 2004, with regard to the ‘528 Patent. (Pl.’s Post-Trial Br. at 53; DTX 121.) In the reexamination

proceedings, Otsuka endeavored to distinguish aripiprazole from certain structurally similar prior art references, including unsubstituted butoxy, which had been disclosed in the '416 Patent as well as Otsuka's German Patent No. 2,912,105 ("the DE '105 Patent"); 2,3 dichloro propoxy, a homolog of aripiprazole that had been disclosed in the DE '105 Patent; and OPC-4392, a compound developed by Otsuka having the chemical name 7-{3-[4-(2,3-dimethylphenyl)-1-piperazinyl]-propoxy}-carbostyryl and disclosed in various references, including the DE '105 Patent. (Pl.'s Post-Trial Br. at 53-54.)<sup>5</sup> Otsuka also referred the Examiner to an article published by one of the inventors of the '416 Patent, Dr. Kazuo Banno, "Studies of 2(1H)-Quinolinone Derivatives as Neuroleptic Agents, I, Synthesis and Biological Activities of (4-Phenyl-1-piperazinyl)-propoxy-2(1H)-quinolinone Derivatives," Chem. Pharm. Bull., Vol. 36, No. 11 (Nov. 25, 1988), at 4377-4388 (the "Banno Article"), which contained references to these three compounds.<sup>6</sup> Otsuka stated in its request for reexamination that it could be argued that the cited documents raised a substantial new question of patentability. See 35 U.S.C. §§ 302-307. Otsuka additionally explained that, with respect to the '416 patent, "it can be argued that the use of the described compounds as antischizophrenia agents is specifically contemplated." (Pl.'s Post-Trial Br. at 54-55.)

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<sup>5</sup> OPC-4392 has a propoxy linker at the 7-position of the carbostyryl core and methyl (CH<sub>3</sub>) substituents at the 2 and 3 positions of the phenyl ring. As with other carbostyryl derivatives at issue here, it could have either a single or a double bond between the 3 and 4 positions on the carbostyryl core; in the case of OPC-4392, it has a double bond, making it a dehydrocarbostyryl (also simply called "carbostyryl") as opposed to a dihydrocarbostyryl like aripiprazole. The term "carbostyryl" was described at trial as being "jargon" and easier to say than the structure's technical name, "quinolinone." (Dkt. entry no. 355, Nichols Tr. at 1520.)

<sup>6</sup> While the Banno article was referred to as a "prior art reference" in the reexamination proceedings, we note that it was published after the priority date of October 31, 1988, and therefore not technically prior art with respect to the '528 Patent.

The USPTO granted Otsuka's request for reexamination and thereafter issued an Office Action rejecting the claims of the '528 Patent as obvious over the disclosures in the '416 Patent and the DE '105 Patent of prior art compounds including unsubstituted butoxy. (Pl.'s Post-Trial Br. at 55.) Otsuka responded to this action by arguing that while the prior art references considered by the examiner "may suggest that their compounds may be useful for treating central nervous disorders, generally, there is no evidence that the five exemplary carbostyryl derivatives identified by the Examiner have such properties, let alone the recited property of treating schizophrenia." (Pl.'s Post-Trial Br. at 55; DTX 121 at OPC 1274.) The USPTO again rejected the claims of the '528 Patent in a second and final Office Action on the basis that one of skill in the art would be motivated to make homologs of compounds in the prior art by changing the linker length from a propoxy to a butoxy. (Pl.'s Post-Trial Br. at 56; DTX 121 at OPC 1320-34.)

Otsuka conducted an interview with the USPTO on September 13, 2005, in response to the USPTO's second Office Action, and filed a Request for Reconsideration on September 14, 2005. (Pl.'s Post-Trial Br. at 56; DTX 121 at OPC 1340-41 and 1342-1400.) Along with its Request for Reconsideration, Otsuka submitted a declaration by Dr. Tsyoshi Hirose (the "Hirose Declaration") including test data for representative claimed compounds of the '528 Patent compared to structurally related prior art propoxy-linked compounds. (Pl.'s Post-Trial Br. at 57; DTX 121 at OPC 1344, 1365-1400.) The USPTO thus ultimately concluded that the closest prior art compounds were those tested in the Hirose Declaration, which included the 2,3-dichloro propoxy compound but not the unsubstituted butoxy compound or OPC-4392. (Pl.'s Post-Trial Br. at 57; DTX 121 at OPC 1368-69.) The Hirose Declaration reported data for an anti-apomorphine stereotypy test on mice to evaluate each "compound's ability to block

neurotransmission of dopaminergic D2-receptors, i.e., its antipsychotic potency.” (Hirose Decl. at 5.) With regard to this test, the Hirose Declaration argued, and the USPTO agreed in allowing the claims, that the structural difference between a butoxy and a propoxy linker chain “shows a clear unexpected result in the ED<sub>50</sub> [50% effective dose] values.” (DTX 121 at OPC 1412, Reexamination – Reasons for Patentability/Confirmation.)<sup>7</sup> Specifically, the Hirose Declaration data indicated that the aripiprazole compound was twenty-three times more potent than the 2,3 dichloro propoxy compound. (Hirose Decl. at 6.)

The USPTO issued a Reexamination Certificate allowing all the claims of the ‘528 patent on June 13, 2006. (DTX 121 at OPC 1426-28.) The Reexamination Certificate also allowed the addition of three new claims, Claims 22-24, which are directed to methods of treating schizophrenia using compositions of the invention. (Id.)

## DISCUSSION

### I. Applicable Legal Standards

#### A. Presumption of Validity and Burden of Proof

A patent is presumed to be valid, and each of its claims are presumed valid independent of the validity of other claims. 35 U.S.C. § 282. An accused infringer seeking to overcome the presumption of validity bears the burden of showing by clear and convincing evidence that the patent is invalid. Robotic Vision Sys., Inc. v. View Eng’g, Inc., 189 F.3d 1370, 1377 (Fed. Cir. 1999).

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<sup>7</sup> ED<sub>50</sub> is a measure of relative potency that establishes the dose at which each compound produces half of its maximal response, or a 50% effect. (Defs.’ Post-Trial Br. at 21; dkt. entry no. 352, Roth Tr. at 1072.)

## **B. Obviousness**

“A patent may not be obtained . . . [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). While the ultimate determination of obviousness under § 103 is a question of law, it is based on several underlying factual findings, including (1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, also known as objective indicia of non-obviousness. Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966). “While the sequence of these questions might be reordered in any particular case, the [Graham] factors continue to define the inquiry that controls.” KSR Int’l Co. v. Teleflex Inc., 550 U.S. 398, 407 (2007).

A 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. Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009).

## **C. Obviousness-Type Double Patenting**

Obviousness-type double patenting is a judicially-created doctrine that prohibits “claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent.” Sun Pharm. Indus., Ltd. v. Eli Lilly & Co., 611 F.3d 1381, 1384 (Fed. Cir. 2010) (quotation and citation omitted); see also Georgia-Pacific Corp. v. U.S. Gypsum Co., 195 F.3d 1322, 1326 (Fed. Cir. 1999) (obviousness-type double patenting prohibits patenting of claims that are “an obvious

variation of an invention disclosed and claimed in an earlier patent by the same inventor”).

Obviousness-type double patenting can apply where the earlier patent and later patent are not part of the same patent family and issue from separate parent applications. Sun Pharm., 611 F.3d at 1389 (holding the ‘826 patent-in-suit invalid for obviousness-type double patenting in view of the earlier ‘614 patent that issued from a different patent family); In re Berg, 140 F.3d 1428, 1435 n.7 (Fed. Cir. 1998) (rejecting claims for obviousness-type double patenting over claims in a patent that were “not related as by continuation, continuation-in-part, or divisional”).

An obviousness-type double patenting analysis involves two steps: “First, as a matter of law the court construes the claim in the earlier patent and the claim in the later patent and construes the differences. Second, the court determines whether the differences in subject matter between the two claims render the claims patentably distinct.” Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 968 (Fed. Cir. 2001) (citing Georgia-Pacific, 195 F.3d at 1326-27). Two claims are not “patentably distinct” if the later claim would have been obvious to a person of ordinary skill in the art based on the earlier claim, in light of additional prior art. In re Longi, 759 F.2d 887, 893 (Fed. Cir. 1985).

#### **D. Inequitable Conduct**

Persons involved in the preparation and prosecution of a patent application “have a duty to prosecute patent applications in the [USPTO] with candor, good faith, and honesty.”

Advanced Magnetic Closures, Inc. v. Rome Fastener Corp., 607 F.3d 817, 829 (Fed. Cir. 2010) (quoting Honeywell Int’l Inc. v. Universal Avionics Sys. Corp., 488 F.3d 982, 999 (Fed. Cir. 2007)). This duty of candor rests on “(1) each named inventor, (2) each attorney or agent that prepares or prosecutes the application, and (3) every other person who is substantively involved

in the preparation or prosecution of the application and who is associated with the inventor or assignee.” Avid Identification Sys., Inc. v. Crystal Import Corp., 603 F.3d 967, 973 (Fed. Cir. 2010) (citing 37 C.F.R. § 1.56(c)). A breach of the duty of candor constitutes inequitable conduct and renders the patent unenforceable. Bristol-Myers Squibb v. Rhone-Poulenc Rorer, Inc., 326 F.3d 1226, 1233 (Fed. Cir. 2003); Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995).

## **II. Validity of Patent**

### **A. Obviousness - § 103**

Defendants contend that the asserted claims are invalid as obvious over the prior art genus of carbostyryl derivatives disclosed in the ‘416 Patent, focusing on three exemplary compounds: the unsubstituted butoxy compound, the 2,3 dichloro propoxy homolog of aripiprazole, and OPC-4392 (a 2,3-dimethyl propoxy analog of aripiprazole). (Defs.’ Post-Trial Br. at 97.)

#### **1. Level of Skill in the Art**

The obviousness analysis is conducted from the perspective of a person of ordinary skill in the prior art. 35 U.S.C. § 103(a). The hypothetical person of ordinary skill “is an objective legal construct who is presumed to be aware of all the relevant prior art.” Janssen Pharmaceutica N.V. v. Mylan Pharm., Inc., 456 F.Supp.2d 644, 653 (D.N.J. 2006) (citation omitted), aff’d, 233 Fed.Appx. 999 (Fed. Cir. 2007). The person of ordinary skill “is also a person of ordinary creativity, not an automaton.” KSR Int’l, 550 U.S. at 421.

At issue in Janssen was the validity of a patent covering the atypical antipsychotic drug risperidone. The Janssen court defined the person of ordinary skill as someone having a master’s

degree in chemistry, medicinal chemistry, or pharmacy, or a bachelor's degree in one of those fields with at least two years of experience in researching antipsychotic drugs, but noted that its ultimate ruling that the patent in suit was nonobvious was "not contingent upon" its determination of the appropriate level of skill in the art because it would find the patent nonobvious "even were it to hold that the person of ordinary skill in the art possessed a doctorate degree." Janssen, 456 F.Supp.2d at 654 n.7. (Pl.'s Post-Trial Br. at 58-59.) Plaintiff's expert Dr. Bryan Roth, who qualified as an expert in schizophrenia, antipsychotic drug discovery, and psychopharmacology with its medicinal chemistry component, testified at trial that this definition was reasonable based on his own experience and personal knowledge of individuals actively engaged in antipsychotic drug discovery both in his lab and elsewhere. (Pl.'s Post-Trial Br. at 12, 58-59.)

Defendants propose a hypothetical person having ordinary skill in the art as "highly skilled, with a Ph.D. in organic chemistry, medicinal chemistry and/or pharmacology or in a related field and at least several years of experience designing and/or testing drug compounds." (Def.'s Post-Trial Br. at 8.) Defendants suggest that the hypothetical "person" of ordinary skill in the art in this case would have the knowledge and skill set of a team of individuals with both medicinal chemistry and pharmacology expertise, because "in 1988, research in the field of antipsychotic drug discovery and development was performed in multi-disciplinary teams." (Id.) Defendants further urge that medicinal chemists and pharmacologists would have a working knowledge of the biological tests that correlate to antipsychotic activity and pertinent side effects of antipsychotic drugs, using in vitro assays and in vivo animal models, in order to determine



structure-activity relationships between changes to molecular structures of chemical compounds and corresponding effects on biological activities. (Defs.' Post-Trial Br. at 8-9.)

We find merit in Defendants' contention that the person of ordinary skill in the art would have knowledge of examining structure-activity relationships through the use of biological tests, as evidence at trial indicated the necessity of such testing in the course of antipsychotic drug development.<sup>8</sup> However, we reject the notion that the "person" of ordinary skill must possess all of the attributes of a multi-member team. The fields of medicinal chemistry and pharmacology are inherently multi-disciplinary, and it is therefore sufficient to consider the skilled artisan to be one having a degree in medicinal chemistry, pharmacology, or a related field with experience in drug research and development. See Daiichi Sankyo Co., Ltd. v. Mylan Pharm. Inc., 670 F.Supp.2d 359, 369 & n.7 (D.N.J. 2009), aff'd, 619 F.3d 1346 (Fed. Cir. 2010). Dr. David Nichols, an expert in both medicinal chemistry and pharmacology who testified on behalf of Otsuka, and Dr. Roth testified that their opinions in this case would not change if the hypothetical person of ordinary skill in the art had a Ph.D. rather than a master's degree. (Pl.'s Post-Trial Br. at 59-60.) This testimony leads the Court to conclude, however, that the hypothetical ordinarily skilled person developing atypical antipsychotic drugs in 1988 would be unlikely to have only a bachelor's degree as opposed to a master's degree.

Accordingly, the Court finds that a person of ordinary skill in the art of antipsychotic drug discovery in October 1988 would be an individual having a master's degree or Ph.D. in medicinal chemistry, pharmacology, or a related field, with experience in research and development of antipsychotic drugs such that the person would be able to evaluate

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<sup>8</sup> The type of testing done in the course of drug discovery is discussed infra.

pharmacological data from in vitro and in vivo screening assays to determine structure-activity relationships.

## 2. Scope and Content of Prior Art

The Court considers the scope and content of the prior art as it existed on October 31, 1988. Prior art is limited to analogous references “from the same field of endeavor” as the claimed invention; if not within the same field of endeavor, a reference may be prior art if it is reasonably pertinent to the particular problem the inventor of the claimed invention was addressing. See In re Bigio, 381 F.3d 1320, 1325 (Fed. Cir. 2004).

### a. ‘416 Patent and Nakagawa Declaration

Defendants contend that the ‘416 Patent, and the declaration of Kazuyuki Nakagawa (“Nakagawa Declaration”) submitted in support thereof during the patent prosecution, disclose the prior art compound unsubstituted butoxy, and that “mouse jumping” data for unsubstituted butoxy teaches toward aripiprazole, in particular a 2,3 dichloro substitution on the phenyl ring and that butoxy-linked compounds are more potent than propoxy-linked compounds. (Defs.’ Post-Trial Br. at 16-23; DTX 214, Nakagawa Declaration dated 2-2-87.) The ‘416 Patent disclosed the unsubstituted butoxy compound as Claim 13.<sup>9</sup>

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<sup>9</sup> The parties apparently do not dispute that the ‘416 Patent constitutes prior art. (See, e.g., dkt. entry no. 340, Press Tr. at 115 (stating that the ‘416 Patent is prior art because it issued before October of 1988); Defs.’ Post-Trial Br. at 92 n.14 (stating that the parties do not dispute that the ‘416 Patent is prior art).) The Court, however, notes that it may not technically qualify as prior art under 35 U.S.C. § 102 because Dr. Oshiro is listed as an inventor on both the ‘416 Patent and the ‘528 Patent, and the ‘416 Patent issued less than one year before the ‘528 Patent’s foreign priority application date of October 31, 1988. 35 U.S.C. § 102(a)-(b); Invitrogen Corp. v. Biocrest Mfg., L.P., 424 F.3d 1374, 1380-81 (Fed. Cir. 2005); In re Katz, 687 F.2d 450, 454-55 (C.C.P.A. 1982); see also Eli Lilly & Co. v. Teva Pharm. USA, Inc., 657 F.Supp.2d 967, 1012-14 (S.D. Ind. 2009); Janssen, 456 F.Supp.2d at 652-53. Because the parties did not address this question, and because the inclusion of the ‘416 Patent and the Nakagawa Declaration in the

Otsuka contends that the ‘416 Patent teaches that Claim 13, the unsubstituted butoxy, is an antihistamine and does not suggest that compound as an antipsychotic agent. Claim 13 does not disclose any specific uses for unsubstituted butoxy, but the unsubstituted butoxy is listed as an example in Claim 116, which by reference to Claim 50 is disclosed as a method for producing an “antihistaminic effect.” Thus, Otsuka argues that the ‘416 Patent does not teach that unsubstituted butoxy is an antipsychotic; rather, the ‘416 Patent covers a broad genus of compounds, some of which may be useful as, inter alia, either antipsychotics or antihistamines. Dr. Roth testified that one skilled in the art would not read the ‘416 Patent’s “laundry list” of potential central nervous system controlling effects to conclude that all carbostyryl derivative compounds covered by the patent are antipsychotics, nor would that person ascertain from the ‘416 Patent how to screen the claimed compounds for antipsychotic activity. (Dkt. entry no. 354, Roth Tr. at 1219.)

The Court finds that Defendants overstate the scope of the ‘416 Patent as it pertains to teaching the uses of unsubstituted butoxy. Rather, the ‘416 Patent teaches that unsubstituted butoxy is an example of the invention having an antihistaminic effect.

As to the Nakagawa Declaration submitted in support of the ‘416 Patent application, Otsuka contends that it is not a “printed publication” form of prior art under 35 U.S.C. § 102(b) because it was not sufficiently accessible to the public prior to the October 31, 1988 priority date. (Pl.’s Post-Trial Br. at 180-87; see also DTX 333, Prosecution History for the ‘416 Patent.) We reject this assertion, as the Nakagawa Declaration comprises part of the prosecution history of the

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Court’s analysis of the scope and content of the prior art would not alter the Court’s ultimate obviousness determination, we decline to address it further at this juncture and proceed on the assumption that the ‘416 Patent is prior art.

earlier-issued '416 Patent and is therefore deemed accessible to the public. See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1363 (Fed. Cir. 2007) (finding that district court properly considered prosecution history of earlier patent and may have committed harmless error by implying that prosecution histories are not accessible to the public). (Dkt. entry no. 377, Defs.' Reply Post-Trial Br. at 2.) Accordingly, to the extent the '416 Patent itself constitutes prior art, we find that the Nakagawa Declaration constitutes a "printed publication" under 35 U.S.C. § 102(b) and is properly considered part of the prior art for purposes of obviousness.

The Nakagawa Declaration tested certain carbostyryl derivatives covered by the '416 Patent as compared to two prior art compounds for "activity for inhibiting jumping behavior in mouse induced by Methamphetamine and L-DOPA" (the "mouse jumping test"). (Nakagawa Decl. at 12.)<sup>10</sup> At trial, Otsuka argued that the mouse jumping data in the Nakagawa Declaration was not intended to provide insight to structure-activity relationships as part of an antipsychotic drug discovery effort. (Pl.'s Post-Trial Br. at 83-84; dkt. entry no. 354, Roth Tr. at 1243-48 (testifying that prior to his involvement in this case, Dr. Roth had never heard of the mouse jumping test, the mouse jumping test is not routinely used in antipsychotic drug discovery, and one skilled in the art would not be able to correlate mouse jumping data with results from the more commonly-used anti-apomorphine stereotypy test).) However, Defendants adduced evidence indicating that Otsuka itself used the mouse jumping test to predict antipsychotic

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<sup>10</sup> The Nakagawa Declaration also contains data for two other tests, both of which measure antihistaminic activity: a guinea pig ileum test, and a halothane anesthesia increasing activity test. (See dkt. entry no. 354, Roth Tr. at 1208-10, 1242.) Neither the guinea pig ileum test nor the halothane anesthesia increasing activity test are used to test for potential antipsychotic activity. (Dkt. entry no. 354, Roth Tr. at 1209-10.)

activity in chemical compounds. (See Defs.’ Post-Trial Br. at 18-19.)<sup>11</sup> Regardless of whether the mouse jumping test was frequently used by researchers in antipsychotic drug discovery in 1988 or whether the intention of the Nakagawa Declaration was to provide data to compare the test compounds against each other as opposed to the two prior art compounds, the Court finds that the Nakagawa Declaration does, on its face, provide comparative data for the potency of certain prior art compounds in a test that could be indicative of potential antipsychotic activity to the skilled artisan, particularly in light of the “Lal article.” (Dkt. entry no. 346, Marshall Tr. at 381-82; DTX 375, H. Lal et al., “Effect of Neuroleptic Drugs on Mouse Jumping Induced by L-DOPA in Amphetamine Treated Mice,” Neuropharmacology, No. 15 (1976), at 669-71.)<sup>12</sup>

Table 8 of the Nakagawa Declaration provides the results from the mouse jumping test. It compares nine carbostyryl derivative test compounds to two prior art compounds. Of the test compounds, eight are propoxy-linked and just one—the unsubstituted butoxy—has a butoxy linker. Three of the test compounds are carbostyryl derivatives with a propoxy linker at the 5-position of the carbostyryl core (“5-linked”), whereas the remainder are carbostyryl derivatives linked at the 7-position (“7-linked”). Both prior art reference compounds have a propoxy linker at the 5-

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<sup>11</sup> For instance, the specification of Otsuka’s U.S. Patent No. 4,619,932 (“‘932 Patent”), claiming “Novel Carbostyryl Derivatives” and issued on October 28, 1986, contains data comparing examples of the claimed compounds to chlorpromazine in the mouse jumping test. (‘932 Patent at col. 43, lines 7-63; see also DTX 471, Amendment Transmittal Letter in support of the ‘932 Patent application referring to mouse jumping test as a method for determining whether a compound will have anti-schizophrenic activity; dkt. entry no. 346, Marshall Tr. at 383-90.) Claim 13 of the ‘932 Patent claims an embodiment of the invention wherein a claimed compound is the active ingredient in “a central nervous system controlling agent.” (‘932 Patent at col. 129, lines 52-57.)

<sup>12</sup> Otsuka contends that Defendants “did not even seek to admit [the Lal article] into evidence.” (Pl.’s Post-Trial Br. at 85.) However, the record indicates that the Lal article, DTX 375, was in fact admitted into evidence. (Dkt. entry no. 346, Marshall Tr. at 385.)

position. The ED<sub>50</sub> values indicate that the most potent compound in the mouse jumping test was Compound 44, a 5-linked propoxy with an ethoxy substituent at the 2 position of the phenyl ring having an ED<sub>50</sub> value of 0.53.<sup>13</sup> A 5-linked unsubstituted propoxy (Compound 5) was the second most potent compound, with an ED<sub>50</sub> of 2.1. Of the relevant 7-linked test compounds, the unsubstituted butoxy (Compound 41) had an ED<sub>50</sub> of 5.5, unsubstituted propoxy (Compound 6) was 9.3, the 2-chloro substituted propoxy (Compound 43) had an ED<sub>50</sub> of 3.4, the 3-chloro substituted propoxy (Compound 39) was 2.5, and the 4-chloro substituted propoxy (Compound 16) was 15.1. A lower ED<sub>50</sub> value is indicative of greater potency in the mouse jumping test.

**b. DE ‘105 Patent and SE ‘945 Application**

The 2,3 dichloro propoxy compound appears in two foreign counterparts to the ‘416 Patent. (Defs.’ Post-Trial Br. at 24.) It is Example 317 in Otsuka’s prior art DE ‘105 Patent. (Id.; DTX 248-T at 68.) It also appears in Example 134 of Otsuka’s prior art SE ‘945 Swedish published patent application. (Defs.’ Post-Trial Br. at 24; DTX 1159-T at 60, 62.)

The SE ‘945 application states that its compounds are useful as, inter alia, antipsychotic or antischizophrenia agents yet cause fewer side effects such as EPS. (Defs.’ Post-Trial Br. at 24.) It discloses that

[t]he compounds according to the present invention are therefore useful as means of controlling the central nervous system as muscle relaxants, sleeping agents, presurgery drugs, antischizophrenia agents, sedatives, anxiolytics, drugs for manic-depressive psychosis, fever-lowering agents, analgesics and “depressors” without showing side effects such as thirst, constipation, tachycardia, parkinsonism and/or delayed dyschezia, which are displayed by conventional agents which act on the central nervous system.

(DTX 1159-T at 5.) It does not disclose aripiprazole. (Dkt. entry no. 346, Press Tr. at 214-15.)

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<sup>13</sup> An “effective dose” for purposes of the mouse jumping test is a dose that decreases jumps per hour from 150 to under 10. (Dkt. entry no. 346, Marshall Tr. at 380.)

Plaintiff notes that, like the '416 Patent, the SE '945 application discloses dozens of carbostyryl compounds. (Pl.'s Post-Trial Br. at 119.) The 2,3 dichloro propoxy is just one of ninety-six different compounds disclosed in Example 134 alone. (DTX 1159-T at 60-68.) The compounds disclosed in the SE '945 application, again like the '416 Patent, are said to have antihistamine action and regulating action on the central nervous system. (Pl.'s Post-Trial Br. at 119; dkt. entry no. 346, Press Tr. at 215.) As with the '416 Patent's "laundry list" of potential central nervous system controlling activities of the claimed compounds, the SE '945 application simply discloses a number of potential therapeutic indications, with no information or data in the SE '945 application that would have informed a person of ordinary skill in the art in October 1988 as to which of the specifically identified compounds, if any, would have antipsychotic activity. (See dkt. entry no. 356, Nichols Tr. at 1689-90; dkt. entry no. 346, Press Tr. at 218-219.)

The disclosure of the DE '105 Patent is substantially the same as the SE '945 application except that the DE '105 Patent omits any mention of potential antipsychotic activity. (Pl.'s Post-Trial Br. at 121; cf. DTX 248-T at 18 (referring to "the agent for the control of the central nervous system").) While the DE '105 Patent contains test data examining antihistamine activity (guinea pig ileum test), halothane anesthesia increasing activity, hexabarbital sleep increasing activity, analgetic activity, and acute toxicity, it does not provide any data for potential antipsychotic activity. (See DTX 248-T at 19-28.) Thus, although the DE '105 Patent and the SE '945 application both disclose 2,3 dichloro propoxy as an example of the invention, they do not specifically teach that 2,3 dichloro propoxy is an antipsychotic as opposed to a different type of central nervous system controlling agent.

**c. OPC-4392**

Several prior art references discuss OPC-4392, an Otsuka compound that was clinically tested in humans. (Defs.' Post-Trial Br. at 26.)<sup>14</sup> OPC-4392 was the only carbostyryl derivative to have been tested in humans as a potential antipsychotic at the time of the priority date of October 31, 1988. (Pl.'s Post-Trial Br. at 66.)

An article by Mitsukuni Murasaki, "New Psycho-Neuro Agents," in the Japanese Journal of Clinical Psychiatry (1987), discusses OPC-4392 as "a totally new compound that is an antipsychotic drug." (DTX 388-T at 1517 ("1987 Murasaki article").) The 1987 Murasaki article reported that "the anti-psychotic action was not strong but the strength of the activating action stood out; . . . improvements were observed in the negative symptoms [and] the extra-pyramidal disturbances are extremely weak." (Id.)

"The New Antipsychotic Drug OPC-4392," published by Tetsuro Kikuchi et al. in the Bulletin of the Japanese Neurochemical Society (1985), discloses that OPC-4392 has "powerful central nervous system anti-dopamine" effects, and acts as an "agonist/antagonist on central nervous system [dopamine] neurons." (DTX 377-T.)

Yasuda et al. published "OPC-4392, A Presynaptic Dopamine Autoreceptor Agonist and Postsynaptic D2 Receptor Antagonist" in Life Sciences (1988). (DTX 104 ("Yasuda article").) The Yasuda article reported that test results suggested that OPC-4392 "acts as a dopamine agonist at presynaptic autoreceptors related to dopamine synthesis and acts as a dopamine antagonist at postsynaptic D2 receptors." (Id.)

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<sup>14</sup> As previously stated, OPC-4392 was a 2,3 dimethyl substituted, propoxy-linked dehydrocarbostyryl. (See n.5 supra & accompanying text.)



Murasaki et al. published “Phase 1 Study of a New Antipsychotic Drug, OPC-4392,” in Progress in Neuro-Psychopharmacology & Biological Psychiatry (January 1988), reporting results of early testing of OPC-4392 in five healthy male volunteers in comparison with two volunteers given chlorpromazine. (DTX 874 (“1988 Murasaki article”).)<sup>15</sup> The 1988 Murasaki article reported that, unlike chlorpromazine, OPC-4392 did not elevate prolactin levels; had a weak EPS effect; and was expected to have fewer side effects than conventional antipsychotic drugs. (Id.) However, at doses of 5 milligrams, the volunteers experienced side effects including “sleepiness, stagger, weakness, fatigability, heavy headedness, lack of motivation and disturbed concentration, which were so severe that they were not able to perform daily routine work.” (PTX 545 at 798.) According to Otsuka’s expert Dr. Roth, 5 milligrams would be considered a very low dose of a potential antipsychotic drug. (Pl.’s Post-Trial Br. at 72; dkt. entry no. 354, Roth Tr. at 1191.)

An abstract published in Psychopharmacology by H. Gerbaldo et al., “Treatment of Negative Symptoms of Schizophrenic Patients with the Partial Dopamine Agonistic Compound OPC-4392” (1988) (“Gerbaldo abstract”), reported that, in a first open study of OPC-4392 in schizophrenia patients, “the most evident observation was an improvement in blunted affect [a negative symptom].” (Pl.’s Post-Trial Br. at 66; DTX 990.)<sup>16</sup> It further reported that in the clinical trials, EPS symptoms were not observed. (Dkt. entry no. 349, Castagnoli Tr. at 641-42.)

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<sup>15</sup> The 1988 Murasaki article was also referred to at trial as PTX 545.

<sup>16</sup> The Gerbaldo abstract was also referred to at trial as DTX 486.

**d. OPC-4139**

A 1981 abstract published in the Eighth International Congress of Pharmacology by Hiyama et al., “Neuropharmacological actions of 7-{3-[4-(3-chlorophenyl)-piperazinyl]propoxy} 3,4-dihydro-2(1H)-quinolone” (“Hiyama abstract”) teaches that OPC-4139 was “a new synthetic compound . . . preclinically shown to have similar pharmacological actions” to typical antipsychotics. (DTX 514.) The compound, a dihydro (single-bond) carbostyryl with a propoxy linker at the 7 position of the carbostyryl core and a chlorine substituent at the 3 position of the phenyl ring, “inhibited jumping behavior of mice, with ED<sub>50</sub> values between 0.9 and 3.0 milligrams per kilogram.” (Id.) The abstract further stated, however, that OPC-4139 did not inhibit apomorphine-induced stereotypy in rats in another biological test used to predict potential antipsychotic activity. (Id.) The authors concluded that the test results suggested that the compound “is potent in suppressing the dopaminergic activity.” (Id.) Defendants thus contend that the Hiyama abstract would have taught the person of ordinary skill in the art the benefits of including a chlorine substituent at the 3 position of the phenyl ring. (Defs.’ Post-Trial Br. at 30.)

**e. Otsuka’s ‘932 Patent**

The ‘932 Patent was issued to Otsuka on October 28, 1986. (DTX 20, ‘932 Patent.) It disclosed a series of Otsuka’s earlier carbostyryl derivative compounds that had alkyl rather than alkoxy linkers that were typically attached at the 6 rather than the 7 position on the carbostyryl core. (Defs.’ Post-Trial Br. at 30.) The ‘932 Patent contains mouse jumping data comparing examples of the claimed compounds to chlorpromazine. (Defs.’ Post-Trial Br. at 30; ‘932 Patent at col. 43, lines 7-63 and Table 2.)

The '932 Patent discloses that the claimed compounds “have antihistaminic effects and central nervous system controlling effects, and are useful for antihistaminic agents and central nervous system controlling agents.” (‘932 Patent at col. 2, lines 26-29.) The specification states that compounds of the invention may be used for central nervous system controlling agents “such as central muscle relaxizing [sic] agents, sleep-inducing agents, pre-operative drugs, anti-schizophrenia agents, sedatives, antianxiety drugs, antimanic depressive psychosis agents, antipyretic agents, analgetic agents and depressors, without showing side-effects such as thirst feeling, constipation, tachycardia, parkinsonism, and/or delayed dyskinesia which are showed by conventional central nervous system controlling agents.” (‘932 Patent at col. 2, lines 60-68.)

**f. Wise Poster**

Plaintiff disputes whether DTX 398, “the Wise Poster,” is a “printed publication” under 35 U.S.C. § 102(b) and therefore constitutes prior art. (Pl.’s Post-Trial Br. at 187 (citing Carella v. Starlight Archery & Pro Line Co., 804 F.2d 135, 138-39 (Fed. Cir. 1986)).) For poster presentations, the Federal Circuit has held that the public accessibility of the poster, and therefore its status as a prior art printed publication under § 102(b), is analyzed according to a multi-factor test in which the court considers whether copies of the presentation were distributed and also “the length of time the display was exhibited, the expertise of the target audience, the existence (or lack thereof) of reasonable expectations that the material displayed would not be copied, and the simplicity or ease with which the material displayed could have been copied.” In re Klopfenstein, 380 F.3d 1345, 1350 (Fed Cir. 2004).

*i.*        **The Wise Poster is Prior Art**

We find that the evidence weighs in favor of finding the Wise Poster to constitute prior art. Dr. Wise provided deposition testimony, which has been designated in this case, authenticating and explaining the circumstances under which the Wise Poster was publicly disclosed and distributed at the 1987 Society for Neurosciences Conference. (Dkt. entry no. 328, Final Pretrial Order, attachment 3, Defendants' designations, at 191-94 (designation of Wise testimony); Wise Dep. 39:4-17.) Dr. Wise was a group leader of the antipsychotic drug discovery project at Warner-Lambert. (Id. at 8:20-9:1.) He testified that he attended the Society for Neurosciences meeting in New Orleans in 1987 as one of eleven thousand attendees. (Id. at 10:6-9; 20:13-18.) Dr. Wise has specific recollection of attending that meeting because it was his first trip to New Orleans. (Id. at 12:20-13:4.)

Dr. Wise's poster session was a half-day standard poster session related to potential drugs. (Id. at 15:17-16:7.) When questioned in his deposition if he could describe what his poster looked like Dr. Wise responded, "[Y]es. I know exactly what [my poster] looked like. It looks exactly like the hand-outs that [Plaintiffs] have today." (Id. at 22:20-22.) Dr. Wise recalled that he made his poster with a "photographic process" so that he could have not only a large poster to display but also smaller duplicate copies to use as handouts. (Id. at 23:1-9.) Dr. Wise testified that he took between "a hundred and two hundred copies" of his poster presentation in handout form to distribute at the presentation and Dr. Wise specifically recalled handing out in excess of a hundred of those poster handouts at the 1987 New Orleans conference. (Id. at 33:20-34:6.)

An internal Otsuka document from September 1988 regarding Parke-Davis's compound PD-116795 (“a structure very similar to OPC-4392, having a coumarin skeleton in which an oxygen atom is substituted for a nitrogen atom in the carbostyryl”) acknowledges that the Parke-Davis coumarin compound “was reported at the Society for Neuroscience (Louisiana, U.S.)” in 1987. (DTX 274-T.) Given this corroboration, we hold that the Wise Poster was sufficiently publicly available to constitute prior art. Although it is directed to coumarins rather than carbostyryls, the two types of compounds are structurally similar, and the Wise Poster is directed to a compound useful for the treatment of schizophrenia, such that it is reasonably pertinent to the particular problem— development of a safe, effective atypical antipsychotic— that Otsuka was addressing. In re Bigio, 381 F.3d at 1325.

**ii. Wise Poster's Teachings**

While Otsuka was working on carbostyryl derivatives, Parke-Davis was working on coumarin derivatives. Carbostyryls and coumarins are structurally similar: the only difference between a carbostyryl and a coumarin is that the NH in the carbostyryl group is replaced by an O. (Defs.' Post-Trial Br. at 31; dkt. entry no. 349, Castagnoli Tr. at 646.) Coumarin derivatives and carbostyryl derivatives are “isosteres” of each other, which means that they have similar electronic configurations. (Defs.' Post-Trial Br. at 31; dkt. entry no. 349, Castagnoli Tr. at 646-647.)

Defendants contend that coumarins and carbostyryls can be expected to have similar chemical, spectral, and reactive properties. (Defs.' Post-Trial Br. at 31; dkt. entry no. 349, Castagnoli Tr. at 646.) In contrast, Otsuka urges that “a person of ordinary skill in the art in October 1988 would not have assumed that the biological properties of coumarins would

translate to carbostyryl derivatives.” (Pl.’s Post-Trial Br. at 106-07 (citing dkt. entry no. 356, Nichols Tr. at 1671).) Specifically, the electronic configuration is different because the nitrogen in carbostyryls could donate a hydrogen bond, whereas the oxygen in coumarins could accept one. (Id.) Thus, those differences in the heterocyclic ring system suggest that the biological properties of coumarins and carbostyryl derivatives may not be parallel, such that the person of ordinary skill in the art would not assume that the biological properties of coumarins would translate to carbostyryls. (Dkt. entry no. 356, Nichols Tr. at 1671.) Given the testimony at trial regarding the unpredictability of structure-activity relationships in pharmaceutical drug discovery, we are persuaded by Otsuka’s position that the teachings of the Wise Poster are not directly transferrable to work regarding carbostyryl derivatives. (See, e.g., dkt. entry no. 352, Roth Tr. at 1140; dkt. entry no. 355, Nichols Tr. at 1540-41.)

The Wise Poster is directed to a class of compounds, thought to work as dopamine autoreceptor agonists, being developed as a “potential therapeutic approach for treatment of cardiovascular and CNS disorders including schizophrenia.” (DTX 398.) Defendants urge that the data provided in the Wise Poster teaches that a 3-chloro substitution on the phenyl ring increases antipsychotic activity. (Defs.’ Post-Trial Br. at 34-37.) This interpretation is unpersuasive, given that the Wise Poster states on its face that (1) dopamine autoreceptor agonism is the theory of antipsychotic activity Parke-Davis was pursuing with that class of compounds, and (2) incorporation of chloro or methyl substituents on the phenyl ring results in “complete loss” of that activity. (DTX 398; see also dkt. entry no. 356, Nichols Tr. at 1675.) The Wise Poster therefore teaches away from phenyl ring substitution, as highlighted by the fact

that the lead compound proposed by the poster (PD-116795) is an unsubstituted propoxy compound.

**g. Parke-Davis's '456 Patent**

Parke-Davis obtained a patent on its coumarin compounds, including some of the compounds disclosed in the Wise Poster. (DTX 629, U.S. Patent No. 4,701,456 (“‘456 Patent”); dkt. entry no. 349, Castagnoli Tr. at 655.) The ‘456 Patent was issued on October 20, 1987, and lists Dr. Wise as one of the inventors. The ‘456 Patent disclosed that these compounds “have been found to have valuable neuroleptic properties, and as such, are useful as antipsychotic agents and as anxiolytic agents.” (‘456 Patent at col. 1, lines 24-26; dkt. entry no. 349, Castagnoli Tr. at 655-656.) The patent lists in Example 3 a 2,3 dichloro propoxy compound that is identical to the 2,3 dichloro propoxy carbostyryl compound disclosed in the SE ‘945 application and DE ‘105 Patent, except that it has a coumarin rather than a carbostyryl core. (‘456 Patent at col. 11, line 45; dkt. entry no. 349, Castagnoli Tr. at 656-659.) However, as with the SE ‘945 application and DE ‘105 Patent, the ‘456 Patent does not indicate whether the claimed 2,3 dichloro propoxy compound is particularly effective as either an antipsychotic or an anxiolytic.

Claim 10 and Claim 11 are directed to a method for treating psychosis, but do not claim the 2,3 dichloro propoxy among the examples therefor. (‘456 Patent at col. 15, lines 1-56.) Claim 11 is directed to a particular a propoxy-linked coumarin compound with no substituents on the phenyl ring. (‘456 Patent at col. 15, lines 53-54; dkt. entry no. 351, Castagnoli Tr. at 899-900.) Thus, to a person of ordinary skill in the art of developing atypical antipsychotic drugs, the

'456 Patent teaches that a coumarin with a propoxy linker and an unsubstituted phenyl ring is useful for the treatment of psychosis.

### **3. Differences Between Claimed Invention and Prior Art**

Where the patent at issue claims a chemical compound, analysis of the differences between the claimed invention and the prior art “often turns on the structural similarities between the claimed compound and the prior art compounds.” Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd., 533 F.3d 1353, 1356 (Fed. Cir. 2008). Thus, the alleged infringer must “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 claimed compound.” Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007). This analysis requires an inquiry into the hypothetical person of skill in the art’s identification of a lead compound, structural differences between the proposed lead compound and the claimed invention, motivation or teachings in the prior art to make the necessary changes to arrive at the claimed invention, and whether the person of skill in the art would have a reasonable expectation of success in making such structural changes. See Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009); Takeda, 492 F.3d at 1356-57. If the patent challenger makes this prima facie showing of obviousness, the patent owner may rebut the showing based on unexpected results demonstrating that the claimed invention exhibits some superior property or advantage that a skilled artisan would have found surprising or unexpected. Daiichi Sankyo Co., Ltd. v. Mylan Pharm. Inc., 670 F.Supp.2d 359, 368 (D.N.J. 2009) (citation and quotation omitted).

The structural differences between aripiprazole and the coumarin compounds that were the subject of the Wise Poster and Parke-Davis’s ‘456 Patent have already been discussed, and



Defendants do not suggest that the person of ordinary skill in the art would have selected a coumarin compound as a lead compound in antipsychotic drug discovery efforts as of October 31, 1988. Therefore, we focus our inquiry on the three compounds put forth by Defendants as possible lead compounds in their obviousness argument: the unsubstituted butoxy carbostyryl compound, the 2,3 dichloro propoxy carbostyryl compound, and OPC-4392.<sup>17</sup>

**a. Unsubstituted Butoxy Compound**

Unsubstituted butoxy differs structurally from aripiprazole in that aripiprazole has chlorine substituents at the 2 position and the 3 position of the phenyl ring, while unsubstituted butoxy has hydrogen atoms at those positions. Defendants contend that a person of ordinary skill in the art would have selected the unsubstituted butoxy compound as a lead compound. (Defs.' Post-Trial Br. at 43.)

As indicated above, the '416 Patent and its foreign counterparts do not disclose unsubstituted butoxy specifically as an antipsychotic. Rather, Claim 116 and Claim 50 of the '416 Patent are directed to an antihistaminic agent, of which unsubstituted butoxy is given as an example. Accordingly, we find that the '416 Patent does not teach the selection of unsubstituted butoxy as a lead compound in antipsychotic drug discovery.

The Nakagawa Declaration also does not teach the skilled artisan to select unsubstituted butoxy as a lead compound. Of nine compounds tested for potential antipsychotic activity, eight were propoxy-linked. The unsubstituted butoxy scored an ED<sub>50</sub> value of 5.5 in the mouse jumping test; four test compounds were more potent, while four compounds were less potent.

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<sup>17</sup> Only Apotex argued that OPC-4392 would have been selected as a lead compound and would render aripiprazole obvious.

Generally, a skilled artisan would be attracted to the most potent compounds in selecting a lead compound for development. (Dkt. entry no. 346, Press Tr. at 263.)

Dr. Roth testified that if the skilled artisan were to select any compound from the Nakagawa Declaration mouse jumping data as a lead compound, it would be the Compound 44, the 5-linked propoxy compound with an ethoxy substituent at the 2 position of the phenyl ring. (Dkt. entry no. 354, Roth Tr. at 1256.) With an ED<sub>50</sub> value of 0.53, Compound 44 was by far the most potent of the compounds tested. Dr. Castagnoli testified that although the skilled artisan would have been attracted to compounds linked at the 5 position of the carbostyryl core, the skilled artisan would select 7-linked compounds over 5-linked compounds “because there were more teachings” as to the former. (Dkt. entry no. 351, Castagnoli Tr. at 792-93; see also dkt. entry no. 345, Press Tr. at 166 (noting that OPC-4392 and OPC-4139 teach toward using the 7-position); Defs.’ Post-Trial Br. at 43 (arguing that the skilled artisan would prefer 7-linked compounds because OPC-4392, a 7-linked dimethylphenyl-substituted compound, had been tested in humans).) Dr. Castagnoli also testified that the skilled artisan would not select Compound 44 of the Nakagawa Declaration as a potential lead compound because the ‘932 Patent disclosed that a 2-ethoxy substituted phenyl ring with a butenyl linker at the 6 position of the carbostyryl core showed a propensity to cause orthostatic hypotension, and thus the skilled artisan would not find the 2-ethoxy substituted phenyl ring with a propoxy linker at the 7 position of the carbostyryl core attractive (or, for that matter, any 2-ethoxyphenyl substitution). (Dkt. entry no. 351, Castagnoli Tr. at 786-90; see ‘932 Patent at col. 44, Table 3.) However, this position regarding the teachings of the ‘932 Patent (imputing negative side effect profile data pertaining to a 6-linked butyl compound and assuming the 2-ethoxyphenyl substitution would

cause the same side effect in a 5-linked propoxy compound) is inconsistent with Defendants' position regarding the Nakagawa Declaration that changing the location of the side chain from the 7 position to the 5 position of the carbostyryl core would be too significant of a structural change to predict potential side effects. Moreover, Defendants' expert Dr. Press conceded that Compound 44's ED<sub>50</sub> value of 0.53 was "striking and . . . worthy of note and certainly probably worthy of pursuit at some point." (Dkt. entry no. 345, Press Tr. at 164.) Prior art references to 7-linked carbostyryl compounds, particularly those reporting on OPC-4392, were neither so voluminous nor so promising as to foreclose contemplation of 5-linked compounds as potential lead compounds in antipsychotic drug discovery.

Defendants also contend that the skilled artisan would use the Nakagawa Declaration mouse jumping data to compare the unsubstituted butoxy, having an ED<sub>50</sub> of 5.5, to the unsubstituted propoxy, having an ED<sub>50</sub> of 9.3, and conclude that it teaches that 7-linked butoxy compounds are preferable to 7-linked propoxy compounds. (Defs.' Post-Trial Br. at 21; dkt. entry no. 345, Press Tr. at 135.) However, Dr. Roth testified that as a general rule, only a threefold or greater difference is "significant" because ED<sub>50</sub> values are log normally distributed. (Dkt. entry no. 354, Roth Tr. at 1323.) The difference in ED<sub>50</sub> values between the unsubstituted propoxy and the unsubstituted butoxy therefore would not be deemed significant enough to "teach" the skilled artisan that 7-linked butoxy compounds are preferable to 7-linked propoxy compounds. Using Defendants' theory that the skilled artisan would make "head to head" comparisons of structurally similar compounds, the skilled artisan would also compare 5-linked unsubstituted propoxy to 7-linked unsubstituted propoxy. (Defs.' Post-Trial Br. at 44; see dkt. entry no. 351, Castagnoli Tr. at 792-93.) The Nakagawa Declaration teaches that an 5-linked

unsubstituted propoxy compound had an ED<sub>50</sub> value of 2.1, as compared to an 7-linked unsubstituted propoxy compound with an ED<sub>50</sub> value of 9.3. This difference is significant because it is greater than threefold, unlike the comparison between the 7-linked unsubstituted propoxy and the 7-linked unsubstituted butoxy compounds, and thus would teach the skilled artisan the superiority of 5-linked propoxy compounds over 7-linked propoxy compounds, especially in light of the fact that the most potent test compound in the Nakagawa Declaration, Compound 44, is also a 5-linked propoxy compound (albeit with an ethoxy substituent at the 2 position of the phenyl ring).

Changing the position of the linker on the core structure, while perhaps not the first or most obvious structural change a person of ordinary skill in the art would make, is nevertheless an accepted way of evaluating structure-activity relationships. (See dkt. entry no. 345, Press Tr. at 94 (“From a medicinal chemist’s standpoint, the preference . . . is really not to change that [core] molecule very much, unless there’s a need or there’s a reason to study some.”) (emphasis added).) See also Takeda, 492 F.3d at 1356-57 (“A known compound may suggest its homolog, analog, or isomer because such compounds often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties. . . .”). The DE ‘105 Patent and SE ‘945 application both disclose 5-linked propoxy compounds, including 2,3 dichloro-substituted compounds, as examples of the invention having central nervous system controlling activity. (DTX 248-T at 19 (Compound 5, 5-linked unsubstituted propoxy dihydrochloride), 59 (Example 219, 5-linked unsubstituted propoxy monohydrochloride), 68 (Example 316, 5-linked 2,3 dichloro propoxy); DTX 1159-T at 62 (5-linked 2,3 dichloro propoxy), 69-70 (claims 3 and 4, claiming carbostyryl derivative with a

phenyl group having 1-3 substituted groups, where the side chain linker “is position 5 or 7 in the carbostyryl skeleton” (emphasis added).)

We conclude that the prior art does not teach toward selection of the unsubstituted butoxy as a lead compound. The Nakagawa Declaration teaches toward selection of a 5-linked compound, based on the superiority of Compound 44 in the mouse jumping test and the comparison of the 5-linked unsubstituted propoxy to the 7-linked unsubstituted propoxy. The teachings of the ‘932 Patent as to the potential of a 2-ethoxyphenyl substitution to cause orthostatic hypotension do not teach away from this interpretation of the Nakagawa Declaration in light of later, closer prior art references such as the DE ‘105 Patent and SE ‘945 application teaching both 5-linked compounds and 2-ethoxyphenyl substitutions. (See, e.g., DTX 248-T at 59 (Example 219, 5-[3-(4-phenyl-piperazinyl)propoxy]-3,4-dihydrocarbostyryl-monohydrochloride); DTX 1159-T at 64 (listing in Example 134, 7-{3-[4-(2-ethoxyphenyl)-1-piperazinyl]propoxy}-carbostyryl).)

**b. 2,3 Dichloro Propoxy Compound**

2,3 dichloro propoxy differs structurally from aripiprazole in that it has a three-methylene propoxy linker connecting the carbostyryl core to the piperazine ring, whereas aripiprazole has a four-methylene butoxy linker connecting the carbostyryl core to the piperazine ring. Defendants contend that aripiprazole is an obvious modification of, inter alia, the 2,3 dichloro propoxy compound because the prior art teaches both the potency of a 2,3 dichloro substitution and the superiority of a butoxy linker over a propoxy linker. (Defs.’ Post-Trial Br. at 47.)

Defendants suggest that the fact that Otsuka and the USPTO considered the 2,3 dichloro propoxy compound to be the closest prior art during the reexamination proceedings supports the

selection of 2,3 dichloro propoxy as a lead compound. (Defs.' Post-Trial Br. at 47.) However, agreement as to the "closest prior art" is not dispositive of the lead compound issue. Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd., 619 F.3d 1346, 1354 (Fed. Cir. 2010).

Defendants contend that the Nakagawa Declaration teaches that adding chlorine substituents at the 2 position and 3 position of the phenyl ring increases antipsychotic activity because both the 2-chloro monosubstituted compound and the 3-chloro monosubstituted compound had low ED<sub>50</sub> values, and a skilled artisan would understand that making a dichloro substitution at those positions would have an "additive effect" that would increase potency. (Defs.' Post-Trial Br. at 45.) Dr. Press concluded from the Nakagawa Declaration's mouse jumping data that because a 2-chloro substitution and a 3-chloro substitution in a propoxy-linked compound showed better ED<sub>50</sub> values than unsubstituted propoxy, whereas a 4-chloro substitution showed a worse ED<sub>50</sub>, the skilled artisan would determine that "there's significant improvement in potency by putting chlorines at the 2 and 3 positions" and worse potency using a 4-chloro substitution. (Dkt. entry no. 345, Press Tr. at 136-37, 167-70.) This is a conclusory statement at odds with the unpredictability of antipsychotic drug discovery and the fact that the Nakagawa Declaration does not provide data for any disubstituted compounds.

Furthermore, Defendants' argument in favor of the "additive effect" disubstitution theory apparently relies on the assumption that the person of ordinary skill in the art "would have recognized that" the SE '945 application "reports that a 2,3 dichloro substitution on the phenyl ring of an unsubstituted propoxy compound led to a compound reported to have antischizophrenic activity." (Defs.' Post-Trial Br. at 45.) As noted previously, such an interpretation strains the scope of the SE '945 application, which simply lists a 2,3 dichloro

compound as one among hundreds of examples that may be useful for an extensive list of potential central nervous system controlling activities. (DTX 1159-T at 5, 60, 62.) The DE '105 Patent and SE '945 application do not teach toward a 2,3 dichloro substitution pattern any more than they teach toward, e.g., 2-ethoxyphenyl (the substitution found in Compound 44 of the Nakagawa Declaration), 3,4,5-trimethylphenyl, or 4-bromophenyl. (DTX 1159-T at 5-6, 64; see also DTX 248-T at 13.)<sup>18</sup> The same example in the SE '945 application listing the 2,3 dichloro propoxy also contains examples of the invention that use a chlorine substituent at the 4-position, which Defendants contend the Nakagawa Declaration teaches away from. (See DTX 1159-T at 62 (listing, inter alia, 7-{3-[4-(3,4-dichlorophenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyryl.) The DE '105 Patent teaches the acceptability of 4-chlorophenyl substitution as well as locating the linker at the 5 position of the carbostyryl core: for instance, the examples in the DE '105 Patent immediately following 5-linked and 7-linked 2,3 dichloro propoxy compounds are 5-linked and 7-linked 3,4 dichloro propoxy compounds. (DTX 248-T at 68 (Examples 316-319); see also id. at 39, Example 49 (7-{3-[4-(4-chlorophenyl)piperazinyl]-propoxy}-3,4 dihydrocarbostyryl.)

Defendants have not shown by clear and convincing evidence that a person of ordinary skill in the art would have selected 2,3 dichloro propoxy as a lead compound or, more generally, would have been motivated to pursue a 2,3 dichloro substitution on the phenyl ring. The Court is

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<sup>18</sup> Otsuka researchers later advised in an article published in 1998 that one or two substituents on the phenyl ring are necessary for activity in 7-linked butoxy carbostyryl compounds, and that the 2-ethoxy substituent is best for monosubstituted compounds, while a 2,3 dichloro substituent is best for disubstituted compounds. (PTX 564, Oshiro et al., "Novel Antipsychotic Agents with Dopamine Autoreceptor Agonist Properties: Synthesis and Pharmacology of 7-[4-(4-Phenyl-1-piperazinyl)butoxy]-3,4-dihydro-2(1*H*)-quinolinone Derivatives," J. of Medicinal Chem., Vol. 41, No. 55 (1998), at 662.)

convinced, after close examination of the prior art references, that there is no reason to expect that the skilled artisan would read these prior art references together to somehow “arrive” at 2,3 dichloro propoxy and subsequently its homolog, aripiprazole.

**c. Bracketing Theory**

Defendants proposed a theory at trial that the skilled artisan would have been motivated to “bracket” the unsubstituted butoxy with the 2,3 dichloro propoxy to arrive at aripiprazole, which is a 2,3 dichloro butoxy. (See, e.g., dkt. entry no. 345, Press Tr. at 101-02.) We find that this is an improper hindsight analysis. See Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1345 (Fed. Cir. 2000); see also Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1379 (Fed. Cir. 2006) (“[M]ere identification in the prior art of each component of a composition does not show that the combination as a whole lacks the necessary attributes for patentability, i.e. is obvious.”). While the unsubstituted butoxy was in the prior art as of October 31, 1988, the ‘416 Patent taught that it is useful as an antihistamine, not an antipsychotic. The Nakagawa Declaration indicated that it was only of middling potency as an antipsychotic in comparison with eight propoxy compounds. And although Defendants argued that the SE ‘945 application and the DE ‘105 Patent teach that a 2,3 dichloro propoxy compound has antischizophrenic activity, those foreign counterparts to the ‘416 Patent did not teach any specific uses for 2,3 dichloro propoxy nor did they contain data that would lead one skilled in the art to conclude that the 2,3 dichloro propoxy, out of the hundreds of other listed examples, would provide better antipsychotic activity or distinguish it in any way from the general teaching of “central nervous system controlling activity” including, inter alia, sedation and antianxiety effects. (See dkt. entry no. 345, Press Tr. at 141.) See Bayer Schering Pharma AG v. Barr Labs.,



Inc., 575 F.3d 1341, 1347 (Fed. Cir. 2009) (stating that an invention is not “obvious to try” where the prior art gives only general guidance as to the particular form of the claimed invention or how to achieve it); Takeda, 492 F.3d at 1358 (stating that prima facie obviousness requires a showing that the prior art “would have suggested making the specific molecular modifications necessary to achieve the claimed invention”); Zenith Goldline, 471 F.3d at 1379 (“[T]o establish a prima facie case of obviousness based on a combination of elements in the prior art, the law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention.”).

We accept Defendants’ contention that a skilled artisan would have been motivated to experiment with a lead compound by varying the length of the linker— i.e., from propoxy to butoxy—because “homologation” is the simplest change a medicinal chemist can make to a compound in terms of evaluating structure-activity relationships. (See Defs.’ Post-Trial Br. at 50; dkt. entry no. 349, Castagnoli Tr. at 668-72; DTX 1012.) But the prior art does not teach either the unsubstituted butoxy or the 2,3 dichloro propoxy compound as a starting point, and mere structural similarity (such as being the adjacent homolog of the prior art) does not by itself render the claimed compound obvious. See Takeda, 492 F.3d at 1357-58 (finding that homologation and “ring-walking,” or moving the location of the linker on the core ring, did not render invention obvious where prior art did not teach selection of proposed lead compound in the first place); Eli Lilly & Co., 471 F.3d at 1378. Simply put, it is inappropriate for Defendants to pluck these particular compounds out of hundreds of disclosed compounds in the prior art and “bracket” them together, because they have not shown by clear and convincing evidence that the skilled artisan would have been motivated to select either one as a lead compound. Instead, it is

apparent that Defendants focused on these compounds because of their structural similarity to aripiprazole.

**d. OPC-4392**

OPC-4392 has a double bond between the 3 and 4 positions of the carbostyryl core, making it a dehydrocarbostyryl, whereas aripiprazole has a single bond at that location as it is a “3,4 dihydrocarbostyryl.” (Defs.’ Post-Trial Br. at 25.) OPC-4392 has a propoxy linker at the 7-position of the carbostyryl core as opposed to aripiprazole’s butoxy linker. (Id.) Finally, OPC-4392 is 2,3 dimethyl substituted on the phenyl ring, as opposed to a 2,3 dichloro substitution; it has methyl (H<sub>3</sub>C and CH<sub>3</sub>) groups where aripiprazole has chlorine atoms. (Id. at 25-26.)

Defendants contend that “routine optimization” of OPC-4392 would have led to the discovery of aripiprazole. (Defs.’ Post-Trial Br. at 49.) Dr. Castagnoli testified that the skilled artisan would be motivated to use OPC-4392 as a baseline in making structural changes because it had been tested in humans and shown to have a good side-effect profile and low toxicity. (Dkt. entry no. 349, Castagnoli Tr. at 620-21; dkt. entry no. 351, Castagnoli Tr. at 802, 805-06.) However, he also stated that clinical studies of OPC-4392 showed that it lacked an antipsychotic component. (Dkt. entry no. 351, Castagnoli Tr. at 803.)

Prior art references such as the 1987 Murasaki article reported that “the anti-psychotic action [of OPC-4392] was not strong.” (DTX 388-T at 1517.) Dr. Roth testified on behalf of Otsuka that the skilled artisan would not select OPC-4392 as a lead compound because the prior art, such as the Gerbaldo abstract, highlighted OPC-4392’s effect on the negative symptoms of schizophrenia and because an antipsychotic drug, by definition, has to treat positive symptoms of schizophrenia, the skilled artisan would not be motivated to pursue OPC-4392 for that purpose.

(Dkt. entry no. 354, Roth Tr. at 1202-03.) With respect to the Gerbaldo abstract's report that OPC-4392 improved negative symptoms, Dr. Roth explained that "[o]ne skilled in the art would be very unimpressed with this statement, knowing, in fact, that drugs that are ineffective in treating schizophrenia frequently in these sorts of trials will show some transient effect on negative symptoms." (Dkt. entry no. 355, Roth Tr. at 1409-1410.) Dr. Roth also expressed concern with regard to the 1987 Murasaki article's statement that the "strength of the activating action stood out" in patients treated with OPC-4392, and that this statement would be a "red flag" to persons familiar with the treatment of schizophrenia because when patients "become more activated, they're more likely to act out on their delusions and hallucinations" and therefore may become dangerous. (Dkt. entry no. 354, Roth Tr. at 1194-95.)

Given that OPC-4392 had already been tested in humans before October 31, 1988, and considered a failure insofar as it did not treat the positive symptoms of schizophrenia and was not well-tolerated in modest doses, we find no evidence to suggest that the person having ordinary skill in the art would have selected it as a lead compound for further testing. (Dkt. entry no. 365, Oshiro Tr. at 1806; dkt. entry no. 354, Roth Tr. at 1206-07; DTX 874, 1988 Murasaki article; see Pl.'s Post-Trial Br. at 104.) Defendants failed to provide convincing evidence that the skilled artisan would have known how to modify OPC-4392 to increase antipsychotic activity. (Pl.'s Post-Trial Br. at 104.) While the prior art references discussing OPC-4392 may have informed the skilled artisan seeking to address side effects of potential antipsychotic drugs, particularly as to EPS and elevated prolactin levels, its documented failures as an antipsychotic teach away from selecting it as a lead compound. Defendants failed to show by clear and convincing evidence that the mere fact that OPC-4392 had been tested in humans would have caused a person of

ordinary skill in the art to remain unwaveringly devoted to pursuing it, or other 7-linked disubstituted compounds which the skilled artisan would then “optimize” by experimenting with the linker length and single versus double bond at the 3,4 position on the carbostyryl core, as an antipsychotic. (See, e.g., dkt. entry no. 351, Castagnoli Tr. at 802, 806.)<sup>19</sup> Many compounds were clinically tested in humans as potential atypical antipsychotics and never became approved by the FDA due to lack of efficacy or an undesirable side-effect profile. (Dkt. entry no. 356, Nichols Tr. at 1575-84; PTX 320; PTX 321; PTX 322.)<sup>20</sup> Cf. Sanofi-Synthelabo v. Apotex Inc., 492 F.Supp.2d 353, 378 (S.D.N.Y. 2007) (discussing Sanofi’s decision to discontinue development of test compound for antiplatelet aggregation that had gone through more than fifty tests from 1980 to 1987, including phase I human trials, at a cost of tens of millions of dollars, because the test compound had been “consistently ineffective in patients” for unknown reasons), aff’d, 530 F.3d 1075 (Fed. Cir. 2008).

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<sup>19</sup> We accept Defendants’ position that a person of ordinary skill in the art would have been motivated to experiment with both double and single bonds connecting the 3 and 4 positions of the carbostyryl core, given that, e.g., the ‘416 Patent discloses examples of the invention (“pharmaceutically useful carbostyryl derivatives”) in terms of both single- and double-bonded compounds (“3,4-dihydrocarbostyryl and its 3,4-dehydro compound”). (‘416 Patent at col. 4, line 25 to col.13, line 47; see also dkt. entry no. 362, Nichols Tr. at 1729-30 (discussing the ‘528 Patent).)

<sup>20</sup> The Court cites Dr. Nichols’s testimony and the accompanying exhibits for the proposition that the fact of a drug being clinically tested in humans, while a relatively unusual occurrence in terms of the number of potential compounds synthesized, is not so rare that a drug company would continue to pursue a compound that had been shown to be not only poorly tolerated but also ineffective for its primary intended use. The compounds listed in PTX 320 and 322 are not being cited here as prior art.

**e. Clozapine- and Risperidone- Like Compounds**

Otsuka argues that as of October 31, 1988, the person of ordinary skill in the art would have been motivated to select a clozapine-like or risperidone-like compound, rather than any of Otsuka's prior art carbostyryl derivatives, as a lead compound for atypical antipsychotic drug discovery.

Clozapine was well-known in the field of antipsychotic drug development as an effective antipsychotic with low propensity to cause EPS in 1988, although it was not yet FDA-approved due to its agranulocytosis side effect. (Dkt. entry no. 355, Nichols Tr. at 1531.) Clozapine was the "gold standard" among antipsychotic drugs in that it treated both positive and negative symptoms of schizophrenia, without causing EPS or elevating prolactin levels. (Dkt. entry no. 356, Nichols Tr. at 1592; dkt. entry no. 354, Roth Tr. at 1334-35.) Researchers did not know in 1988, and do not know now, why clozapine is an atypical antipsychotic that does not cause EPS. (Dkt. entry no. 355, Nichols Tr. at 1533.) Many researchers in antipsychotic drug development focused on clozapine-like compounds prior to 1988. For instance, Defendants' expert Dr. Press testified that researchers sought to develop compounds that had "an activity profile like clozapine," and that in his own antipsychotic drug discovery efforts toward that end in the late 1970s and 1980s, his research team focused on tricyclic systems that were structurally related to clozapine. (Dkt. entry no. 346, Press Tr. at 196-200 (stating that compounds investigated by Press were isosteres of clozapine).)

Risperidone was also known to researchers in 1988. (Dkt. entry no. 356, Nichols Tr. at 1610.) By coincidence, the Gerbaldo abstract concerning OPC-4392, published in March 1988, is found on the same page as two abstracts relating to risperidone. (Pl.'s Post-Trial Br. at 67; dkt.

entry no. 354, Roth Tr. at 1203; DTX 990.) Based on the information in these three abstracts, risperidone would have appeared promising to a person of ordinary skill in the art in October 1988 as a lead compound for antipsychotic drug discovery. (Dkt. entry no. 354, Roth Tr. at 1205.) Like the Gerbaldo abstract reporting on OPC-4392, the two abstracts pertaining to risperidone reported results from testing in human schizophrenia patients. (DTX 990.) Risperidone was reported to improve both positive and negative symptoms of schizophrenia, which were “highly positive results.” (Dkt. entry no. 354, Roth Tr. at 1203-1204; see also dkt. entry no. 346, Press Tr. at 209 (“I believe that risperidone was at a stage of development [by October 1988] where it was in the clinic and was showing good effect.”); DTX 990.) Moreover, the abstracts state that risperidone was “very well-tolerated” in doses up to 20 milligrams per day, and despite the patients having been taken off drugs to treat EPS side effects, “no increase of EPS was observed, notwithstanding the high doses of risperidone.” (DTX 990, Pietoun et al., “Therapeutic Effect and Safety of Increasing Doses of Risperidone in Psychotic Patients.”) It was reported that “risperidone, at a mean daily dose of 5 mg, combined a very efficient antipsychotic effect with a significant improvement of negative and dysthymic symptoms, without inducing [EPS].” (DTX 990, Heylen et al., “Risperidone Versus Haloperidol in Chronic Psychotic Patients: An 8 Week Multicenter Double-Blind Comparative Trial.”)

In contrast to risperidone, nothing in the Gerbaldo abstract indicated that OPC-4392 had antipsychotic activity. (Dkt. entry no. 354, Roth Tr. at 1205.) The 1988 Murasaki article reported that OPC-4392 was not well-tolerated at doses of just 5 milligrams per day. (DTX 874.) According to Dr. Roth, the contrast between the risperidone and OPC-4392 clinical results was striking. (Dkt. entry no. 354, Roth Tr. at 1203-1204; DTX 990.)

Clozapine and risperidone are both structurally dissimilar to aripiprazole. (See, e.g., dkt. entry no. 356, Nichols Tr. at 1586-87.) Therefore, selection of a clozapine-like or risperidone-like lead compound would not render aripiprazole prima facie obvious. The prior art supports Otsuka's position that a clozapine-like or risperidone-like structure would have been an attractive lead compound, and does not teach that the unsubstituted butoxy, 2,3 dichloro propoxy, or OPC-4392 would be an effective antipsychotic. In light of the scope and content of the art as it existed on October 31, 1988, we therefore reject the notion that a person of ordinary skill in the art would have selected the unsubstituted butoxy, 2,3 dichloro propoxy, OPC-4392, or selected structural features thereof as a lead compound in an atypical antipsychotic drug discovery program.

Accordingly, we conclude that Defendants have not demonstrated 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, aripiprazole, nor have had a reasonable expectation of success in doing so based on those teachings.

#### **4. Secondary Considerations of Non-Obviousness**

So-called "secondary considerations" of objective evidence of non-obviousness include evidence of long-felt but unmet need, failures of others, commercial success, copying, unexpected results, and industry acclaim. Although we have determined that Defendants did not succeed in establishing a prima facie case of obviousness, we will nonetheless consider these indicia. Cf. Eli Lilly & Co. v. Actavis Elizabeth LLC, No. 07-3770, 2010 WL 3210516, at \*17 (D.N.J. Aug. 12, 2010) ("As Defendants have failed to demonstrate obviousness in accordance

with the initial Graham factors, the Court need not consider the objective indicia of nonobviousness.”) (citing Takeda, 492 F.3d at 1363).

**a. Long-Felt but Unmet Need**

As of 1988, there was a long-standing medical need for an improved antipsychotic drug that could treat the positive symptoms of schizophrenia with reduced side effects. (Pl.’s Post-Trial Br. at 122.) All antipsychotics marketed in the United States in 1988 were first-generation typical antipsychotics such as haloperidol and chlorpromazine, which treated the positive symptoms of schizophrenia but caused serious and sometimes irreversible side effects such as EPS and tardive dyskinesia. (Dkt. entry no. 352, Roth Tr. at 1143-45.) The first-generation typical antipsychotics tended to worsen negative symptoms of schizophrenia and had little to no effect on cognitive deficits. (Dkt. entry no. 352, Roth Tr. at 1144.)

Defendants have not challenged this long-felt need for an improved antipsychotic drug. Instead, Defendants point to atypical antipsychotic compounds, including risperidone, that were discovered prior to October 1988, but marketed later, and contend these drugs met this long-felt need prior to the discovery of aripiprazole. (Defs.’ Post-Trial Br. at 67.) Those compounds were not FDA approved as of October 1988 and therefore were not generally available for use by the public in October 1988. (Dkt. entry no. 352, Roth Tr. at 1143, 1134.) The Court therefore concludes that there remained an unmet need as of October 1988. See Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 364 F.Supp.2d 820, 852 (S.D. Ind. 2005) (“Because risperidone was not prescribed or otherwise available to schizophrenic patients at the time the ‘382 patent was filed, olanzapine met the long-felt but unsolved need for a safe, atypical antipsychotic.”).



As the Janssen court previously found, it is “undisputed that there was a long-felt but unsolved need for a safe, atypical antipsychotic that did not cause EPS or TD from at least the 1960s until 1985 and beyond.” Janssen, 456 F.Supp.2d at 670. Aripiprazole met that long-felt but unmet need for a safe and effective antipsychotic with reduced side effects. (Dkt. entry no. 352, Roth Tr. at 1151-53; dkt. entry no. 354, Roth Tr. at 1159-63; PTX 86; PTX 294; dkt. entry no. 367, Jarosz Tr. at 2054-60; PTX 357.)

**b. Failures of Others**

Researchers attempted for years to create an improved antipsychotic that would treat the positive symptoms of schizophrenia without causing EPS, tardive dyskinesia, or other adverse effects such as agranulocytosis. Those efforts largely failed, as reflected, for example, by the fact that the FDA did not approve a single new antipsychotic drug between loxapine in 1975 and clozapine in 1990. (Pl.’s Post-Trial Br. at 123.) See Janssen, 456 F. Supp. 2d at 670 (finding that there was a failure to develop a safe atypical antipsychotic prior to 1985). These widespread failures further establish that aripiprazole would not have been obvious.

Insofar as Defendants contend that the Court should not infer non-obviousness from the failures of others because the ‘416 Patent operated as a “blocking patent” foreclosing others from researching carbostyryl derivatives, this conflicts with record evidence establishing that Teva filed patent applications relating to methods of producing carbostyryl derivatives both before and after the ‘416 Patent expired in March 2005. (See infra p.52.) This indicates that entities other than Otsuka have in fact pursued carbostyryl derivatives despite Otsuka’s patent position. Additionally, Dr. Press testified that a medicinal chemist could seek to develop a patentably

distinct compound within a broad genus patent, with a view toward patenting the distinct compound when the genus patent expired. (Dkt. entry no. 345, Press Tr. at 175.)

Dr. Press's testimony regarding his research efforts directed at developing an atypical antipsychotic stated that he "personally made a compound called olanzapine" while working at Lederle Laboratories in the early- to mid-1980s, but the company's entire antipsychotic development program was shut down shortly thereafter when it was discovered that Eli Lilly & Company ("Lilly") already had patent protection for that compound. (Defs.' Post-Trial Br. at 68; dkt. entry no. 345, Press Tr. at 80-81, 190.) In litigation over the validity of Lilly's patent covering olanzapine, the court discussed certain broad genus patents filed in the mid-1970s covering compounds called thienobenzodiazepines. Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 364 F.Supp.2d 820, 832-33 (S.D. Ind. 2005). Considering the evidence of failed attempts by others "to develop a safe, atypical antipsychotic prior to the time Lilly filed its olanzapine patent application" in 1990, the court determined that this factor supported a finding of non-obviousness of Lilly's olanzapine patent. Id. at 906. The court did not consider the failure of others to develop olanzapine specifically, or consider the effect Lilly's prior art genus patents may have had on others' ability to pursue thienobenzodiazepines generally or 2-methyl-thienobenzodiazepine specifically. Id. at 830, 832-33, 906. Defendants offer no support for their position that "failure of others" refers to the development of aripiprazole specifically as opposed to the broader problem of developing a safe and effective atypical antipsychotic. See Janssen, 456 F.Supp.2d at 670-71 (considering "failure of others to develop a safe, atypical antipsychotic drug prior to the time Janssen filed its risperidone patent application" and noting that pharmaceutical companies' research efforts failed to result in an FDA-approved drug).

We therefore find that the evidence of failure of researchers to develop a safe and effective atypical antipsychotic as of October 31, 1988 supports a finding that aripiprazole would not have been obvious. Adv. Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1285 (Fed. Cir. 2000).

**c. Commercial Success**

Otsuka's witness Mr. Jarosz, an expert in economics and intellectual property valuation, credibly testified at trial to the extraordinary commercial success of Abilify<sup>®</sup>, the commercial embodiment of the compound and methods claimed in Claim 12, Claim 17, and Claim 23 of the '528 Patent, aripiprazole. (See Pl.'s Post-Trial Br. at 124-25; dkt. entry no. 367, Jarosz Tr. at 2002.) Total sales in the United States of Abilify<sup>®</sup> from the time it entered the market in November 2002 through February 2010 have been \$12.5 billion. (Pl.'s Post-Trial Br. at 125.) In 2009, sales of Abilify<sup>®</sup> were exceeded by just one other atypical antipsychotic drug, Seroquel, and Abilify<sup>®</sup> is the sixth largest-selling drug in the United States. (Pl.'s Post-Trial Br. at 126.) Defendants contend that aripiprazole's commercial success must be viewed in the light of the '416 Patent, which they assert functioned as a "blocking patent" discouraging competitors from pursuing carbostyryl derivatives as antipsychotic agents. (Defs.' Post-Trial Br. at 135.)

We have found that the prior art did not disclose aripiprazole nor did its teachings render aripiprazole obvious. We have also rejected Defendants' contention that the '416 Patent foreclosed competitors from investigating carbostyryl derivatives. Defendants' concern that some of the commercial success of Abilify<sup>®</sup> must be attributed to the '416 Patent is therefore of no moment. (Defs.' Post-Trial Br. at 135-36.) We find that the commercial success of Abilify<sup>®</sup> constitutes objective evidence of non-obviousness.

**d. Copying**

Defendants propose that their ANDA filings seeking approval to market generic aripiprazole products do not constitute compelling evidence of copying, due to the fact that bioequivalency is required for FDA approval. (Defs.' Post-Trial Br. at 134.) See Purdue Pharma Prods. L.P. v. Par Pharm., Inc., Nos. 09-1553, 09-1592, 2010 WL 2203101, at \*4 (Fed. Cir. June 3, 2010). However, the rationale that an invention is non-obvious because others have copied it “has been recognized as weak, but not irrelevant,” in the ANDA context. Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm., Inc., No. 07-5855, 2010 WL 2428561 at \*16 (D.N.J. June 9, 2010).

Otsuka points out that “[a]t least seven different generic drug companies have filed ANDA applications to various aripiprazole products, including aripiprazole tablets, aripiprazole orally disintegrating tables, and aripiprazole oral solutions.” (Pl.’s Post-Trial Br. at 208.) Otsuka also introduced evidence of copying beyond Defendants’ ANDA filings. For example, Teva filed a patent application on December 16, 2004, claiming “methods of preparing aripiprazole crystalline forms.” (PTX 612, U.S. Patent Application No. 2005-0203299 A1 (published September 15, 2005).) Another Teva patent application claiming a “process for preparing aripiprazole” was filed on February 7, 2005. (PTX 613, U.S. Patent Application No. 2005-0215791 A1 (published September 29, 2005).) Teva also filed international counterparts to these applications under the Patent Cooperation Treaty. (See PTX 620 (claiming methods of preparing aripiprazole crystalline forms); PTX 624 (claiming process for preparing aripiprazole).)

We therefore find that Otsuka has established some evidence of copying of aripiprazole. Because Defendants did not make out a prima facie case of obviousness, Otsuka does not bear the burden of rebutting the same by clear and convincing evidence on this point.

**e. Unexpected Results**

Unexpected results include “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). Aripiprazole has a number of unexpected therapeutic benefits that Otsuka contends could not have been predicted in 1988, including its broad efficacy in treating the positive symptoms of schizophrenia and low propensity to cause the serious side effects associated with typical antipsychotic drugs such as EPS, TD, sedation, weight gain or other metabolic effects, prolactin elevation, and orthostatic hypotension. (Pl.’s Post-Trial Br. at 131.) Defendants, contending that aripiprazole’s increased antipsychotic activity and favorable side-effect profile could have been predicted at the relevant time based on the prior art, focus on the Hirose Declaration submitted by Otsuka to the USPTO during the 2005 reexamination proceedings. (Defs.’ Post-Trial Br. at 55.)

Defendants’ argument that an effective antipsychotic drug with a favorable side-effect profile would have been expected by bracketing the unsubstituted butoxy and the 2,3 dichloro propoxy to arrive at 2,3 dichloro butoxy, or aripiprazole, has already been addressed and rejected by this Court. (Defs.’ Post-Trial Br. at 56.) Defendants’ arguments that aripiprazole’s efficacy was not unexpected because Otsuka withheld certain internal test data from the USPTO, or because data in the Hirose Declaration purporting to show “unexpected results” are unreliable due to bias and confound in the anti-apomorphine stereotypy test, are discussed below with

respect to Defendants' charge of inequitable conduct and will not be repeated here. (Defs.' Post-Trial Br. at 121-23; see infra pp.60-69.) At this juncture, we merely note that Dr. Roth testified credibly at trial that aripiprazole "has an exceedingly complex pharmacology," even as compared to other atypical antipsychotics. (Dkt. entry no. 352, Roth Tr. at 1043-51; see also PTX 406, Roth et al., "Magic Shotguns Versus Magic Bullets: Selectively Non-Selective Drugs for Mood Disorders and Schizophrenia," Nature Reviews, Vol. 3 (April 2004), at 355-56 (noting that "considerable controversy exists" regarding aripiprazole's mechanism of action, and its complex pharmacology precludes researchers from determining why it is effective).)

#### **f. Industry Acclaim**

Abilify<sup>®</sup> has received wide acclaim from others in the industry. In 2004, Frost & Sullivan awarded its Product Innovation Award for the U.S. antipsychotic medications market to Otsuka for Abilify<sup>®</sup>. (Pl.'s Post-Trial Br. at 157.)<sup>21</sup> The award was described as being "bestowed on the company that successfully develops and commercializes a medication which is believed to provide a unique set of benefits over existing products in the market." (Id.; PTX 357.) In its report covering the award, Frost & Sullivan stated: "With a comparable efficacy and superior side effect profile, Abilify<sup>®</sup> may become the new standard against which all new antipsychotics are judged." (Id.)

Abilify<sup>®</sup> has won a number of other awards throughout the world over the years. Among those awards, Abilify<sup>®</sup> won the Prix Galien award in 2006 (France) for being the most innovative pharmaceutical product on the market, the Pharmaceutical Executive Magazine

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<sup>21</sup> Frost & Sullivan is a market research firm that examines a wide range of industries, including the pharmaceutical industry. (Dkt. entry no. 367, Jarosz Tr. at 2040.)

Central Nervous System Compound of the Year for 2004 (United States), and a variety of other awards in Germany, Japan, France, and Spain. (Id.; PTX 375.) These awards are indicative of the acclaim that aripiprazole has received in the pharmaceutical industry. See Zenith Goldline, 364 F.Supp.2d at 853 (observing that olanzapine won the Prix Galien award in 1997 and noting that “[a]lthough the inventor of risperidone received the Prix Galien Award in 1996, . . . that fact does not vitiate the industry acclaim held by olanzapine.”).

**B. Obviousness-Type Double Patenting**

Defendants contend that the asserted claims disclosing aripiprazole and its uses are not patentably distinct from unsubstituted butoxy, which is disclosed by Claim 13 of the ‘416 Patent. (Defs.’ Post-Trial Br. at 88, 92-96.)

We have already found that the unsubstituted butoxy compound disclosed in Claim 13 of the ‘416 Patent does not render aripiprazole obvious. The ‘416 Patent teaches that unsubstituted butoxy is useful as an antihistamine, and contains no data or other information that would lead a person of ordinary skill in the art to conclude that the unsubstituted butoxy, out of the nine trillion compounds covered by the ‘416 Patent and the hundreds of examples listed, would be an effective antipsychotic. In considering the claim of the earlier patent, the Court is to consider its meaning and utility in the context of the entire patent. Sun Pharm. Indus. Ltd. v. Eli Lilly & Co., 611 F.3d 1381, 1388 (Fed. Cir. 2010) (observing “‘fundamental rule’ that claim terms ‘are construed with the meaning with which they are presented in the patent document’”) (citing Phillips v. AWH Corp., 415 F.3d 1303, 1316 (Fed. Cir. 2005)). To the extent that the ‘416 Patent claims that all compounds of the invention have both antihistaminic and central nervous system controlling activity, it does not follow that all compounds of the invention are useful

specifically as antipsychotics or antischizophrenics. ('416 Patent at col. 2, lines 50-52 ("The compounds of the present invention . . . have antihistaminic and central nervous controlling effects"); id. at col. 3, lines 13-19 (listing ten examples of uses for central nervous controlling agents, including antischizophrenia agents); cf. Defs.' Post-Trial Br. at 92-93.) Cf. Janssen, 456 F.Supp.2d at 657-58 (rejecting generic manufacturers' proposed lead compound, pirenperone, in § 103 obviousness analysis, on basis that prior art taught that pirenperone had potential as an anti-anxiety drug, not an antipsychotic); U.S. Patent No. 4,342,870, "Novel 3-(1-piperidinylalkyl)-4H-pyrido[1,2-A]pyrimidin-4-one Derivatives" (issued to Janssen on August 3, 1982) (covering, inter alia, pirenperone, and disclosing in specification that compounds of the invention as "useful as cardiovascular agents and to act on the central nervous system" but not specifically mentioning either antianxiety or antipsychotic effects).

Aripiprazole is distinct from unsubstituted butoxy in that it has chlorine atoms at the 2 and 3 positions of the phenyl ring, whereas unsubstituted butoxy has hydrogen atoms. The Court has already found that the prior art, including the Nakagawa Declaration, the DE '105 Patent, the SE '945 application, OPC-4392, and the Wise Poster did not teach the person of ordinary skill in the art to pursue a 2,3 dichloro substitution on the phenyl ring to achieve antipsychotic activity. (See Defs.' Post-Trial Br. at 94 (referring to these prior art references in support of their obviousness-type double patenting argument).) Because Defendants have failed to prove that the '528 Patent covering aripiprazole was obvious in light of the '416 Patent and the prior art references cited by Defendants, it has also failed to prove that aripiprazole was obvious in light of Claim 13 of the '416 Patent. See Sanofi-Synthelabo v. Apotex Inc., 492 F.Supp.2d 353, 393 (S.D.N.Y. 2007); accord Eli Lilly Co. v. Zenith Goldline Pharms., Inc., 364 F.Supp.2d 820, 910-



12 (S.D. Ind. 2005) (rejecting claim of obviousness-type double patenting where court had already found that earlier genus patent generically claiming class of compounds including the claimed invention and specifically disclosing homolog of claimed invention did not render claimed invention obvious), aff'd, 471 F.3d 1369 (Fed. Cir. 2006).

### **C. Conclusion on Obviousness**

We find that Defendants failed to carry their burden of proving by clear and convincing evidence that Claim 12, Claim 17, or Claim 23 of the '528 Patent are invalid as obvious over the prior art references or constitute an impermissible double patenting of Claim 13 of the '416 Patent.<sup>22</sup>

### **III. Enforceability of Patent–Inequitable Conduct**

Defendants contend that Otsuka breached its duty of candor to the USPTO, rendering the '528 Patent unenforceable, by (1) withholding the Nakagawa Declaration during the prosecution of the '528 Patent, (2) withholding internal Otsuka data that was inconsistent with the data presented in the Hirose Declaration during the '528 Patent reexamination proceedings, and (3) making false statements regarding the experimental methodology used in the anti-apomorphine stereotypy test for the Hirose Declaration, in that the protocol stated that stereotyped behavior

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<sup>22</sup> Defendants challenged the utility of the '528 Patent in the Final Pretrial Order, but mentioned the issue only tangentially in their post-trial brief. (Dkt. entry no. 328, Final Pretrial Order at 124-25, 164 (“Defendants’ Legal Issues . . . 3. Whether claims 12, 17, and 23 are invalid under 35 USC sections 101 and/or 112 because the disclosure in the specification of the '528 patent is not adequate to support the use of aripiprazole as antischizophrenic”; cf. Defs.’ Post-Trial Br. at 113.) In light of the Court’s findings that the '528 Patent is commercially successful, not obvious, and infringed by Defendants, Defendants have not proven lack of utility or enablement, and we will not invalidate the '528 Patent on that basis. See Raytheon Co. v. Roper Corp., 724 F.2d 951, 959-60 (Fed. Cir. 1983) (“If a party has . . . infringed, proof of that device’s utility is thereby established. People rarely, if ever, appropriate useless inventions.”).

would be evaluated by “an observer blind to the treatment received by the mice,” but two observers were actually involved. (Defs.’ Post-Trial Br. at 148-53.)

**A. Alleged Withholding of the Nakagawa Declaration and Representations Concerning Superiority of ‘528 Compounds over Prior Art Compounds**

Defendants allege that Otsuka failed to disclose the Nakagawa Declaration during the prosecution of the ‘528 Patent, and that the Nakagawa Declaration was highly material because Otsuka argued to the Examiner during the reexamination proceedings that there was no evidence that the five exemplary prior art compounds had been identified as useful for treating schizophrenia, yet the Nakagawa Declaration indicated that some of those compounds, including the unsubstituted butoxy and the 2,3 dichloro propoxy, “perform[ed] excellent” in the mouse jumping test. (DTX 214 at 14; Defs.’ Post-Trial Br. at 155.)<sup>23</sup> Defendants conclude that therefore Otsuka must have known that its statement during the reexamination that the five exemplary prior art compounds had not been shown to exhibit antipsychotic activity was false and misleading because Dr. Oshiro, at least, had been aware of the mouse jumping data for the unsubstituted butoxy in the prosecution of the ‘416 Patent, and he was involved in the ‘528 Patent reexamination proceedings. (Defs.’ Post-Trial Br. at 157-58.)<sup>24</sup>

Otsuka’s argument on reexamination that a butoxy linker led to an unexpected result of increased antipsychotic activity relied on data in the Hirose Declaration. (DTX 399.) The Hirose

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<sup>23</sup> As previously stated, the Nakagawa Declaration was part of the prosecution history of the ‘416 Patent. (See n.9 *supra* & accompanying text.)

<sup>24</sup> We note that Defendants do not appear to contend that the 1987 Nakagawa Declaration should have been brought to the attention of the USPTO during the initial prosecution of the ‘528 Patent in the early 1990s, but only that it should have been raised during the reexamination proceedings that took place in 2004-2005.

Declaration, like the '528 Patent itself, provides data for an anti-apomorphine stereotypy test, whereas the Nakagawa Declaration provided data for the mouse jumping test described by Lal. et al. in 1975. (DTX 375; DTX 214; DTX 399.) Otsuka introduced credible evidence at trial that these two tests are different, the anti-apomorphine stereotypy test being a relatively specific test for compounds that antagonize postsynaptic D<sub>2</sub> dopamine reception; the mouse jumping test is not commonly used in antipsychotic drug discovery, while the anti-apomorphine stereotypy test has been very successful as a screen for potential antipsychotic activity; and results from the two types of tests cannot be correlated. (Dkt. entry no. 354, Roth Tr. at 1243-51; see also dkt. entry no. 346, Press Tr. at 253; dkt. entry no. 351, Castagnoli Tr. at 851-52.) Whereas the Nakagawa Declaration claimed that the inhibition of mouse jumping was "excellent" in all nine test compounds, including the unsubstituted butoxy, later test data for the unsubstituted butoxy in the anti-apomorphine stereotypy test showed that the unsubstituted butoxy was "virtually inactive" at antagonizing postsynaptic D<sub>2</sub> receptor activity, further compelling the conclusion that the mouse jumping test and the anti-apomorphine stereotypy test cannot and should not be correlated. (Pl.'s Post-Trial Br. at 234; PTX 564, Oshiro et al., "Novel Antipsychotic Agents with Dopamine Autoreceptor Agonist Properties: Synthesis and Pharmacology of 7-[4-(4-Phenyl-1-piperazinyl)butoxy-3,4-dihydro-2(1*H*)-quinolinone Derivatives," J. of Medicinal Chem., Vol. 41, No. 5 (1998), at 661 (showing ED<sub>50</sub> value of >28, with the notation, "inactive at below given dose").)

Insofar as the '528 Patent and Otsuka's statements during the reexamination thereof relied on anti-apomorphine activity data to show the usefulness and superiority of the claimed invention as an antipsychotic, the mouse jumping data in the Nakagawa Declaration cannot be

correlated. We will not infer a contradiction, or falsity of Otsuka's representation that the superiority of butoxy-linked compounds over propoxy-linked compounds was unexpected, based on a comparison of these two different tests. Even if we were to compare the two, however, we have already found that the Nakagawa Declaration did not teach the superiority of butoxy-linked compounds. Otsuka's contention that the superiority of butoxy-linked compounds was unexpected is not undermined by the Nakagawa Declaration. Additionally, the evidence indicates that the mouse jumping data in the Nakagawa Declaration would not have been material to the Examiner during the reexamination proceedings. Otsuka submitted the Banno article during the reexamination proceedings, which contained mouse jumping data for several of the compounds at issue here, including unsubstituted butoxy, unsubstituted propoxy, and OPC-4392. (See supra p.10; DTX 84.) The Examiner did not cite to any of these mouse jumping data in the reexamination proceedings, confirming that these data, which were distinct from the stereotypy data disclosed in the '528 Patent and presented in the Hirose Declaration, were not relevant to the patentability of the '528 Patent claims. (Pl.'s Post-Trial Br. at 236; PTX 121.)

We find that Defendants have not shown by clear and convincing evidence that Otsuka's failure to disclose the Nakagawa Declaration during the '528 Patent reexamination proceedings was either material or made with intent to deceive the USPTO. Star Scientific, Inc. v. R.J. Reynolds Tobacco Co., 537 F.3d 1357, 1365 (Fed. Cir. 2008).

**B. Hirose Declaration and '528 Patent Reexamination Proceeding; Alleged Withholding of "Internal Otsuka Data"**

During the reexamination proceedings for the '528 Patent, the Examiner rejected the claims of the '528 Patent as unpatentable over compounds claimed by the '416 Patent,

specifically looking to five exemplary prior art compounds in the same genus as aripiprazole that the Examiner stated the ‘416 Patent taught as being useful in “central nervous system disorders in which anti schizophrenia [sic] is also disclosed.” (Defs.’ Post-Trial Br. at 71; DTX 121, ‘528 Reexamination History, at OPC 1324-27.) In seeking reconsideration of the Examiner’s final rejection, Otsuka represented to the Examiner that the prior art did not teach that the exemplary compounds had the recited property of treating schizophrenia, and submitted the Hirose Declaration to support its argument that the selection of a butoxy linker over a propoxy linker led to unexpected superiority of the butoxy-linked compound. (DTX 399, Hirose Decl.; Defs.’ Post-Trial Br. at 71.)<sup>25</sup> The Examiner ultimately found that the claims of the ‘528 Patent were allowable because the change from a propoxy to a butoxy linker showed “a clear unexpected result in the ED<sub>50</sub> values.” (DTX 121 at OPC 1411-12.)

The Hirose Declaration compared four butoxy-linked compounds representative of the invention claimed in the ‘528 Patent, numbered Test Compounds 1, 5, 6, and 8, to four homologous propoxy-linked prior art compounds claimed in, e.g., the DE ‘105 Patent and the ‘416 Patent, labeled Test Compounds A, B, C, and D. (DTX 399 at 2-5.) Test Compound 1 was aripiprazole, and Test Compound A was the 2,3 dichloro propoxy. (DTX 399 at 3-5.)

Two tests were conducted on each group of compounds. The first was an anti-apomorphine stereotypy test, to indicate the “compound’s ability to block neurotransmission of

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<sup>25</sup> To the extent Defendants broadly characterize Otsuka’s representation as encompassing all prior art, the full statement makes clear that Otsuka was arguing that the ‘416 Patent, ‘840 Patent, and DE ‘105 Patent specifically did not contain evidence that the five prior art compounds had the property of treating schizophrenia, a point that has already been addressed herein. (See Pl.’s Post-Trial Br. at 238-39.) We concur with Otsuka that this statement indicated only that the ‘416 Patent and DE ‘105 Patent lacked test data concerning antipsychotic activity. (DTX 459 at 12.)

dopaminergic D<sub>2</sub>-receptors, i.e., its antipsychotic activity.” (DTX 399 at 5.) The second was the anti-epinephrine lethality test, to indicate the “compound’s ability to block neurotransmission of α-receptors, i.e., its cardiovascular side effects such as orthostatic hypotension.” (DTX 399 at 6.)

The anti-apomorphine stereotypy test indicated an ED<sub>50</sub> value of 0.28 for aripiprazole, and an ED<sub>50</sub> value of 6.47 for the 2,3 dichloro propoxy. (DTX 399 at 6.) Thus, Otsuka represented to the Examiner that the fact that aripiprazole was twenty-three times more potent than its 2,3 dichloro propoxy homolog was indicative of the unexpected superiority of the butoxy-linked compound.

Defendants contend that this 23-fold difference is at odds with “internal Otsuka data” wherein an anti-apomorphine stereotypy test comparing, inter alia, aripiprazole with 2,3 dichloro propoxy resulted in a mere 6-fold difference, with aripiprazole having an ED<sub>50</sub> of 0.4 and 2,3 dichloro propoxy having an ED<sub>50</sub> of 2.5. (DTX 59-T, Synthesis Research Group Year 1987 Research Presentation: Development of Brain Function Improvement Drug, Table 4, “Effect of Side Chain Length,” at OPC 717014; Defs.’ Post-Trial Br. at 150.)

We note that Defendants did not present evidence concerning the test conditions underlying the 1987 internal Otsuka test data or whether these test data may be validly compared with the 2005 Hirose Declaration test data. (See dkt. entry no. 366, Oshiro Tr. at 1901-03.) Rather, Defendants improperly attempt to shift their burden of proving the elements of inequitable conduct to Otsuka: “Neither Dr. Oshiro, nor any other Otsuka witness, offered an explanation as to why [the allegedly contradictory internal Otsuka data] would not be material, or why it was not disclosed to the PTO.” (Defs.’ Post-Trial Br. at 151.) Otsuka’s alleged failure to explain why the internal Otsuka test data were not submitted in connection with the

reexamination proceedings does not satisfy Defendants' burden of proving inequitable conduct by clear and convincing evidence.

Defendants contend that the internal Otsuka data contained in the 1987 year-end presentation contradict Otsuka's representations during the reexamination proceedings regarding the "unexpected" superiority of butoxy-linked compounds based on Dr. Oshiro's testimony regarding a different report and different compounds. Dr. Oshiro testified at trial regarding a December 1986 monthly report discussing post-OPC-4392 research efforts. (PTX 35-T.) The December 1986 report compared OPC-4310, a propoxy-linked compound thought to have a 2-chloro, 6-methyl substitution on the phenyl ring, to OPC-14542, the butoxy-linked homolog of OPC-4310, and observed that extending the methylene chain from 3 to 4 caused a "dramatic 15-fold increase in the dopamine blocking action" that was "totally unexpected." (PTX 35-T at OPC 768540-41.)<sup>26</sup> Dr. Oshiro testified that his research group decided to make this same structural modification to OPC-4392, but that it did not result in the same "15-fold activity increase" he had seen in comparing OPC-4310 to OPC-14542:

A: As I indicated earlier, when the propoxy in 4310 was changed to butoxy, such as in 14542, the activity increased 15-fold. And so we wanted to confirm as to whether or not the OPC-4392 which was undergoing clinical testing would have the same activity increase, which is the 15-fold activity increase, if the propoxy was changed to butoxy. So we decided to synthesize the compound.

Q: And what did you find?

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<sup>26</sup> A February 1987 report states that Otsuka researchers realized that the chlorine positions on the phenyl ring for OPC-4310 and OPC-14542 were wrong, due to an error on the label of a starting material, in that the chlorine previously stated as being at the 6 position was actually at the 3 position; "[t]hat is, they should be 3-chloro 2-methyl instead of 2-chloro 6-methyl." (PTX 37-T at OPC 768547.)

A: We did not find a considerable increase in the activity such as when we saw from 4310 to OPC-14542. In other words, even if the propoxy was changed to butoxy, we did not see a surprising increase, such as the 15-fold increase.

(Dkt. entry no. 365, Oshiro Tr. at 1772-73.)

Defendants argue that Dr. Oshiro testified here that a six-fold difference in stereotypy test results is not surprising, because test data reported in later monthly reports showed six-fold difference in the stereotypy test results for OPC-4392 versus the butoxy-linked analog. Dr. Oshiro's testimony does not support that interpretation. He merely acknowledged that the December 1986 report stated that OPC-4392 had an ED<sub>50</sub> of 9.3 in the anti-apomorphine stereotypy test, and that the February 1987 report stated that OPC-14565, identical to OPC-4392 except that it had a butoxy linker instead of a propoxy linker, had an ED<sub>50</sub> of 1.4 in the anti-apomorphine stereotypy test. (Dkt. entry no. 366, Oshiro Tr. at 1842-45; PTX 35-T at OPC 768541; PTX 37-T at OPC 768548.) Defendants did not directly ask Dr. Oshiro his opinion concerning a six-fold increase in stereotypy test data and further never asked Dr. Oshiro if the internal Otsuka test data was inconsistent with the test data reported in the Hirose Declaration. Moreover, his testimony regarding the six-fold increase was not particularly indicative of a full understanding of the relevant question or his agreement therewith:

Q: So OPC-4392 with a butoxy linker was actually six times more active in the Anti-Apomorphine Test than OPC-4392 with a propoxy linker.

Do you see that?

A: The results in the Mouse Test or Mice Test is that way, yes.

(Dkt. entry no. 366, Oshiro Tr. at 1845.)



Thus, the only testimony on this point was in regard to data concerning OPC-4392 and its butoxy homolog, and OPC-4310 and its butoxy homolog. None of these reports or testimony by Dr. Oshiro concerned a comparison of aripiprazole to the 2,3 dichloro propoxy. Defendants cannot now attempt to construct what answers Dr. Oshiro might have provided in response to questions Defendants never posed. Defendants' inferential interpretation of Dr. Oshiro's testimony cannot satisfy their burden of proving materiality of the "internal Otsuka data" by clear and convincing evidence.

Defendants have also not proven that any individual knowingly withheld this allegedly inconsistent data. Defendants allege that Dr. Oshiro was aware of the contents of the Hirose Declaration and therefore must have intentionally withheld the allegedly contradictory internal data with an intent to deceive the PTO. (Defs.' Post-Trial Br. at 151.) Dr. Oshiro did not affirmatively testify, however, that he was aware of the test data submitted in the Hirose Declaration. He merely testified that "most likely this draft – draft of this declaration was sent to me as an attachment to an e-mail requiring or requesting me to check the wording for the way things are worded in this document." (Dkt. entry no. 366, Oshiro Tr. at 1897.) Dr. Oshiro's testimony, which reflects his uncertain memory in this regard, does not establish that Dr. Oshiro was aware of the specific details of the test data reported in the Hirose Declaration. Because Defendants have not shown that Dr. Oshiro was aware of the specific data in the Hirose Declaration, they cannot prove that he was aware of any contradiction.

Defendants also failed to offer any evidence concerning additional details underlying their allegation that Dr. Oshiro knowingly withheld contradictory test data. Defendants never inquired as to whether Dr. Oshiro recalled in 2005 the specific stereotypy test data Defendants cite. That

data was generated in 1987, 18 years earlier, and was among dozens of test results reported in Dr. Oshiro's notebooks. (DTX 59T.) It is therefore not apparent that in 2005 Dr. Oshiro would have recalled the details of the 1987 data and Defendants have not carried their burden of proof that he did. See MPEP 2001.04 (holding that the duty to disclose only applies to contemporaneously known information).

Defendants also never inquired as to whether Dr. Oshiro believed there was any contradiction between the Hirose Declaration data and the internal stereotypy data Defendants cite. On their face, data showing a six-fold improvement and data showing a 23-fold improvement are not contradictory, and Defendants have not presented any evidence that Dr. Oshiro believed to the contrary even had he been aware of these data.

Finally, Defendants suggest Dr. Hirose may have been aware of the allegedly contradictory test data because he generated test data for aripiprazole in 1987. This does not prove that Dr. Hirose was aware of the specific data Defendants cite, and Dr. Hirose testified that he did not recall whether he had seen any other comparative data concerning the compounds tested in the Hirose Declaration. (Dkt. entry no. 366, Hirose Tr. at 1968-70.)

Accordingly, Defendants have not met their burden of proof by clear and convincing evidence that any individual knowingly withheld contradictory test data. We cannot find the '528 Patent unenforceable for inequitable conduct with respect to the allegedly withheld internal Otsuka data or the representations made in the traverse during the reexamination proceedings. (DTX 459 at 12.)

### **C. Methodology Used in Hirose Declaration**

The protocol for the anti-apomorphine stereotypy test in the Hirose Declaration indicated that “observation for stereotyped behavior will be performed by an observer blind to the treatment received by the mice.” (DTX 399-A at 9.) Defendants contend that this statement indicates that only a single observer conducted all of the stereotypy testing and that this single observer would be blinded to the identity of the compound being tested, not just the doses of the compounds administered. (Defs.’ Post-Trial Br. at 152.) Because two observers conducted the stereotypy experiments and because these observers were blinded to the doses administered but not the compounds, Defendants argue that Dr. Hirose did not follow his study protocol and suggest he did so with an intent to deceive. (Id. at 152-53.)

The protocol, however, does not support Defendants’ interpretation. The isolated statement cited by Defendants merely indicates that individual mouse observations would be performed by a single individual. It does not state that only one individual would be involved in the overall conduct of the study, as Defendants contend. (DTX 399-A.) To the contrary, the protocol specifically identifies two individuals, Dr. Hirose and Dr. Kikuchi, as the investigators who carried out the testing. (DTX 399-A at 2.) Dr. Roth and Dr. Hirose each explained that it was therefore clear that two individuals would score the stereotypy testing. (Dkt. entry no. 352, Roth Tr. at 1100-01; dkt. entry no. 367, Hirose Tr. at 1983-86.)

Defendants did not offer any testimony in response to Dr. Roth’s and Dr. Hirose’s testimony in this regard. Dr. Beninger, Defendants’ only witness on this issue, did not refer in any way to the listing of two investigators in the protocol and, in fact, did not provide any clear testimony in support of Defendants’ position that the Hirose protocol indicated that only a single

individual would perform the stereotypy testing. (Docket entry no. 351, Beninger Tr. at 958.) Accordingly, Defendants have not shown that the protocol indicates that the testing would be performed by a single individual.

Defendants also did not establish that the protocol indicated that the observers would be blinded to the identity of the compound being studied. The statement in the protocol refers to the “treatment received by the mice.” (DTX 399-A at 9.) Because the observers were blinded to the dosage of compound administered to the mice, or whether the mice were instead administered the placebo, they were in fact blinded to the treatment received by the mice. As Dr. Roth explained, the statement in the protocol does not necessarily indicate that the observer was blinded to both the identity of the compound and the dose of compound administered. (Dkt. entry no. 352, Roth Tr. at 1113-14.) Dr. Hirose similarly explained that the mention of blinding in the protocol was referring to the fact that the observer was in fact blinded to the dose of test compound administered to the mice, which was in fact the treatment received by the mice. (Dkt. entry no. 367, Hirose Tr. at 1930-31.) Moreover, Dr. Roth explained that the blinding methodology used by Dr. Hirose, where the observer was blinded to the dose administered to the mice, was sufficient to effectively blind the study. (Dkt. entry no. 352, Roth Tr. at 1113-14.)

Defendants’ expert Dr. Beninger, an expert in behavioral pharmacology, testified that the Hirose Declaration’s anti-apomorphine stereotypy data was not capable of meaningful interpretation because the protocol introduced a confound by having different observers rating different compounds, thus “confound[ing] the compounds they are testing with the rater doing the testing.” (Dkt. entry no. 351, Beninger Tr. at 931.) Dr. Beninger also testified that because the observers knew which compounds they were testing, although not the dose, the data could

have been biased by the observers' expectations that the claimed compounds would be superior. (Dkt. entry no. 351, Beninger Tr. at 946-47.) Although we understand Dr. Beninger's concerns regarding the reliability of the data, we credit Dr. Roth's testimony that the raw data in fact showed "a high degree of interrater reliability" and that the blinding was adequate. (Dkt. entry no. 352, Roth Tr. at 1108-15; PTX 487-T; accord dkt. entry no. 355, Thisted Tr. at 1458-65, 1481-85.) As Dr. Hirose further explained, this blinding methodology was the standard method employed at Otsuka, and Otsuka had used this same blinding methodology in experiments conducted for generating data for submission to the FDA and for publications in peer-reviewed journal articles. (Dkt. entry no. 367, Hirose Tr. at 1931-33.)

Therefore, Defendants have not proven that the Hirose protocol inaccurately described the experimental procedures or that the testing methodology rendered the data unreliable. Because there was no misrepresentation or withholding of material information on this count, nor any intent to deceive, it cannot serve as the basis for allegedly inequitable conduct by Otsuka.

#### **IV. Otsuka's Motion to Strike**

Otsuka filed a motion to strike certain arguments made by Defendants in their post-trial brief that Otsuka contends Defendants had not included in the Final Pretrial Order or Defendants' Trial Brief, and therefore were raising for the first time post-trial. (Dkt. entry no. 372, Mot. to Strike.) Otsuka contends that Defendants' argument that (1) the 2,3 dichloro propoxy would have been selected as a lead compound for purposes of obviousness, and (2) Otsuka committed inequitable conduct before the USPTO by allegedly withholding internal anti-apomorphine stereotypy data for aripiprazole and the 2,3 dichloro propoxy, should be stricken pursuant to Rule 16(e).

The Court has considered all of the arguments made by Defendants in their post-trial brief, and determined that they lack merit. Accordingly, Otsuka's motion to strike will be denied as moot.

## **V. Remedies**

Otsuka seeks a permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), enjoining Defendants and their officers, directors, employees, agents, successors, affiliates and assigns, and all persons and entities acting in concert or participation with them, from engaging in the commercial manufacture, use, marketing, sale, or offer for sale within the United States, or from importing into the United States, generic aripiprazole products, including the aripiprazole products described in Defendants' ANDA filings, until the expiration of the '528 Patent. (Pl.'s Post-Trial Br. at 241; Final Pretrial Order at 164.) See eBay Inc. v. MercExchange, L.L.C., 547 U.S. 388, 391 (2006) (“[A] plaintiff seeking a permanent injunction must . . . demonstrate: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction.”).

We find that a permanent injunction is appropriate. Infringement of the '528 patent, which the Court has found to be valid, is an irreparable injury, and remedies such as monetary damages are inadequate to compensate for that injury. Ortho-McNeil Pharm., Inc. v. Mylan Labs. Inc., No. 04-1689, 2007 WL 869545, at \*1 (D.N.J. Mar. 20, 2007), aff'd, 520 F.3d 1358 (Fed. Cir. 2008). The balance of hardships as to the parties and public interest in protecting valid patents further weigh in favor of Otsuka's request for a permanent injunction. Having considered

these factors, the Court concludes that Otsuka has shown that it is entitled to a permanent injunction.

Otsuka also seeks an order resetting the effective date of Defendants' ANDAs to a date not earlier than the expiration of the '528 Patent. (Pl.'s Post-Trial Br. at 240; Final Pretrial Order at 164.) In light of our findings as to infringement, obviousness, and enforceability, it will be so ordered. 35 U.S.C. § 271(e)(4)(A).

### CONCLUSION

For the foregoing reasons, the Court holds that the '528 Patent is not invalid as obvious under 35 U.S.C. § 103; not invalid over Claim 13 of the '416 Patent pursuant to the judicially-created doctrine of obviousness-type double patenting; and not unenforceable for inequitable conduct. The Court will enter judgment in favor of Otsuka on its claims of infringement of Claim 12, Claim 17, and Claim 23 of the '528 Patent. Judgment will be entered in favor of Otsuka and against Defendants on Defendants' counterclaims seeking judgment of non-infringement, invalidity, and unenforceability of the '528 Patent. The Court will permanently enjoin Defendants from marketing their generic aripiprazole products until such time as the '528 Patent expires, and will reset the effective date for Defendants' ANDAs until such time. The Court will enter an appropriate order and final judgment.

s/Mary L. Cooper  
**MARY L. COOPER**  
United States District Judge

Dated: December 14, 2010