**NOT FOR PUBLICATION** **CLOSED**

**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF NEW JERSEY**

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| ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LIMITED, | : | |
| Plaintiffs, | : | |
| v. | : | |
| ANCHEN PHARMACEUTICALS, INC. | : | Civil Action No. 10-cv-1835 (JAP)(TJB) |
| OSMOTICA PHARMACEUTICAL CORPORATION, | : | Civil Action No. 10-cv-4203 (JAP)(TJB)<br>Civil Action No. 11-cv-2484 (JAP)(TJB) |
| TORRENT PHARMACEUTICALS LIMITED and TORRENT PHARMA INC., | : | Civil Action No. 10-cv-4205 (JAP)(TJB)<br>Civil Action No. 10-cv-4971 (JAP)(TJB) |
| MYLAN PHARMACEUTICALS INC. and MYLAN INC., | : | Civil Action No. 10-cv-5519 (JAP)(TJB)<br>Civil Action No. 11-cv-2483 (JAP)(TJB) |
| Defendants. | : | **OPINION** |

PISANO, District Judge.

## I. INTRODUCTION

These are several Hatch-Waxman Act patent infringement actions brought by plaintiffs AstraZeneca Pharmaceuticals LP and AstraZeneca UK Limited against Anchen Pharmaceuticals, Inc. ("Anchen"); Osmotica Pharmaceutical Corporation ("Osmotica"); Torrent Pharmaceuticals Limited and Torrent Pharma Inc. (together, "Torrent"); and Mylan Pharmaceuticals Inc. ("Mylan Pharms") and Mylan Inc. (together, "Mylan"). The patent-in-

suit claims sustained release formulations of the antipsychotic compound quetiapine and a method for treating psychotic states by administering an effective amount of the claimed formulations.

A 12-day bench trial was held in October 2011. Upon hearing the testimony on behalf of the parties and reviewing documentary evidence presented at trial, the Court herein sets forth its findings of fact and conclusions of law, and finds in favor of Plaintiffs.

## II. BACKGROUND

### A. Procedural Background

Plaintiffs in all actions are AstraZeneca Pharmaceuticals LP ("AZLP") and AstraZeneca UK Limited ("AZUK") (collectively, "AstraZeneca" or "Plaintiffs"). Below is a summary of the instant civil actions:[1]

*Anchen*

- On April 10, 2010, AstraZeneca filed a complaint against Anchen (Civil Action No. 10-1835) alleging that Anchen's filing of its Abbreviated New Drug Application ("ANDA") No. 90-757 infringed the '437 patent under 35 U.S.C. § 271(e)(2)(A).

*Osmotica*

- On August 16, 2010, AstraZeneca filed a complaint against Osmotica (Civil Action No. 10-4203) alleging that Osmotica's filing of its ANDA No. 201424 infringed the '437 patent under 35 U.S.C. § 271(e)(2)(A).

[1] Plaintiffs settled with certain defendants prior to the conclusion of trial. Those civil actions that were concluded prior to the end of trial are not listed here.

- On July 11, 2011, AstraZeneca filed a second complaint against Osmotica (Civil Action No. 11-2484) alleging that Osmotica's filing of its ANDA No. 202587 infringed the '437 patent under 35 U.S.C. § 271(e)(2)(A).

*Torrent*

- On August 16, 2010, AstraZeneca filed a complaint against Torrent (Civil Action No. 10-4205) alleging that Torrent's filing of its ANDA No. 201996 infringed the '437 patent under 35 U.S.C. § 271(e)(2)(A).
- On September 28, 2010, AstraZeneca filed a second complaint against Torrent (Civil Action No. 10-4971) alleging that Torrent's filing of its ANDA No. 202000 infringed the '437 patent under 35 U.S.C. § 271(e)(2)(A).

*Mylan*

- On October 22, 2010, AstraZeneca filed a complaint against Mylan (Civil Action 10-5519) alleging infringement of the '437 patent under 35 U.S.C. § 271(e)(2)(A) based on Mylan Pharms's submission of an ANDA No. 202228.
- On April 29, 2011, AstraZeneca filed a second complaint against Mylan (Civil Action No. 11-2483) alleging infringement of the '437 patent under 35 U.S.C. § 271(e)(2)(A) based on Mylan Pharms's submission of an amendment to its ANDA No. 202228.

Claims 1-13 of the '437 patent are asserted against defendants Anchen and Mylan. Claims 1, 2, 10-13 are asserted against defendants Osmotica and Torrent. Anchen, Osmotica, and Mylan have conceded infringement but assert, along with Torrent, that the '437 patent is invalid for obviousness. The trial of this matter proceeded in essentially two parts. The first

part of the trial was directed to Plaintiffs' infringement claims against Torrent. The second part of the trial was directed to Defendants' defense of invalidity based upon obviousness.

B. Witnesses at Trial

During the 12-day bench trial, all parties were provided the opportunity to present evidence. On the claim of infringement against Torrent, AstraZeneca called two witnesses, both expert witnesses: Dr. Martyn Davies (Bench Trial Transcript ("Tr.") at 24-41), an expert in pharmaceutical delivery systems including sustained release formulations; and Dr. Robert Prud'homme (Tr. at 42-125), an expert in gels, pharmaceutical formulation and drug delivery. AstraZeneca also presented the video deposition testimony of William Blakemore, the 30(b)(6) witness for FMC Corporation, the manufacturer of the sustained release ingredient in Torrent's ANDA product.

In response, Torrent proffered two fact witnesses on the issue of infringement: Kamesh Venugopal (Tr. at 176-198), president of Torrent's U.S. subsidiary, and Rajiv Shah (Tr. at 199-275), director of the patent department at Torrent. Torrent also presented testimony by video deposition of Mr. Blakemore.

On the issue of obviousness, Defendants called two witnesses for their case-in-chief, Dr. Niham Park (Tr. at 375-570), an expert in the area of pharmaceutical formulation and drug delivery and, particularly, in formulating sustained release solid oral dosage form using hydroxypropyl methylcellulose; and Dr. Lee Kirsch (Tr. at 572-706), an expert in the field of formulation development and pharmaceutical delivery system including sustained release formulations.

AstraZeneca responded to Defendants' obviousness case with the following seven witnesses, five of whom were expert witnesses and two of whom are fact witnesses: David

DiCicco (Tr. at 746-787), President of Acumen Research and a specialist in marketing research for pharmaceuticals; Dr. Stuart Montgomery (Tr. at 787-898), an expert and practicing psychiatrist and a researcher in psychiatric illnesses; Dr. Philip Seeman (Tr. at 947-1044), an expert in neuropsychopharmacology with particular emphasis in antipsychotic drugs and how they affect the dopamine d2 receptor; Henry Grabowski (Tr. at 1045-1199), an expert in the economics of pharmaceutical industry; Dr. Joseph Calabrese (Tr. at 1201-1390), an expert in the clinical development of treatment options for psychotic diseases and in the use of quetiapine containing drug products in the treatment of those diseases; Dr. Prud'homme (Tr. at 1391-1500); and Sandford Sommer (Tr. at 1537-1610), Executive Director of Commercial Operations for AstraZeneca's Seroquel IR and XR business.

In rebuttal, Defendants called three expert witnesses: Dr. Robert Mark Hamer (Tr. at 1614-1666), an expert in biostatistics, clinical trial methodology and research methodology; Dr. Christopher Reist (Tr. at 1697-1819), an expert in the area of the treatment of psychiatric patients, including patients that need antipsychotic medication; and Harry Boghigian (Tr. at 1848-1952), an expert in the areas of commercialization,[2] marketing and lifecycle management of pharmaceutical drug products.

The testimony of a number of witnesses was also submitted by both Plaintiffs and Defendants on the question of obviousness through deposition testimony. Defendants submitted deposition testimony of the following witnesses:

Dr. William Addicks, a former AstraZeneca employee, is one of the inventors of the '437 patent. Dr. Addicks testified about AstraZeneca's development of a sustained release quetiapine formulation.

[2] In this context, "commercialization" is limited to marketing and sales.

Dr. Glenn Meyer is the Chief Scientific Officer of Osmotica. Dr. Meyer testified about Osmotica's work in developing a sustained release form of quetiapine.

Dr. Jamie Mullen, a psychiatrist, is an AstraZeneca employee. Dr. Mullen testified about AstraZeneca's clinical trials relating to its sustained release quetiapine formulations.

Dr. Svante Nyberg, a psychiatrist and AstraZeneca employee, has conducted extensive research on the effect of Seroquel IR and Seroquel XR at various receptors in the brain. Defendants rely on Dr. Nyberg's testimony about dosing regimens.

Dr. Bhavnish Parikh, a former AstraZeneca employee, is one of the inventors of the '437 patent. Dr. Parikh testified about work at AstraZeneca on sustained release quetiapine formulations.

Dr. Steven Potkin is a physician who participated in clinical trials of Seroquel IR and Seroquel XR.

Dr. Robert Sepelyak is an AstraZeneca employee who testified as a Rule 30(b)(6) witness about AstraZeneca's research work on sustained release quetiapine formulations.

Dr. Robert Timko, an AstraZeneca employee, is one of the inventors of the '437 patent. Dr. Timko testified regarding AstraZeneca's work on sustained release quetiapine formulations.

Dr. Martin Deberardinis is an AstraZeneca employee who testified about AstraZeneca's work on sustained release quetiapine.

Mr. Marcelo Ricci is Vice President of Product Development of Osmotica Pharmaceutical Argentina. Mr. Ricci testified about Osmotica's work on sustained release quetiapine formulations.

Plaintiffs presented deposition testimony of the following witnesses:

Mr. Daragh Bradley was an employee of Biovail Technologies (Ireland) Ltd., an affiliate of former defendants Biovail Laboratories International SRL, Biovail Corporation, and BTA Pharmaceuticals, Inc. ("Biovail").[3] Mr. Bradley worked on Biovail's quetiapine fumarate sustained release formulation project. Mr. Bradley testified that quetiapine has pH-dependent solubility, and that this characteristic is a complicating factor in formulating a drug for sustained release.

Mr. James Dunne was also an employee of Biovail. He worked on Biovail's quetiapine fumarate sustained release formulation project and testified that "dose dumping" is a concern when formulating a sustained release dosage form.

Mr. Graham Jackson is an employee of Biovail. Mr. Jackson testified as a 30(b)(6) witness on behalf of Biovail and was the lead formulator in Biovail's quetiapine fumarate sustained release formulation project. Mr. Jackson testified regarding the challenge of formulating a sustained release drug with pH-dependent solubility.

Dr. Jonathan Embleton is an employee of Catalent Pharma Solutions LLC ("Catalent"), a collaborator of Handa Pharmaceuticals, LLC ("Handa")[4] in developing its proposed sustained release quetiapine products. Dr. Embleton was designated by Catalent, and testified under Rule 30(b)(6), regarding the advantages to patients of Seroquel XR over the immediate release version.

Dr. Fang-Yi Liu testified as a 30(b)(6) witness on behalf of Handa, where he is president and CEO. Dr. Liu testified that formulation science is unpredictable, and he explained the need to perform experimentation before assessing whether something will work.

[3] Biovail is a defendant in a related civil action brought by AstraZeneca that was dismissed prior to the conclusion of trial.

[4] Handa is a defendant in a related civil action brought by AstraZeneca that was dismissed prior to the conclusion of trial.

Mr. Howard Martin testified as a 30(b)(6) witness on behalf of Mylan regarding the expected market performance of Seroquel XR and Mylan's proposed generic version. Mr. Martin testified that Mylan forecasted significant growth in the market for Seroquel XR.

Dr. Svante Nyberg, a psychiatrist and AstraZeneca employee, is discussed above.

With respect to the witnesses testifying live at trial, having had had the opportunity to observe their demeanor and hear their testimony, the Court has made certain credibility determinations as well as determinations relating to the appropriate weight to accord various testimony. Such determinations are set forth *infra* where relevant.

## III. FINDINGS OF FACT AND CONCLUSIONS OF LAW

### A. Nature of Case[5]

The present actions are for patent infringement under 35 U.S.C. § 271(e)(2)(A) and the Hatch-Waxman Act, codified in part at 21 U.S.C. § 355(j). AstraZeneca Pharmaceuticals LP sells quetiapine fumarate sustained-release tablets as described in New Drug Application ("NDA") 22-047 under the trade name Seroquel XR. The U.S. Food and Drug Administration's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (known as the "Orange Book"), identifies U.S. Patent No. 5,948,437 (the " '437 patent"), which is entitled "Pharmaceutical Compositions Using Thiazepine", in connection with NDA 22-047.

The United States Patent Office ("USPTO") issued the '437 patent on September 7, 1999. According to the Orange Book, the expiration date of the '437 patent is May 28, 2017. The '437 patent claims sustained release formulations of the antipsychotic compound quetiapine and a method for treating psychotic states or hyperactivity by administering an

[5] These facts recited in this section have been stipulated by the parties in the Stipulated Facts ("Stip.") filed at Docket Entry No. 156 unless otherwise indicated by citation to a different source.

effective amount of the claimed formulations. The patent contains 15 claims, and claims 1 through 13 are asserted in this action.

AZLP is the holder of NDA No. 22-047, by which the FDA first granted approval for sustained release tablets containing the active ingredient 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl] dibenzo [b,f][1,4] thiazepine (known as "quetiapine") in the form of its pharmaceutically acceptable hemifumarate salt ("quetiapine fumarate"). AZUK is the owner by assignment of the '437 patent.

The FDA approved sustained release quetiapine fumarate tablets for the treatment of schizophrenia in May 2007. AstraZeneca began selling those tablets under the name Seroquel XR in or about August 2007. AstraZeneca sells its Seroquel XR extended release quetiapine fumarate product in five dosage strengths: 50 mg, 150 mg, 200 mg, 300 mg and 400 mg. Each dosage strength is sold in the form of a tablet, which is a solid oral dosage form. Seroquel XR has been approved by the FDA for the treatment of a number of conditions, specifically, schizophrenia; the acute treatment of manic or mixed episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex; the acute treatment of depressive episodes associated with bipolar disorder; the maintenance treatment of bipolar I disorder as an adjunct to lithium or divalproex; and the adjunctive treatment of major depressive disorder ("MDD"). Quetiapine fumarate is the active pharmaceutical ingredient ("API"), in Seroquel XR. Seroquel XR is formulated to be administered once-a-day.

Defendants Anchen, Torrent, Osmotica and Mylan each filed an ANDA with the FDA seeking approval to commercially sell quetiapine fumarate extended release tablets prior to the expiration of the '437 patent. Each ANDA included a certification with respect to the

’437 patent pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (known as a “Paragraph IV Certification”) that, in the opinion of the defendant, the ’437 patent will not be infringed by the product that is the subject of the ANDA or is invalid.

**B. The ‘437 Patent[6]**

The ’437 patent issued from an application (No. 08/864,306) filed with the USPTO on May 28, 1997, naming as inventors Bhavnish Vinod Parikh, Robert Joseph Timko and William Joseph Addicks (“the ’437 patent application”). The ’437 patent application as filed in the USPTO contained 15 claims. Those claims issued unchanged as claims 1-15 of the ’437 patent.

Claim 1 of the ’437 patent reads as follows: “A sustained release formulation comprising a gelling agent and 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients.”

The term “a sustained release formulation” in claim 1 has been construed by the Court to mean “[a] solid oral dosage form that releases its active pharmaceutical ingredient over an extended period of time.” The term “gelling agent” in claim 1 has been construed by the Court to mean “any substance which forms a gel when in contact with water.” The parties agree that the term “excipient” in claim 1 means “any substance other than an active pharmaceutical ingredient.”

Claim 2 of the ’437 patent reads as follows: “A sustained release formulation according to claim 1 wherein the gelling agent is hydroxypropyl methylcellulose.” Hydroxypropyl methylcellulose is commonly referred to as “HPMC.” As noted in the patent,

[6] These facts recited in this section have been stipulated by the parties in the Stipulated Facts filed at Docket Entry No. 156 unless otherwise indicated by citation to a different source.

HPMC is commercially available under several trademarks, *e.g.* Methocel E, F, J, and K from the Dow Chemical Company, U.S.A. and Metalose SH from Shin-Etsu, Ltd. Japan. JTX-1, col. 3, lines 3-5.

Claim 3 of the ’437 patent reads as follows:

> A sustained release formulation according to claim 2 comprising about 5 to 50% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a) a hydroxypropyl methylcellulose having a viscosity of about 40 to 60 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of from about 7 to less than 9% by weight, (b) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of about 7 to 12% by weight, (c) a hydroxypropyl methylcellulose having a viscosity of about 80 to 120 cps, a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of from about 7 to less than 9% by weight and (d) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of about 7 to 12% by weight, or mixtures thereof; with the proviso that if the formulation contains a hydroxypropyl methylcellulose described under (d) above the total amount of hydroxypropyl methylcellulose present in the formulation must be greater than 25.8% by weight.

Claim 4 of the ’437 patent reads as follows: “A sustained release formulation according to claim 3 comprising about 5 to 40% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a) – (d) or mixtures thereof.”

Claim 5 of the ’437 patent reads as follows: “A sustained release formulation according to claim 4 comprising about 8 to 35% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a) – (d) or mixtures thereof.”

Claim 6 of the ’437 patent reads as follows: “A formulation according to claim 5 comprising about 10 to 30% by weight of a hydroxypropyl methylcellulose selected from the groups (a) – (d) or mixtures thereof.”

Claim 7 of the ’437 patent reads as follows: “A formulation according to claim 6 comprising about 15 to 30% by weight of a hydroxypropyl methylcellulose selected from the groups (a) – (d) or mixtures thereof.”

Claim 8 of the ’437 patent reads as follows: “A formulation according to claim 7 wherein the one or more pharmaceutically acceptable excipients are selected from the group consisting of microcrystalline cellulose, lactose, magnesium stearate, sodium citrate and povidone.”

Claim 9 of the ’437 patent reads as follows:

> A formulation according to claim 8 wherein the one or more pharmaceutically acceptable excipients are selected from the group consisting of (a) about 4 to 20% by weight of microcrystalline cellulose, (b) about 5 to 20% by weight of lactose, (c) about 1 to 3% by weight of magnesium stearate, (d) about 10 to 30% by weight of sodium citrate and (e) about 1 to 15% by weight of povidone.

Claim 10 of the ’437 patent reads as follows: “A formulation according to claim 1 wherein [quetiapine] is in the form of a hemifumarate salt.”

Claim 11 of the ’437 patent reads as follows: “A formulation according to claim 1 wherein one of the one or more pharmaceutically acceptable excipients is a pH modifier.” The term “a pH modifier” in claim 11 has been construed by the Court to mean “one or more excipients capable of changing pH.”

Claim 12 of the ’437 patent reads as follows: “A formulation according to claim 11 wherein the pH modifier is sodium citrate.”

Claim 13 of the ’437 patent reads as follows: “A method of treating psychotic states or hyperactivity in a warmblooded animal which comprises administering to said warmblooded animal an effective amount of a formulation according to [any one] of claims 1-12.” The

parties agree that the terms "treating," "psychotic states," and "an effective amount" in claim 13 have their plain and ordinary meaning.

**C. Prosecution History of '437 Patent**

In the '437 patent application, the applicants informed the USPTO that, in the treatment of a number of diseases, it is desirable to provide the active pharmaceutical ingredient in a sustained release form, and that, desirably, the sustained release provides a generally uniform and constant rate of release over an extended period of time. According to the '437 patent application, this achieves a stable and desired blood plasma level of the active ingredient "without the need for frequent administration of the medicaments." JTX-2 at 10. The applicants also informed the USPTO that there are "numerous" sustained release formulations known in the art that use gelling agents such as HPMC, but that "it has been found to be difficult to formulate sustained release formulations of soluble medicaments and gelling agents, such as [HPMC], for several reasons." JTX-2 at 10.

In a paper filed in the USPTO on September 2, 1997, the applicants identified 47 prior art references for the USPTO Examiner. Those references were listed on a form called "Form PTO-1449." Applicants also provided a copy of those prior art references for the USPTO Examiner. JTX-2 at 78-83. On March 9, 1998, the Examiner in charge of the '437 patent application placed his initials next to 46 of the 47 prior art references cited by applicants, indicating that he considered those references. JTX-2 at 80-83. These prior art references considered by the USPTO Examiner during the prosecution of the '437 patent application are listed on the face of the '437 patent. JTX-1.

On April 1, 1998, the USPTO issued an Office Action, rejecting all 15 claims of the application for obviousness over the '288 patent and acknowledging receipt of the applicant's

Form PTO-1449. JTX-2 at 85-86. On October 5, 1998, the applicant responded to the Office Action. JTX-2 at 100-102. In its Response, the applicant acknowledged that the U.S. Patent No. 4,879,288, entitled "Novel Dibenzothiazepine Antipsychotic" ("the '288 patent")[7] discloses pharmaceutical compositions containing quetiapine. But, the applicant argued that one skilled in the art would not have been motivated by the '288 patent (referred to by the applicant as "Warawa") to prepare the claimed sustained release formulations. In particular, the applicant argued as follows:

> The Examiner has not identified any motivation in Warawa to modify the compositions disclosed therein and prepare the sustained release formulations recited by the instant claims. Warawa does not specifically disclose a sustained release formulation. Additionally, there is no suggestion in Warawa that it would be beneficial to administer the compounds disclosed therein in a sustained release formulation. In fact, Warawa does not disclose any pharmacokinetic data for the compounds disclosed therein. Thus, one skilled in the art would not be motivated by Warawa to prepare the instantly claimed sustained release formulation.

JTX-2 at 101.

The applicant also argued that there was nothing in the '288 patent that would have provided a POSA with a reasonable expectation that a sustained release formulation of quetiapine successfully could be prepared. In particular, the applicant argued as follows:

> Secondly, the Examiner has not identified anything in Warawa that would have provided one skilled in the art with a reasonable expectation that the instantly claimed sustained release formulation could have been prepared. As disclosed in the instant specification at page 1, lines 13-28, it has generally been found to be difficult to formulate sustained release formulations of soluble medicaments and gelling agents. The Examiner has not identified any suggestion in Warawa that the instantly claimed sustained release formulations could successfully have been prepared.

[7] AZLP is the owner of the '288 patent (JTX-423), which was issued by the U.S. Patent and Trademark Office on November 7, 1989. The '288 patent expired on September 26, 2011. It claims, *inter alia*, quetiapine fumarate, the pharmaceutically active ingredient in Seroquel XR. The '288 patent is no longer at issue in these actions. Stip. Fact 4, 5, 95.

JTX-2 at 101.

Following the October 5, 1998 Response, the Examiner allowed all 15 claims, and the '437 patent issued on September 7, 1999. JTX-2 at 105-106; JTX-1 at 1.

**D. The Proposed ANDA Products[8]**

The proposed ANDA products of all of the defendants are tablets (*i.e.*, solid oral dosage forms). All contain quetiapine as the pharmaceutically active ingredient, in the form of quetiapine hemifumarate, a pharmaceutically acceptable salt of quetiapine. All release quetiapine over an extended period of time. All contain pharmaceutically acceptable excipients.

The proposed ANDA products of Anchen, Osmotica and Mylan Pharms contain HPMC, the preferred gelling agent of the '437 patent. Anchen, Mylan and Osmotica have not contested that their proposed ANDA products would infringe various claims of the '437 patent if those claims are not found to be invalid.

Torrent seeks approval to commercially market generic quetiapine fumarate sustained release tablets in 50, 150, 200, 300 and 400 mg dosage strengths. Torrent's proposed ANDA product does not contain HPMC as the sustained release agent, but rather contains an ingredient called "carageenan lambda." Torrent obtains the carageenan lambda used in its proposed ANDA products from FMC Corporation, and the particular carageenan lambda in Torrent's product is FMC's Viscarin GP 209 NF ("Viscarin 209"). Torrent's proposed ANDA products contains about 25-30% by weight of Viscarin 209, JTX-88 at 3; PTX-1175; Tr. 90:9-17; Tr. 254:19-21, and contain divalent magnesium cations, Tr. 92:22-93:6, 94:3-11.

[8] These facts recited in this section have been stipulated by the parties in the Stipulated Facts filed at Docket Entry No. 156 unless otherwise indicated by citation to a different source.

It is undisputed that Torrent uses Viscarin 209 in its ANDA products to cause the sustained release of quetiapine. *See* Torrent Amended Proposed Findings at Finding 1.

As discussed in more detail below, Torrent has argued that given its use of Viscarin 209 in its ANDA products as the sustained release agent, its products do not meet the limitations of and therefore do not infringe claim 1 or claim 2 of '437 patent. However, Torrent concedes that if the Court finds that Torrent infringes claim 1 or claim 2, then claims 10, 11 and 13 are also infringed. Tr. 71:14-16.

**E. Infringement**

Plaintiffs contend that Torrent's ANDA products literally infringe claims 1, 10, and 11, infringe claim 2 under the doctrine of equivalents, and that Torrent would induce infringement of the method of claim 13 of the '437 patent.

1. Burden of Proof and Legal Standards

Plaintiffs have the burden of proving Torrent's infringement of the '437 patent by a preponderance of the evidence. *Carroll Touch Inc. v. Electro Mechanical Systems, Inc.*, 15 F.3d 1573, 1578 (Fed. Cir. 1993). It is an act of infringement to submit an application under § 505(j) of the Federal Food, Drug, and Cosmetic Act (*i.e.*, 21 U.S.C. § 355(j)) for a drug claimed in a patent or the use of which is claimed in a patent, if the purpose of such submission is to obtain approval to engage in the commercial manufacture, use, or sale of that same drug before the expiration of such patent. *See* 35 U.S.C. § 271(e)(2)(A); *see also Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1346 (Fed. Cir. 2000) ("[M]ere act of filing an ANDA constitutes infringement."). The question under 35 U.S.C. § 271(e)(2)(A) is whether the drug that is the subject of the ANDA will infringe the patent when approved and marketed. *See Bristol-Myers Squibb Co. v. Royce Labs., Inc.*, 69

F.3d 1130, 1135 (Fed. Cir. 1995). Thus, to meet its preponderance of the evidence burden, the patentee must show that it is more likely than not that the proposed ANDA product would, if commercially marketed, meet the claim limitations of the patent-in-suit. *See Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1287 (Fed. Cir. 2010); *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1341 n.15 (Fed. Cir. 2005).

The infringement analysis proceeds in two steps—the first is proper construction of the relevant claims, and the second is a comparison of those claims to the accused product or method. *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1288 (Fed. Cir. 2009). To prove infringement, the patentee must show that an accused product or method is within the claim limitations of the patent-in-suit either literally or under the doctrine of equivalents. *See Amgen*, 580 F.3d at 1374; *Warner Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 21 (1997). "A patent is infringed if any claim is infringed … for each claim is a separate statement of the patented invention." *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1220 (Fed. Cir. 1995). Infringement, whether literal or under the doctrine of equivalents, is a question of fact. *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

*a. Literal Infringement*

Literal infringement exists if any one of a patent's asserted claims covers the alleged infringer's product or process. *See Markman v. Westview Instr.*, 517 U.S. 370, 374 (1996). Literal infringement is shown where each limitation of at least one asserted claim of the patent-in-suit is found in the alleged infringer's product or process. *See Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1562 (Fed. Cir. 1990); *Panduit Corp. v. Dennison Mfg. Co., Inc.*, 836 F.2d 1329, 1330 n.1 (Fed. Cir. 1987). Proof of literal infringement may be based on direct or circumstantial evidence. *See Martek Biosciences*

*Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009) ("A patentee may prove infringement by any method of analysis that is probative of the fact of infringement … and circumstantial evidence may be sufficient ….") (citations and internal quotes omitted).

*b. Doctrine of Equivalents*

Under the doctrine of equivalents, an accused product or process "that does not literally infringe upon the express terms of a patent claim may nonetheless be found to infringe if there is 'equivalence' between the elements of the accused product or process and the claimed elements of the patented invention." *Warner Jenkinson*, 520 U.S. at 21 (quoting *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 609 (1950)). "Infringement under the doctrine of equivalents requires that the accused product contain each limitation of the claim or its equivalent." *AquaTex Indus., Inc. v. Techniche Solutions*, 419 F.3d 1374, 1382 (Fed. Cir. 2005). An element of an accused product is equivalent to a claim limitation if the differences between the two are insubstantial, a question that turns on whether the element of the accused product "performs substantially the same function in substantially the same way to obtain the same result" as the claim limitation. *Absolute Software, Inc. v. Stealth Signal, Inc.*, 659 F.3d 1121, 1139-40 (Fed. Cir. 2011) (quoting *AquaTex*, 419 F.3d at 1382).) Infringement under the doctrine of equivalents thus exists where the differences between the patented invention and the accused product or process are insubstantial. *See Festo*, 535 U.S. at 733 ("The doctrine of equivalents allows the patentee to claim those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes."); *Hilton Davis Chem. Co. v. Warner-Jenkinson Co., Inc.*, 62 F.3d 1512, 1517 (Fed. Cir. 1995) (en banc), *rev'd on other grounds*, 520 U.S. 17 (1997).

The doctrine of equivalents prevents an accused infringer from avoiding liability for infringement where its product has insubstantial or minor differences from the claimed invention, while retaining the invention's essential identity. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 234 F.3d 558, 564 (Fed. Cir. 2000), *overruled on other grounds*, 535 U.S. 722 (2002). The Federal Circuit has ruled that "to permit imitation of a patented invention which does not copy every literal detail would be to convert the protection of the patent grant into a hollow and useless thing." *Toro Co. v. White Consolidated Indus., Inc.*, 266 F.3d 1367, 1370 (Fed. Cir. 2001).

One test often used to assess the substantiality of the differences under the doctrine of equivalents is the "function-way-result" test. This analysis "asks whether an element of an accused product 'performs substantially the same function in substantially the same way to obtain the same result' as an element of the patented invention." *American Calcar, Inc. v. American Honda Motor Co., Inc.*, 651 F.3d 1318, 1338 (Fed. Cir. 2011).

Proof of equivalency can be made in any form: "through testimony of experts or others versed in the technology; by documents, including texts and treatises; and, of course, by the disclosures of the prior art." *Hilton Davis*, 62 F.3d at 1520 (quoting *Graver Tank*, 339 U.S. at 609). The Federal Circuit has noted that to support a finding under the doctrine of equivalents

> a patentee must ... provide particularized testimony and linking argument as to the 'insubstantiality of the differences' between the claimed invention and the accused device or process, or with respect to the function, way, result test when such evidence is presented to support a finding of infringement under the doctrine of equivalents. Such evidence must be presented on a limitation-by-limitation basis.

*Texas Instruments, Inc. v. Cypress Semiconductor Corp.*, 90 F.3d 1558, 1567 (Fed. Cir. 1996); *see also American Calcar*, 651 F.3d 1338-39.

2. Anchen, Mylan and Osmotica

Anchen and Mylan concede infringement of claims 1-13 of the '437 patent if these claims are found to be valid. Stip. Fact 75-76. Similarly, Osmotica concedes infringement of claims 1-2 and 10-12 if these claims are found to be valid. Stip. Fact 82.

3. Torrent

The only infringement claim addressed during the October trial was that against Torrent, and the questions to be resolved at trial related to the infringement claim against Torrent were fairly limited. Specifically, the questions addressed were (1) whether the ingredient in Torrent's ANDA product that causes the sustained release, namely FMC's Viscarin 209, is a "gelling agent" within the meaning of claim 1 of the '437 patent; and (2) whether Viscarin 209 is the equivalent of the gelling agent recited in claim 2. The Court addresses each of these in turn. As set forth below, the Court finds that the Viscarin 209 used in Torrent's ANDA product to cause the sustained release is a "gelling agent" as that term is used in claim 1. The Court also finds that Viscarin 209 is the equivalent of the gelling agent recited in claim 2.

*a. Whether Viscarin 209 is a "gelling agent" within the meaning of claim 1*

This Court has construed "gelling agent" in claim 1 of the '437 patent to mean "any substance which forms a gel when in contact with water." *See* Opinion at Docket Entry 69 in Civil Action No. 10-1835. Thus, the precise question before the Court is whether Viscarin 209, as it is used in Torrent's ANDA products, forms a gel when it come into contact with water. If so, Torrent's ANDA products infringe claim 1 of the '437 patent.

Viscarin 209 is made up of different types of carrageenans. Carrageenan is a naturally-occurring hydrophilic polymer that hydrates and swells in the presence of water. Tr. 78:22-79:4, 79:20-25; JTX-10 at 3. There are three main types of commercially important carrageenans: kappa, iota and lambda. All three types hydrate and swell in the presence of water, but they have different abilities to form a gel in the presence of water. Kappa-type carrageenan forms a gel more easily than iota-type carrageenan, and iota forms a gel more easily than lambda-type carrageenan. Tr. 78:25-80:18; JTX-10 at 10.

Viscarin 209 is a mixture of these three types of carrageenans. Tr. 82:23-24. Viscarin GP209 is approximately 40% kappa type, 30% iota type, and 30% lambda type. Tr. 83:5-84:4. FMC considers Viscarin GP209 to be a mixture of 70% kappa type related (*i.e.*, kappa type and iota type) and 30% lambda type related. Blakemore Dep. 31:14-21; JTX-12 at 1. The Viscarin 209 in Torrent's proposed ANDA products hydrates in the presents of water. Tr. 255:25 to 256:2.

FMC promotes Viscarin 209 as a non-gelling carrageenan that is useful for a variety of applications including "cream, lotion, suspension, controlled release, taste masking, and film forming applications." JTX 10 at 2. According to FMC's literature, different concentrations of Viscarin 209 are used for different applications. For example, high viscosity solutions useful in preparing creams and lotions are produced when levels of 0.1% to 1.0% are produced. JTX 10 at 2, 33. Controlled release applications, however, use higher concentrations ranging from 10% to 100%. JTX 10 at 31. According to an FMC presentation regarding the use of FMC products in controlled release formulations, Viscarin 209 can be used to form a viscous barrier in a pharmaceutical tablet to obtain sustained release of the drug. JTX 15 at 12-13.

In support of its argument that Viscarin 209 forms a gel when it comes into contact with water, AstraZeneca presented testimony from two experts at trial. Dr. Davies testified that tests performed by him on the Viscarin 209 ingredient in Torrent's proposed ANDA product demonstrated that Viscarin 209 forms a gel when it comes in contact with water. In particular, Dr. Davies performed a test used by FMC for measuring the "gel strength" (the "Gel Strength Test") of Viscarin 209. *See* JTX 12; JTX 244 (describing test). This is a test performed by FMC as part of its quality control procedure that measures the "gel strength" of Viscarin 209 in order to confirm that the product has the correct proportion of the different carrageenans that make up the product. Tr. 85:11-18; JTX 244; Tr. 86: 4-9; JTX 12. The Gel Strength Test measures the ability of Viscarin 209 to form a gel when present in an amount of 1.4% in a solution containing 98% water and 0.6% potassium chloride. In performing this test, a plunger is pushed into the test material and the force necessary for the plunger to enter the material (*i.e.*, the "break force strength") is the measure of the gel strength of the material. Tr. 30:22-24; 85:19-86:3; Blakemore Dep. 59:11-22; JTX 12. This is the only test used by FMC for testing the gel strength of Viscarin 209. Blakemore Dep. 45:17-24.

According to an FMC email dated September 17, 2010, when tested, Viscarin 209 typically exhibits a break force strength of 20-50g. JTX 12. The email states that this figure "is significantly lower than what would be obtained with strong gelling carrageenans such as kappa type." *Id.* at 1. However, according to Plaintiffs' expert Dr. Prud'homme, if there is any measured break force strength it means a gel was formed. Tr. 87:10 to 88:5. Indeed, FMC's representative testified that, under the conditions of the Gel Strength Test, Viscarin 209 forms a gel, albeit a weak one. Blakemore Dep. 43:18-23.

In the September email, FMC advised that it may be possible for FMC to develop a product that would exhibit a break force strength of 0g in the Gel Strength Test. JTX 12 at 1. However, there is no evidence that Torrent sought such a specially-designed product from FMC. *See* Blakemore Dep. 44:13 to 45:5.

Plaintiffs' expert Dr. Davies performed FMC's Gel Strength Test on Visacrin 209, and he concluded that Viscarin 209 forms a gel when tested. Tr. 31:15 to 32:2. JTX 12. Dr. Davies replicated the Gel Strength Test with a single exception. Tr. 31:15 to 32:18. The only exception was that, instead of measuring the actual gel strength of the resulting material using a plunger, Dr. Davies placed a coin on the surface of the material, and the material supported the coin. *Id.* Based on his testing, Dr. Davies concluded that Viscarin 209 formed a gel when in contact with water. Tr. 33:22 to 34:1.

Dr. Davies photographed the results of his experiment. *See* JTX 245; JTX 246. The photographs show two crystallizing dishes, one containing plain water and the other containing the sample of Viscarin 209 prepared using the procedures outlined for the Gel Strength Test. *Id.*; Tr. 32:21 to 33:5. Dr. Davies placed a coin (a British penny) in each of the dishes. Tr. 33:14-18. As seen in photographs, the penny sinks to the bottom of the dish containing the water (as one would expect). However, in the second dish, the coin is supported on the top of the Viscarin 209 sample. Dr. Prud'homme testified that the photographs "show[] …the formation of a gel." Tr. 89:15-20.

According to FMC's Blakemore, increasing the concentration of Viscarin 209 above 1.4% in the Gel Strength Test would be expected to increase the gel strength. Blakemore Dep. 60:4-8, 60:24-61:17. This is consistent with the testimony of Dr. Prud'homme, who testified that the concentration of carrageenan impacts the ability of the carrageenan to gel.

Tr. 82:3-18 . Torrent's proposed ANDA products contain approximately 25-30% by weight of Viscarin 209, many times the concentration used in the Gel Strength Test. According to Dr. Prud'homme, that 25-30% of Viscarin 209 would be expected to produce an "exceedingly strong" gel. JTX-88 at 3; PTX-1175; Prud'homme Tr. 90:9-17, 90:25-91:19.

Furthermore, Torrent's ANDA products contain divalent magnesium cations, as they contain magnesium oxide as a pH modifier. Tr. 92:22-93:6; Torrent Request for Admissions Response 27, 28. The addition of divalent cations to formulations containing Viscarin 209 would be expected to result in stronger gels being formed. Tr. 92:22-93:6, 94:3-11; Blakemore Dep. 61:18-22, 62:2-18, 63:17-64:7. The fact that the FMC Gel Strength Test uses potassium cations and Torrent's accused ANDA products contain magnesium cations does not affect the opinion of Dr. Prud'homme that Viscarin 209 forms a gel when in contact with water. Tr. 92:11-93:18.

In defense of the infringement claims, Torrent points to evidence showing that Viscarin 209 is promoted by FMC as a non-gelling carrageenan. For example, an FMC product brochure describes the product as a "non-gelling carrageenan … [that] can be used in cream, lotion, suspension, controlled release, taste masking and film formation application. JTX 10 at 2. An FMC presentation on controlled release formulation describes the "gel texture" of Viscarin 209 as "no gel." JTX 15 at 15. ,FMC's Blakemore testified that "under normal circumstances [Viscarin] 209 does not gel." Blakemore Dep. 58:25 to 59:3. However, Blakemore also testified that "normal usage" of Viscarin 209 is an amount "up to about 1 percent." Blakemore Dep. 42:18-19, and At higher concentrations, according to Blakemore, Viscarin 209 will form a gel. Blakemore Dep. 59:3-7.

Further, while it is true that the FMC presentation entitled "FMC Pharmaceutical Carrageenans" cited by Torrent reports the texture of Viscarin 209 to be "viscous,' it does not say that the product cannot not form a gel in water. JTX 16 at 27. Similarly, the FMC marketing document entitled Marine Colloid Carrageenan simply reports that lambda carrageenan is "less likely to form a gel structure" than other carrageenans, not that it cannot form a gel under any circumstances. DTX 2038 at 5.

Weighing the evidence presented at trial, the Court concludes that the Viscarin 209 product as used in Torrent's ANDA product forms a gel when in contact with water and is a gelling agent according to the '437 patent. In reaching that conclusion, the Court has given substantial weight to the testimony of Drs. Prud'homme and Davies based upon their expertise and experience, as well as the overall credibility of their testimony. The Court finds that Torrent literally infringes claims 1, 10, and 11.

*b. Whether Viscarin 209 is the equivalent of the gelling agent recited in claim 2*

The Court also concludes that Torrent infringes claim 2 under the doctrine of equivalents. The Viscarin GP209 ingredient in Torrent's proposed ANDA products works in substantially the same way as HPMC does in the formulation of '437 patent claim 2. Both provide sustained release by forming a gel layer around the matrix tablet when placed in contact with fluids. JTX-319 at 1-2; Tr. 96:6-97:4, 97:24-98:2; 257:4-12; Blakemore Dep. 82:8-84:17; DTX-2980 at 7.

According to FMC, "[c]arrageenan, (kappa, iota and lambda) has been investigated for use in controlled release tablets" where "release rate can be altered or controlled by using carrageenan use levels from 10-100%." JTX-10 at 31. FMC discloses that "[a]s the compressed tablet comes into contact with the dissolution media, the carrageenan on the

surface will hydrate and create a thin gel layer around the remaining dry tablet." JTX-10 at 31.

The Viscarin GP209 ingredient in Torrent's proposed ANDA products, upon contact with water, forms an outer layer that expands and swells, with the thickness of that layer increasing as the layer expands. Tr. 257:7-12. The Viscarin GP209 ingredient in Torrent's proposed ANDA products achieves substantially the same result as HPMC in the formulation of '437 patent claim 2. PTX-1172 at 68-69 ("pharmacokinetic[s] . . . comparable to that of the reference drug"). Both provide sustained release of quetiapine over time. Prud'homme Tr. 98:3-20; PTX-1172 at 68-69. Consequently, the Court finds that the evidence at trial shows that Viscarin 209 is the equivalent of the gelling agent recited in claim 2.

**F. Obviousness**

Defendants argue that all asserted claims of the '437 patent are invalid under 35 U.S.C. § 103(a) because the differences between the prior art and the patented subject matter are such that the claimed subject matter as a whole would have been obvious to a person of ordinary skill in the art to which that subject matter pertains ("POSA") at the time the invention was made (*i.e.*, May 28, 1997). As discussed in more detail below, in determining obviousness, the Court must evaluate a number of facts, including the level of ordinary skill in the pertinent art, the scope and content of the prior art, the differences between the prior art and the asserted claims, and the extent to which objective evidence of nonobviousness exists. Also, and in accordance with the evidence presented by the parties at trial, the Court must consider whether a person skilled in the art as of May 1997 would have been motivated to develop a sustained release form of quetiapine, would have combined the prior art in the manner suggested by defendants' experts, and would have had a reasonable expectation of

successfully preparing a solid oral dosage form sustained release quetiapine formulation within the scope of the '437 patent claims.

In their case-in-chief, defendants called two experts, Dr. Park and Dr. Kirsch. As noted earlier, Dr. Park was accepted as an expert in the area of pharmaceutical formulation and the drug delivery of freely soluble and freely non-soluble drugs and, in particular, in formulating sustained release solid oral dosage forms using HPMC. Tr. 386:11-19. Dr. Kirsch was accepted as an expert in the field of formulation development and pharmaceutical delivery systems including sustained release formulations. Tr. 578:15-20.

Both Dr. Park and Dr. Kirsch testified about (a) the skills and knowledge possessed by a POSA, (b) whether a POSA as of May 1997 would have been motivated to develop a sustained release form of quetiapine, (c) whether a POSA would have combined the prior art in the manner suggested by defendants' experts, and (d) whether a POSA as of May 1997 would have had a reasonable expectation of being able to successfully make a sustained release formulation of quetiapine within the scope of the patent claims. Dr. Park testified about the obviousness of '437 patent claims 1, 2 and 10-13, and Dr. Kirsch testified about the obviousness of '437 patent claims 3-9 and 13. Neither Dr. Park nor Dr. Kirsch testified about any of the objective evidence of nonobviousness relied on by AstraZeneca.

As noted earlier, in its response case on obviousness, AstraZeneca called five experts, Drs. Montgomery, Seeman, Calabrese, Prud'homme and Grabowski, and two fact witnesses, Messrs. DiCicco and Sommer.

Dr. Montgomery is a practicing psychiatrist from London, England. He was accepted as an expert practicing psychiatrist and researcher in psychiatric illnesses. Tr. 797:8-13. Dr. Montgomery testified that, based on what a POSA knew from the pre-May 1997 literature

describing clinical trials of quetiapine in the treatment of schizophrenia, a POSA as of May 1997 would not have been motivated to prepare or use a sustained release form of quetiapine in the treatment of schizophrenia.

Dr. Seeman, a researcher in antipsychotic drugs at the University of Toronto, who testified live via video link from Toronto, was accepted as an expert in neuropsychopharmacology with particular emphasis in antipsychotic drugs and how they affect the dopamine D2 receptor. Tr. 953:11-17. Dr. Seeman described the dopamine D2 receptor target for antipsychotic drugs, described what was known as of May 1997 about the level of dopamine D2 receptor occupancy required for antipsychotic efficacy, described what was known at that time about the level of dopamine D2 receptor occupancy produced by immediate release quetiapine, and testified that, based on that information, a POSA as of May 1997 would not have been motivated to prepare or use a sustained release form of quetiapine in the treatment of schizophrenia.

Dr. Calabrese, a professor at Case Western Reserve University and a practicing psychiatrist from Cleveland, Ohio, was accepted as an expert in the clinical development of treatment options for psychotic diseases and in the use of quetiapine-containing drug products in the treatment of those diseases. Tr. 1207:5-13. Dr. Calabrese testified about the skills and knowledge possessed by a POSA as of May 1997. He described how physicians treated schizophrenia and bipolar disorder as of May 1997, and he testified that, based on such practices and what was known about quetiapine at that time, a POSA as of May 1997 would not have been motivated to prepare or use a sustained release form of quetiapine to treat those conditions. Dr. Calabrese also testified regarding the unexpected clinical benefits provided by the sustained release formulation of quetiapine described and claimed in the '437 patent.

Dr. Prud'homme testified about the skills and knowledge possessed by a POSA as of May 1997, about how a POSA as of May 1997 would have gone about developing a sustained release pharmaceutical formulation in general, and of quetiapine in particular, and that, based on what was known as of May 1997 about quetiapine and making sustained release pharmaceutical formulations, a POSA as of May 1997 would not have had a reasonable expectation of being able to successfully make a sustained release formulation of quetiapine.

Dr. Grabowski was accepted as an expert in the economics of the pharmaceutical industry. Tr. 1051:10-11; 1053:9-14. He testified that Seroquel XR was a commercial success and that such success was due to the merits of the patented invention and not to factors such as marketing and promotion.

Mr. Sommer, the AstraZeneca employee in charge of its Seroquel XR business, testified about AstraZeneca's sales and marketing of Seroquel XR in support of AstraZeneca's claims of commercial success for that product.

Mr. DiCicco, the President of Acumen Research, a company that performs surveys for the pharmaceutical industry, testified about a survey of physicians he designed and conducted regarding why the physicians prescribe Seroquel XR.

In their rebuttal case, defendants called three experts, Dr. Hamer, Dr. Reist and Mr. Boghigian. Dr. Reist, a practicing psychiatrist from the University of California, Irvine, was accepted as an expert in the treatment of psychiatric patients, including those needing antipsychotic medications. Tr. 1708:23-1709:23. He testified that a POSA would have been motivated to try a sustained release form of quetiapine as of May 1997, and that none of the medical benefits of Seroquel XR was unexpected.

Dr. Hamer was accepted as an expert in biostatistics and clinical trial and research methodologies as they relate to biostatistics. Tr. 1619:19-1620:18. He testified about the requirements of clinical trials.

Mr. Boghigian was accepted as an expert in the marketing and life cycle management of pharmaceutical drug products and the commercialization of pharmaceutical drug products as it relates to marketing and sales. Tr. 1856:2-10, 1851:21-1860:19. He testified that Seroquel XR has not been a commercial success and that any commercial success was not the result of the merits of the invention of the '437 patent but was due to other factors such as marketing and promotion.

1. Burden of Proof

Every claim of an issued patent is independently presumed valid. *See* 35 U.S.C. § 282. Consequently, a party challenging the validity of a patent claim must prove invalidity by clear and convincing evidence, and although the burden of production may switch to the patentee, the burden of proof always remains with the challenger. *See id.*; *Microsoft Corp. v. i4i Ltd. Partnership*, -- U.S. --, 131 S. Ct. 2238, 2243 (2011); *Innovative Scuba Concepts, Inc. v. Feder Indus.*, Inc., 26 F.3d 1112, 1115 (Fed. Cir. 1994). Clear and convincing evidence is a higher burden of proof than preponderance of the evidence. *See Colorado v. New Mexico*, 467 U.S. 310, 316 (1984). It is evidence that places in the mind of the finder of fact an abiding conviction that the truth of the factual contentions is highly probable. *See id.* Clear and convincing evidence should "instantly tilt[] the evidentiary scales" in favor of its proponent when weighed against the opposing evidence.

2. Legal Standard

"A patent may not be obtained … if the differences between the subject

matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious 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). "The [obviousness] analysis is objective" and judged as of the "time the invention was made." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S 398, 406 (2007) (citation omitted).

The ultimate determination of obviousness is a question of law based on underlying factual findings, including the level of ordinary skill in the pertinent art; the scope and content of the prior art; the differences between the claimed invention and the prior art; and objective indicia of nonobviousness, *i.e.*, evidence of factors such as whether the claimed invention is a commercial success, provides unexpected benefits, satisfies a long-felt need, or succeeds where others have failed. *See id*.; *see also Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966) ("[Obviousness] lends itself to several basic factual inquiries. Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined."). While party defending a patent may offer evidence of secondary considerations of nonobviousness, secondary considerations of nonobviousness may not overcome a strong prima facie case of obviousness. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

Importantly, "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR*, 550 U.S. at 427. Where the issue of obviousness is, as here, based on a combination of elements found in the prior art, "the combination must do more than yield a predictable result." *Id.* at 416. In fact, "a combination of familiar elements

according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* This is because "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility." *Id.* at 419. "In other words, obviousness exists when 'a finite, and in the context of the art, small or easily traversed number of options . . . would convince an ordinarily skilled artisan of obviousness.'" *Purdue Pharma Products L.P. v. Par Pharmaceutical, Inc*, 642 F. Supp. 2d 329, 368 (D. Del. 2009) (quoting *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008)).

Prior to *KSR*, the Federal Circuit imposed a rigid "teaching-suggestion-motivation" test for obviousness. Under that test, the patent challenger was required to prove that "some motivation or suggestion to combine the prior art teachings" could be found "in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art." *KSR*, 550 U.S. at 407 (internal citations omitted). The Supreme Court in *KSR* rejected the Federal Circuit's test in favor of a more flexible obviousness standard. The Court held that a patent may be obvious in light of the combination of prior art if the combination was "obvious to try." *Id.* at 421. This more flexible standard expands the obviousness analysis beyond just "published articles and the explicit content of issued patents." *Id.* at 419. Other forces, including forces such as market demand, may also be examined to determine whether it would be obvious to combine more than one known element. *Id.* In broad terms, "any need or problem known in the field of endeavor at the time of the invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. The Federal Circuit has noted that a finding of obviousness under the "obvious to try"

standard "does not require absolute predictability of success ... all that is required is a reasonable expectation of success." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)); *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (same); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[T]he expectation of success need only be reasonable, not absolute" nor "a guarantee.").

In the obviousness analysis, the claimed invention must be viewed in light of the art that existed at the time the invention was made. *See* 35 U.S.C. § 103(a); *Uniroyal*, 837 F.2d at 1050-51. "The term 'prior art' as used in section 103 refers at least to the statutory material named in 35 U.S.C. § 102" that was available to a hypothetical POSA at the time the invention was made. *Riverwood Int'l Corp. v. R.A. Jones & Co., Inc.*, 324 F.3d 1346, 1354 (Fed. Cir. 2003). "To ascertain the scope of the prior art, a court examines the field of the inventor's endeavor and the particular problem with which the inventor was involved." *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998) (citations and internal quotes omitted).

What a reference teaches is a question of fact. *In re Bell*, 991 F.2d 781, 784 (Fed. Cir.1993). The Court should not "analyze each prior art reference in isolation without considering the prior arts' teaching as a whole in light of the creativity and common sense of a person of ordinary skill." *Duramed Pharms., Inc. v. Watson Labs., Inc.*, 2011 WL 1086573, at *4 (Fed. Cir. Mar. 5, 2011). Importantly, the Federal Circuit has admonished against the use of the claimed invention to define the prior art:

> Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness .... By importing the ultimate solution into the problem facing the inventor, the district court adopted an

> overly narrow view of the scope of the prior art. It also infected the district court's determinations about the content of the prior art.

*Monarch Knitting*, 139 F.3d at 881 (citations omitted).

All teachings in the prior art must be considered in the obviousness determination, "including that which might lead away from the claimed invention." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). "[A] reference must be considered as a whole, including the portions that argue against or teach away from the claimed invention." *Armament Sys. & Procedures, Inc. v. Monadnock Lifetime Prods., Inc.*, 1998 WL 537746, at *8 (Fed. Cir. Aug. 7, 1998) (citing *Bausch & Lomb*, 796 F.2d at 448). "Where the prior art contains apparently conflicting teachings (*i.e.*, where some references teach the combination and others teach away from it) each reference must be considered for its power to suggest solutions to an artisan of ordinary skill[,] considering the degree to which one reference might accurately discredit another." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (citation and internal quotes omitted).

Importantly, courts have warned against improperly using hindsight in the obviousness analysis. It is impermissible to use "hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Laboratories*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008); *see also KSR*, 550 U.S. at 421; *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) ("Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field."), *abrogated on*

*other grounds*, *In re Gartside*, 203 F.3d 1305 (Fed. Cir. 2000). "A factfinder should be aware ... of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." *KSR*, 550 U.S. at 421.

Obviousness is determined from the perspective of a hypothetical POSA at the time the invention was made. *See Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 447-48 (Fed. Cir. 1986). This hypothetical person

> is presumed to be aware of all the pertinent art. The actual inventor's skill is irrelevant to this inquiry, and this is for a very important reason. The statutory emphasis is on a person of ordinary skill. Inventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something--call it what you will--which sets them apart from the workers of ordinary skill, and one should not go about determining obviousness under § 103 by inquiring into what patentees (*i.e.*, inventors) would have known or would likely have done, faced with the revelation of references.

*Bausch & Lomb*, 796 F.2d at 448.

The reason that the obviousness analysis is conducted from the perspective of one skilled in the art "is to assure an appropriate perspective of the decisionmaker, and to focus on conditions as they existed when the invention was made." *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 956 (Fed. Cir. 1997). "Good ideas may well appear 'obvious' after they have been disclosed, despite having been previously unrecognized." *Id.* "Because patentability is assessed from the perspective of the hypothetical person of ordinary skill in the art, information regarding the subjective motivations of inventors is not material." *Merck Sharp & Dohme Pharms., SRL v. Teva Pharms. USA, Inc.*, 2009 WL 3153316, at *46 (D.N.J. Aug. 19, 2009) (citations and internal quotes omitted); *see also KSR*, 550 U.S. at 419 ("In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls.").

A POSA may be defined according to several factors, including: "(1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696 (Fed. Cir. 1983). However, the Federal Circuit has made clear that while the educational background of the inventors themselves may be a factor in determining the level of ordinary skill in the art, it is not conclusive. *See Bausch & Lomb*, 796 F.2d at 449-50.

The POSA may be a composite of different types of individuals. *See Medinol Ltd. v. Guidant Corp.*, 341 F. Supp. 2d 301 (S.D.N.Y. 2004) (POSA was "an engineer working with a physician" or a "stent design team"); *Univ. of Rochester v. G.D. Searle & Co.*, 249 F. Supp. 2d 216, 228 n.6 (W.D.N.Y. 2003) (POSA was "a team of scientists, with skills in medicinal chemistry, molecular biology, biochemistry, and pharmacology."). The POSA for a claimed method of treatment may include the skills of a clinician or medical professional. *See, e.g.*, *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 347 F.3d 1367, 1371 (Fed. Cir. 2003) (POSA for a patented method of treating osteoporosis had a medical degree, experience treating patients, and knowledge of pharmacology); *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 2004 WL 1724632, at *33 (S.D. Ind. July 29, 2004) (POSA for a patented method of using fluoxetine to treat premenstrual syndrome was not limited to clinical researchers but included a medical doctor—an OB/GYN, family practice physician, or psychiatrist—who regularly saw and treated patients suffering from PMS and was familiar with the prior art); *Boots Labs., Inc. v. Burroughs Wellcome Co.*, 223 U.S.P.Q. 840, 845, 848 (E.D. Va. 1984) (defining POSA as a chemist or medical doctor with practical experience in testing pharmaceutical

products; crediting testimony of physician, but discounting testimony of biochemist who did not address evidence of medical difficulties involved); *Merck & Co., Inc. v. Danbury Pharmacal, Inc.*, 694 F. Supp. 1, 30 (D. Del. 1988) (for method of using cyclobenzaprine to treat muscle disorders, defining the art as "skeletal muscle relaxants" and the level of ordinary skill to include "some degree of clinical or experimental seasoning to an understanding of the pace of development and sticking points in the art"), *aff'd*, 873 F.2d 1418 (Fed. Cir. 1989)).

In sum, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. However, "[i[f a person of ordinary skill in the art can implement a predictable variation, and would see the benefit of doing so, § 103 likely bars its patentability." *Id.* at 417. In examining these questions, a court must guard against an impermissible reliance on hindsight. As noted above, each fact forming the factual foundation upon which the court bases its ultimate conclusion regarding obviousness must be established by clear and convincing evidence. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 292 (Fed. Cir. 1985).

3. Level of Ordinary Skill in the Art

There appears to be no dispute among the parties that the person of ordinary skill in the art in this case would have had an advanced degree, masters or Ph.D., in biochemistry, chemical engineering, pharmacy or a related field and a few years of practical experience working in the field of sustained release pharmaceutical formulations ("formulation scientist"). Alternately, that person could have had only a bachelors degree but with a greater number of years of relevant experience. Tr. 65:6-19; 389:3-13; 579:12-580:19.

However, the parties disagree about whether the POSA also should include the knowledge and skills of either a physician who treats psychotic disorders in patients with antipsychotic drugs (a "clinician"), or a researcher familiar with the use of antipsychotic drugs in the treatment of psychotic disorders (an "antipsychotic drug researcher"), or both. AstraZeneca contends that, in view of the nature of the subject matter described and claimed in the '437 patent, the POSA includes such a clinician or antipsychotic drug researcher, or would be a formulation scientist who is informed about antipsychotic drugs by such a clinician or researcher. Defendants, contend that the POSA is limited to the formulation scientist.

The patent is clear that the inventions of the '437 patent are not limited merely to sustained release formulations of quetiapine. The disclosed and claimed inventions of the '437 patent also include the use of such formulations in a method for treating patients suffering from psychotic states such as schizophrenia. For example, the '437 patent states as follows:

> As mentioned above, the compound [quetiapine], and its pharmaceutically acceptable salts, exhibit useful antidopaminergic activity and may be used, for example, as an antipsychotic agent (for example, for the management of the manifestations of psychotic disorders) or as a treatment for hyperactivity. Thus, the present invention also provides a method of treating psychotic states, for example psychosis, in a warm-blooded animal, such as man, which comprises administering an effective amount of the formulation of the present invention to said warm-blooded animal.

JTX-1 at 6:15-26. This method of treating aspect of the invention of the '437 patent is reflected in patent claim 13, which discloses "[a] method of treating psychotic states or hyperactivity in a warm-blooded animal which comprises administering to said warm-blooded animal an effective amount of a formulation of [any one] of claims 1-12. JTX-1 at 16:14-17.

As such, the "art" pertinent to the '437 patent includes both the field of antipsychotic drugs and their use in treating patients with psychotic states such as schizophrenia, as well as the field of formulating pharmaceutically active compounds into sustained release formulations. Tr. 55:14-17; 1212:15-22. It seems logical, therefore, that the person of ordinary skill in that art would include persons familiar with both fields. A formulation scientist would be knowledgeable about the field of formulating pharmaceutically active compounds into sustained release formulations. A person familiar with the field of antipsychotic drugs and their use in treating patients with psychotic states such as schizophrenia would include either a clinician or an antipsychotic drug researcher or both. Tr. 1212:23-1213:1, 1213:8-10; *see also* Tr. 66:8-14, 67:12-15, 70:8-12.

Defendants' formulation expert, Dr. Park, when examined on the identity of a POSA, testified that the '437 patent is "all about formulation" and that no clinician is necessary. Tr. 397:16-21. Defendants' other formulation expert, Dr. Kirsch, agreed. Tr. 579:16-21. Both also testified that the presence of method of treatment claim 13 did not affect their opinion that the POSA in this case need not include a clinician. They reasoned that the earlier '288 patent disclosed both the use of quetiapine to treat psychotic states and a range of doses that would be effective (1 to 40 mg per kilogram of body weight). Tr. 544:7-545:22; Tr. 587:23-589:5. For several reasons, set forth *infra*, the Court gives less weight to Dr. Park's and Dr. Kirsch's testimony on the issue of whether a POSA should include a clinician.

As an initial matter, the '437 patent itself states that the effective dose of quetiapine will be determined by a clinician after consideration of many factors. In particular, the '437 patent states as follows:

> The dose of the compound of the present invention which is administered will necessarily be varied according to principles well known in the art taking account of the route of administration, the duration of treatment, the severity of the psychotic condition, the size and age of the patient, the potency of the active component and the patient's response thereto. An effective dosage amount of the active component can thus readily be determined by the clinician after a consideration of all criteria and using his best judgment on the patient's behalf.

JTX-1 at 8:28-37.

Secondly, as Dr. Park testified, within the dose range disclosed by the '288 patent, a clinician will determine which dose is effective. Tr. 501:3-10, 518:9-23. And, Dr. Kirsch stated that he, a formulator, does not decide what an effective dose of quetiapine is, and that, in general, a physician, perhaps in consultation with a clinical pharmacist, would come up with an appropriate dosage regimen. Tr. 614:10-20.

Third, according to Dr. Calabrese, a practicing psychiatrist, the lower end of the dose range disclosed by the '288 patent (50 mg/day for a 50 kilogram person) would be ineffective. Tr. 1232:10-18. Dr. Kirsch, a formulator, did not know whether the 50 mg/day dose would be effective. Tr. 616:6-617:9.

Fourth, Dr. Reist, a psychiatrist, understands that part of the invention of the '437 patent is the treatment of patients with effective amounts of a particular quetiapine formulation. Tr. 1774:23 to 1775:14. Dr. Reist also testified that the administration of an effective amount of quetiapine would require the knowledge of a clinician. Tr. 1775:15-19. Dr. Reist's testimony on this point was consistent with that of AstraZeneca's psychiatrist witness, Dr. Calabrese, who testified that it would be "impossible" to determine the effective amount without the assistance of a clinician, and that it is "inconceivable" that one could

study an antipsychotic drug without a clinician to dose the medicine. Tr. 1214:7-10, 1289:3-7.

Last, the development of the invention of the '437 patent included a clinical trial comparing two sustained release formulations to an immediate release formulation. Tr. 1279:3-1280:14; JTX-1 at 7:37-8:26.

Dr. Calabrese testified that a POSA must have clinical knowledge because a formulator alone would not know whether there was a medical need for a particular formulation. Tr. 1213:16-1214:19. Further, problems encountered in the art of sustained release pharmaceutical formulations as of May 1997 related to both clinical considerations and formulation considerations. Tr. 56:16-24. For example, determining whether a formulation would achieve potential advantages, such as controlling a condition more rapidly or reducing or eliminating side effects would require the input of a clinician. Tr. 568:4-8, 10-14. Clinical problems include identifying the condition to be treated, determining how to treat it, the amount of drug one needs to deliver, the rate of delivery, and the effective and toxic concentrations of the drug. Tr. 56:20-23.

Consequently, upon examination of all of the evidence presented at trial, the Court finds that the person of ordinary skill in the art pertinent to the '437 patent would include a clinician or an antipsychotic drug researcher in addition to a formulation scientist as described earlier. The clinician would have been a practicing physician, such as a psychiatrist, with a medical degree and several years of clinical experience diagnosing and treating patients suffering from disorders such as schizophrenia or bipolar disorder, with antipsychotic drugs. Tr. 1286:18-1287:2. The antipsychotic drug researcher would have been a scientist with either a medical degree or a Ph.D. in a relevant science, such as neuropsychopharmacology,

or both, and several years of experience in researching antipsychotic drugs and their use in treating psychotic disorders such as schizophrenia. Tr. 1287:3-8.

4. Scope and Content of Prior Art - State of the Art as of May 1997[9]

Schizophrenia is a serious psychiatric illness. It is characterized by positive symptoms (hallucinations, delusions, paranoia, disorganized behavior) and negative symptoms (apathy and difficulty interacting in society). It can be dangerous; an acute episode of schizophrenia presents a serious medical emergency in which bizarre, psychotically ill patients are dangerous to themselves and others. Ten percent of schizophrenics kill themselves. Tr. 1215:11-24, 1216:3-18, 1219:11-13, 1220:10-16. Schizophrenia, bipolar disorder, and major depression account for 40% of all medical disability in the age group 15-44. Tr. 1219:18-22; PTX-1057 at 1. Seroquel XR is approved to treat all three conditions. Tr. 1220:3-6.

Beginning in the 1950s, researchers discovered drugs that effectively treated some symptoms of schizophrenia—the delusions, hallucinations, and paranoia. These drugs included haloperidol and chlorpromazine. Chlorpromazine, marketed as Thorazine, was approved in 1953. Haloperidol was approved in 1971. Tr. 1221:21-1222:9.

While effective in treating the positive symptoms, these drugs caused potentially disabling motor and other neurological side effects, known as extrapyramidal symptoms ("EPS"), including one type known as tardive dyskinesia, which could become irreversible. In 1996, it was estimated that 50% of patients treated with these medicines developed EPS. These side effects led the industry to actively look for and develop new drugs. Tr. 1222:10-1223:19, 1224:15-24, 1225:23-1226:13; *see also* Tr. 810:1-20; PTX-1062 at 2.

[9] This section discusses the state of the art generally at the relevant time period. Specific prior art references relied upon by the parties are discussed in more *infra*.

In 1989, clozapine became available. Clozapine was unique because it not only treated both the positive and negative symptoms of schizophrenia, it did so without causing EPS side effects. While it did not cause EPS, clozapine was associated with additional side effects, including agranulocytosis, a potentially fatal blood disorder. Clozapine was considered the gold standard for the treatment of schizophrenia, but it was a dangerous drug to use. Tr. 1224:25-1225:22.

Clozapine became known as the first "atypical" antipsychotic drug because of its freedom from EPS. The early drugs like haloperidol and chlorpromazine then became known as "typical" antipsychotics. Tr. 1223:20-1224:1, 1224:20-1225:3. Other atypical antipsychotics were developed and approved in the early 1990s, including risperidone and, in September 1997, quetiapine. PTX-1062 at 3; PTX-1288; DTX-2626.

Bipolar disorder is a mood disorder in which a patient swings between a manic phase and a depressed phase. The disorder affects a person's work, family and social life. It is one of two major mood disorders, the other being major depressive disorder ("MDD") (formerly known as unipolar depression). In MDD, the depressions come and go, but there are no mood swings. Tr. 1243:21-24. Bipolar disorder is associated with a high suicide rate. Tr. 1244:7-21.

There are two types of bipolar disorder, bipolar I and bipolar II. In bipolar I, the highs are manic, often accompanied by psychotic symptoms, and the mood swings are severe. The ratio of time spent in the manic and depressed phases is 1:3. Calabrese Tr. 1243:17-20, 1243:25-1244:6. In bipolar II, the highs are less severe and the amount of time spent manic to depressed is 1:40. It is in the depressive phase that people kill themselves. Tr. 1243:17-20, 1243:25-1244:16.

As of May 1997, clinicians had no approved treatment for bipolar depression. Tr. 1246:18-24. The drug options available to a clinician for treating bipolar *disorder* as of May 1997 were even more limited than the options available to treat schizophrenia. As of May 1997, the primary treatment option for bipolar disorder was lithium. It had good antimanic properties, but it was only effective in about half of patients and was primarily viewed as having efficacy in mania with only poor to moderate efficacy in the depressed phase of the illness. Tr. 1246:3-14.

To treat the depressed phase of bipolar disorder, clinicians as of May 1997 would typically have started a patient on lithium and hoped that it would show some efficacy in the depressed phase. Clinicians also typically used different drugs (sometimes without regulatory approval for doing so) in an attempt to treat the different phases of the illness. For example, lithium or other antimanic agents would have been used to target the mania or hypomania, and the traditional antidepressants would have been used to treat the depressed phase. Tr. 1246:18-24, 1247:2-8, 1249:6-8. As of May 1997, no drug had been shown to have equal efficacy in both phases of bipolar disorder. Tr. 1247:9-13.

As of May 1997, no antipsychotic drug had been approved for the treatment of bipolar depression. Tr. 1767:18-20. At that time, it had been reported and it was believed that one side-effect associated with antipsychotic medication was depression. Tr. 1247:5-1248:3, 1778:9-1779:12; JTX-194 at 5. Consequently, it was generally not thought to use a drug that causes depression to treat that same disease. *See* Tr. 1778:22-1779:12. Dr. Calabrese testified that if researchers believed as of May 1997 that antipsychotics could be used to treat bipolar depression, there would have been clinical trials underway to test that hypothesis. However, there were none. Tr. 1255:15-1256:13.

Turning to the field of pharmaceutical formulations, as detailed further in the discussion below, at the relevant time the field of formulation science was complex and could be unpredictable. Also, there were many available formulation systems for a POSA to try who wished to create a sustained release formulation. As such, in developing a sustained release formulation, a POSA would need to consider the strengths and weaknesses of each type of formulation system relative to the particular properties of the active drug being formulated. Tr. 1412:7-11

During trial the parties relied upon various prior art references. Dr. Park testified that asserted claims 1, 2 and 10-13 were obvious in light of five prior art references: the '288 patent (JTX-423), a 1987 Dow Brochure (DTX-2980), Published European Patent Application No. 0 661 045 A1 (JTX-304), a 1985 publication by Ford (JTX-457), and a 1991 publication by Skoug (JTX-327). Dr. Park also testified that claims 11 and 12 were obvious in light of five prior art references: the '288 patent (JTX-423), the 1987 Dow Brochure (DTX-2980), the Melia reference (JTX-180), Sako (JTX-304), and the 1994 Handbook of Pharmaceutical Excipients (JTX-332). Dr. Kirsch testified that asserted claims 3-9 and 13 were obvious in light of the '288 patent in combination with any one of several Dow Brochures (DTX-2980, DTX-2979, DTX-2690) or International Patent Application Publication No. WO 94/04138 (JTX-442). The content of these and other prior art references relied upon by the parties are discussed in more detail in the appropriate sections below.

5. Motivation to Try to Make Sustained Release Quetiapine

*a. Testimony on Motivation at Trial*

In their obviousness case-in-chief, defendants' two formulation experts, Drs. Park and Kirsch, testified on motivation. Tr. 425:21-427:1; 589:15-592:10. Defendants' psychiatrist

expert, Dr. Reist, testified more extensively on motivation, in defendants' rebuttal case. Tr. 1712:3-1739:22, 1749:1-1752:8.

Dr. Park testified that specific motivation existed to try sustained release quetiapine because, in general, sustained release formulations had benefits, discussed further below, over immediate release forms that had been known for decades. According to Dr. Park, with the exception of insulin, all other immediate-release ("IR") drugs would benefit if made in sustained release form; no factors would mitigate against that. Tr. 425:21-426:13, 556:3-559:23. Dr. Park stated that, except perhaps for a patent on a sustained release form of an existing drug that relied on a new polymer to achieve sustained release, in his opinion no patent for a sustained release form of an existing drug would be valid as nonobvious. Tr. 559:24-560:21. Said another way, Dr. Park testified that it was his opinion that any patent for a sustained release formulation of a previously known drug would be invalid for obviousness unless it involved a novel or improved sustained release technology. The Court finds such a broad conclusion, among other things, lessened Dr. Park's credibility,[10] particularly in light of earlier testimony by Dr. Park stating that he would need more information before he could answer the question of whether a patent for a sustained-release version of an existing drug that uses HPMC as the sustained release agent could be valid as nonobvious. Tr. 553:11 to 554:7 (stating he would need to "study the claims, study prior art").

Dr. Park also testified, as did Dr. Kirsch, that specific motivation existed to try sustained release quetiapine because, in general, (1) sustained release improves patient compliance in comparison to IR drug forms; and (2) sustained or extended release

[10] The Court also found Dr. Park's generalized and sometimes overly simplistic approach to the issues presented to him to diminish his credibility. For example, Dr. Park testified that one can make a sustained release formulation simply by mixing an active ingredient with Jell-O. Park Tr. 402:4-21, 412:5-20.

formulations reduce side effects associated with IR drug forms. Tr. 425:21-426:13; 589:15-590:5; 425:21-426:13, 532:10-533:8; *see* 379:13-20. Dr. Kirsch further stated that specific motivation existed to try sustained release quetiapine because of a general desire to reduce fluctuations in drug blood levels associated with IR drug forms, but Dr. Kirsch offered no explanation of why, based on that reason, a POSA would have been motivated specifically to try sustained release quetiapine. Kirsch Tr. 589:15-591:23.

Dr. Kirsch also testified that motivation existed to try sustained release quetiapine because of "marketing" or "economic" reasons. In support, Dr. Kirsch stated that pharmaceutical companies sometimes either needed to find a product to compete with once-a-day products already in the marketplace or to "manage a product's life cycle" (*i.e.*, come up with another version of an existing drug). In response to several questions from the Court to identify the pharmaceutical reasons why an existing drug substance might be suitable for a sustained release form, "putting aside" economics, Dr. Kirsch eventually testified that, to answer that question, one would consult the clinical literature and clinical pharmacists. Tr. 598:20-600:19.

In response to Defendants' case-in-chief on motivation, AstraZeneca, through its three experts, Drs. Montgomery, Seeman and Calabrese, presented evidence in support of their position that a POSA would not have been motivated to develop or try a sustained release form of quetiapine as of May 1997. Dr. Calabrese described how physicians treated schizophrenia, the only disease for which quetiapine was contemplated as a possible treatment as of May 1997, and why a sustained release antipsychotic drug was contraindicated to treat that illness at that time. He also explained why a POSA in May 1997 would not have been

motivated to try sustained release quetiapine because of any general desire to reduce side effects, or improve compliance, in IR drug forms. Tr. 1215-1239.

Dr. Montgomery's testimony was entirely directed to the issue of motivation. Dr. Montgomery discussed the teachings of pre-May 1997 quetiapine clinical trial literature. He testified that, based on what that literature reported about quetiapine's modest efficacy at doses up to 750 mg/day, the informed physician or antipsychotic drug researcher at that time would have been motivated only to use even higher doses in an effort to improve efficacy, exactly the opposite of what a sustained release formulation would provide. Tr. 798:12-835:7. Much of Dr. Mongomery's testimony was unrebutted.

Similarly, virtually all of Dr. Seeman's testimony was devoted to the motivation issue. Dr. Seeman testified that pre-May 1997 antipsychotic drug literature reported that certain threshold levels of dopamine D2 receptor occupancy (60-80%) were required for antipsychotic efficacy without EPS. Based on pre-May 1997 literature reports that quetiapine achieved dopamine D2 receptor occupancy of only about 37%, Dr. Seeman testified that a clinician or antipsychotic drug researcher at that time would only have been motivated to increase quetiapine's low dopamine D2 receptor occupancy by increasing the quetiapine dose, in an effort to improve quetiapine's low efficacy. Dr. Seeman further testified that, because a sustained release form of quetiapine would only have lowered quetiapine's peak plasma levels, and, as a result, its dopamine D2 receptor occupancy, such a form would have been contraindicated. Tr. 953:19-978:23. As discussed below, the Court found Dr. Seeman's testimony highly credible and entitled to significant weight.

During his direct examination rebuttal testimony, Dr. Reist responded to Drs. Calabrese, Montgomery and Seeman, expressing his opinion that a POSA would have been

motivated to pursue an extended release formulation of quetiapine in May 1997. Tr. 1721:9-11. He based his opinion on three factors. He testified that an extended release formulation would be expected to improve compliance and reduce side effects. Tr. 1713:2-24. He also testified that specific motivation existed to try sustained release quetiapine because sustained release forms of other drugs existed. Tr. 1712:3-11, 1712:23-1713:17.

*b. Prior Art Taught Away From Trying to Develop Sustained Release Quetiapine*

i. Mechanism of Action

Dr. Seeman testified regarding the mechanism of action of antipsychotic drugs and, in particular, the dopamine D2 receptor target for antipsychotic drugs. Dopamine is a neurotransmitter chemical that acts in the brain. When it is released from a nerve cell, it attaches to a receptor on an adjacent nerve cell. As a result, the cell with the receptor is electrically stimulated. One particular dopamine receptor is known as the dopamine "D2" receptor. Tr. 953:4-10, 953:19-954:15.

High levels of dopamine can cause hallucinations and delusions; by blocking the receptors, antipsychotic drugs interfere with the action of dopamine and thereby alleviate schizophrenic symptoms. Tr. 954:16-955:4. The "dopamine hypothesis" of antipsychotic drug action is the hypothesis that all antipsychotic drugs work by interfering with dopamine transmission. By May 1997, this hypothesis of how antipsychotic drugs worked had become widely accepted. Tr. 954:16-22, 960:14-22; Tr. 1768:25-1769:3. In particular, it was understood that the affinity of a drug for the D2 receptor correlates to the drug's potency and therefore the required dose. Tr. 954:16-22, 957:7-23, 958:4-22; PTX-1111 at 1; PTX-1112 at 2.

All effective antipsychotic drugs occupy a significant percentage of the dopamine D2 receptors in the brain. Tr. 960:25-961:3. The percentage of dopamine D2 receptors occupied by an antipsychotic drug can be reliably estimated in living patients using a technique called Positron Emission Tomography ("PET"). Tr. 961:4-962:2. By May 1997, the dopamine hypothesis had been supported by consistent PET data showing high D2 receptor occupancies in patients responding to a number of antipsychotic drugs. Tr. 963:3-13; PTX-1018 at 1; PTX-1100 at 1.

By May 1997, it was well-established that to achieve antipsychotic effect, an agent must produce a dopamine D2 receptor occupancy of at least 60%, and that a compound tended to produce EPS side effects at D2 receptor occupancies above 80%. Tr. 962:5-16, 972:13-21, 974:4-11. Dr. Reist confirmed that D2 occupancy beyond 70 or 80% could lead to EPS. Tr. 1770:5-8. According to Dr. Seeman, there are no known exceptions to the rule that 60% occupancy is the therapeutic threshold. Tr. 972:13-973:2. Even clozapine, which appeared to be efficacious at lower occupancies in some studies, had been measured in 1992 as having at least 59% occupancy within an hour after dosing. Tr. 972:23-973:6; PTX-1109 at 2-3.

In 1988, Farde reported the D2 receptor occupancies of a variety of drugs. PTX-1018. The study involved schizophrenic patients who were responding well to treatment with eleven chemically-distinct antipsychotic drugs as well as a patient being treated with an antidepressant for a mood disorder. Using the PET technique, D2 receptor occupancies were determined in each patient 6 hours after dosing. In the antidepressant-treated patient, no significant D2 receptor occupancy was obtained. In the patients being well treated with the

antipsychotic drugs, D2 receptor occupancies between 65% and 85% were obtained. These results prompted the authors to conclude as follows:

> Our finding that clinical doses of all 11 chemically distinct antipsychotic drugs induce a 65% to 85% occupancy of the central D2-dopamine receptors, but that an antidepressant drug did not, represents evidence in living patients that the mechanism of action of antipsychotic drugs is indeed related to a substantial degree of D2-dopamine receptor occupancy.

PTX-1018 at 4. The authors also acquired some data relating the occurrence of EPS to D2 occupancy. They hypothesized that a different, lower D2 receptor occupancy may be required for antipsychotic effect than for EPS side effects:

> The low frequency of extrapyramidal side effects in all the neuroleptic-treated patients and the observations in this haloperidol-treated patient indicate that a lower receptor occupancy may be required for the antipsychotic effect than the occupancy required for extrapyramidal side effects.

PTX-1018 at 4. According to the authors, "[b]y relating D2-dopamine receptor occupancy to antipsychotic effect, it may be possible to define a 'threshold occupancy' for antipsychotic effect." PTX-1018 at 5.

In 1992, Farde reported the results of another study involving schizophrenic patients treated with conventional doses of a number of different antipsychotic drugs. PTX-1100. Patients who exhibited EPS had average D2 receptor occupancy of 82%. In patients who did not exhibit EPS side effects, but who responded to the treatment, the average D2 receptor occupancy was 74%. The authors stated as follows:

> The patients who had EPS had a significantly higher $D_2$ dopamine receptor occupancy than those who did not ($P<.001$). This finding is the first direct demonstration that EPS are quantitatively related to central $D_2$ dopamine receptor occupancy.

*  *  *

> The results of the present study indicate that there is a threshold for EPS between 74% and 82% $D_2$ occupancy (Fig. 3) which seems to be higher than a threshold for the antipsychotic effect, since the patients with occupancy below 74% were clinical responders.

PTX-1100 at 6; Tr. 965:24-966:13, 967:8-968:19.

As of May 1997, a POSA would have known that a D2 receptor occupancy of 60-80% was required for antipsychotic effect. Tr. 972:13-973:2. Indeed, studies reported after May 1997 confirmed the likelihood of clinical response when the dopamine D2 receptor occupancy was at least 60%, while EPS side effects tended to occur when the D2 occupancy exceeds 80%. PTX-1110 at 5, 6 fig. 7; Seeman Tr. 972:13-21, 974:4-11.

At least one study examined the D2 occupancies specifically for quetiapine. In 1995, Gefvert examined D2 receptor occupancies for quetiapine dosed at 150 mg three times daily for four weeks. PTX-1101. PET scans were performed at four time points in the 26-hour period after the last dose. The resulting D2 receptor occupancies were 44% (2 hours), 30% (8 hours), 27% (12 hours), and 0% (26 hours). PTX-1101; Tr. 968:20-969:5, 969:18-970:5. Because most studies reporting D2 receptor occupancy of other antipsychotic drugs at that time also included a 6-hr time point, Dr. Seeman interpolated Gefvert's occupancy data and noted that Gefvert's 6-hour D2 receptor occupancy for quetiapine to be about 37%. Tr. 970:6-13.

According to Dr. Seeman, a 37% D2 receptor occupancy would not provide therapeutic antipsychotic effect. Tr. 970:14-25. Thus, a POSA would have considered that 150 mg of quetiapine given three times a day was too low. Dr. Seeman, in fact, recommended to AstraZeneca in the late 1990s that the entire daily dose should be given in a single dose

rather than multiple times a day to raise quetiapine's D2 receptor occupancy. Tr. 971:15-22, 1039:8-14.

Dr. Seeman testified that it was the consensus of those working in the field of antipsychotic drugs as of May 1997 was that the D2 receptor occupancy of quetiapine needed to be raised to achieve efficacy. Tr. 971:8-22. Higher doses of an antipsychotic drug result in higher D2 receptor occupancy. Tr. 971:1-7, 971:23-972:12. Consequently, in May 1997 a POSA would have believed that a sustained release formulation of quetiapine was contraindicated because it would result in lower peak plasma concentration, and, thus, lower D2 receptor occupancy, resulting in inadequate efficacy. Tr. 978:2-23. According to Dr. Seeman, sustained-release quetiapine would have been expected to smooth out peaks in the blood concentration of the drug, which would have been counterproductive because having a high peak level of drug was necessary for therapeutic results. Tr. 1043:23-1044:2. Defendants' expert, Dr. Reist, confirmed that, if the goal was to obtain a higher peak concentration of quetiapine, one would prefer an immediate release version over a sustained release version. Tr. 1771:24-1772:24. Further, a study by Dr. Nord and Dr. Nyberg confirmed that there is a higher peak occupancy of the D2 receptor with immediate release quetiapine than with sustained release quetiapine. Nyberg Dep. 98:21-101:16; JTX-68 at 2-3. This is also shown in Figure 2 of the '437 patent. JTX-1 at 4.

The above evidence shows that a POSA in May 1997 would have been motivated to increase the IR quetiapine dose and to dose it rapidly in an effort to increase dopamine D2 receptor occupancy, and, hence, efficacy, rather than formulating quetiapine for sustained release. Based on what was known about the relationship between antipsychotic effect and dopamine D2 receptor occupancy, and quetiapine's low D2 receptor occupancy, a POSA

would not have been motivated to try sustained release quetiapine in May 1997; a sustained release form of quetiapine in fact would have been contraindicated. As Dr. Montgomery testified, as of May 1997, for this reason a physician treating psychotic patients and researchers who studied antipsychotic drugs would have considered the development of an oral, sustained-release form of quetiapine to be counterproductive. Tr. 798:4-18.

The Court notes that in reaching its conclusions herein, it has given substantial weight to the testimony of Dr. Seeman. The Court found him to be entirely credible based on the manner in which he testified and the depth of his expertise and experience. Although Dr. Reist opined that Dr. Seeman's opinion is incorrect because a POSA would have allegedly known that quetiapine and clozapine were effective at D2 occupancies below 60%, and, thus, were exceptions to the 60% rule, Tr. 1749:1-24, 1769:4-1770:4, Dr. Reist acknowledged that Dr. Seeman is an expert in this area and knows much more than he about the effects of antipsychotic drugs on the dopamine receptors. Tr. 1767:25-1768:24. Indeed, as of May 1997, Dr. Reist held no views regarding the dosing of quetiapine based on known information about its receptor occupancy while Dr. Seeman was actively recommending to AstraZeneca and others that the dosing should be modified to increase that occupancy. Tr. 1771:3-23; *see also* Tr. 1039:8-1040:1.

Furthermore, Dr. Seeman explained that clozapine had been shown prior to May 1997 not to be an exception and that it in fact did achieve approximately 60% occupancy very quickly. Tr. 1002:25-1003:14. A 1999 article confirmed that at least a dozen antipsychotics had therapeutic action when they occupy 60-80% of the D2 receptors, including clozapine and quetiapine if measured at the appropriate time point. PTX-1110 at 6 fig. 7; Tr. 977:9-978:1.

Dr. Reist also conceded that Dr. Seeman later demonstrated that quetiapine had transient D2 occupancy of about 60%. Tr. 1773:8-21; *see* Tr. 974:19-975:15. Earlier measurements of quetiapine's D2 occupancy had been low because (1) the dose used was too low and (2) the PET scans needed to have been measured at the one or two-hour time point rather than the six-hour time point because the high occupancy is a transient phenomenon. Tr. 976:4-20. Finally, a 2000 paper confirmed that antipsychotics in general (and quetiapine specifically) are efficacious when dosed so as to produce transiently high D2 receptor occupancies:

> There can be little doubt that one needs repeated dosing of oral antipsychotics, but one should not assume that one needs sustained (i.e., every hour of every day) levels of high occupancy for inducing or maintaining response.

JTX-197 at 6.

*ii. Clinical Literature*

Clinical literature at the time also supports the conclusion that as of May 1997, a sustained release formulation of quetiapine would have been contraindicated. The pre-May 1997 literature that describes clinical trials of quetiapine in schizophrenia includes a 1995 Fabre paper, a 1995 Wetzel paper, a 1996 Borison paper, a 1996 Casey paper and a 1996 Hirsch paper. JTX-195; JTX-189; JTX-445; JTX-181; JTX-187.

Dr. Montgomery testified about each of the pre-May 1997 quetiapine clinical trial literature references. The 1995 Fabre paper described a placebo-controlled, "exploratory" trial of quetiapine in twelve moderately-ill hospitalized schizophrenia patients. JTX-195. The initial quetiapine daily dose of 25 mg/day was increased in increments of 25-50 mg about every four days until all 8 patients in the treatment group reached a final daily dose of 250 mg. The other 4 patients received placebo. Eleven patients completed the study. Tr. 803:14-804:21; JTX-195.

Quetiapine was well tolerated in the trial reported in the Fabre paper, with no evidence of EPS side effects. The authors concluded that quetiapine had "potential" as a treatment for the symptoms of schizophrenia and that higher doses should be tested in more seriously-ill patients for further evidence of quetiapine's efficacy. Tr. 805:14-806:6; JTX-195.

The 1995 Wetzel paper described an open label trial of quetiapine in 12 moderately ill schizophrenic patients. JTX-189. An open label trial, where both the physician and the patient know what drug is administered, provides useful information about how dosing should be modified. Seven of the 12 patients received a maximum dose of 750 mg per day; all patients received at least 600 mg per day; the average dose was 696 mg per day. Clinically satisfactory improvement was obtained in only 4 of the 12 patients, which the authors characterized as "rather moderate." Eight patients dropped out because of lack of efficacy. Tr. 807:14-808:6, 819:16-21; JTX-189.

Quetiapine was well tolerated in the trial reported in the Wetzel paper; virtually no EPS side effects were observed. Despite doses of 600-750 mg per day, the authors concluded that the trial demonstrated only that quetiapine "could be" an effective antipsychotic but that studies with higher doses "with presumably better efficacy" were needed. Tr. 808:18-809:3, 809:18-25, 897:18-898:7; JTX-189. As to the risk of inducing EPS side effects with higher doses, the authors stated that "we would assume that dose escalation of seroquel beyond 750 mg/day should not be prevented by disturbing side effects." JTX-189 at 8; Montgomery Tr. 810:21-811:7.

The 1996 Borison paper described the results of two other placebo-controlled quetiapine trials (Studies 6 and 8). JTX-445. Compared to Study 4 (the Fabre study – 12 patients, 3 weeks), Studies 6 and 8 were much larger (Study 6: 109 patients; Study 8: 286

patients) and longer (both 6 weeks). In Study 6, quetiapine was administered over 6 weeks to 54 patients; 55 patients received placebo. The mean daily quetiapine dose was 305 mg. At endpoint (on treatment day 42), the overall improvement in the treated patients was only "marginally significant." Although quetiapine was well tolerated with a low incidence of EPS side effects, a POSA would have understood that quetiapine was not efficacious in Study 6. Tr. 811:13-812:11, 812:19-25; JTX-445.

The 1996 Casey paper and the 1996 Hirsch paper reviewed the results of a number of quetiapine clinical trials, including Phase 2 Studies 5, 7 and 8, and Phase 3 trials 12 and 13. JTX-181; JTX-187. Study 8 compared both a "high" quetiapine dose (up to 750 mg/day with a mean daily dose of 360 mg) and a "low" quetiapine dose (up to 250 mg/day, with a mean daily dose of 209 mg) to placebo. Tr. 814:5-15; JTX-181 at 11-12. In both treatment groups, quetiapine initially was dosed at 75 mg/day and the dose was titrated upward depending on each patient's clinical response. The high dose was significantly better than placebo at the end of the trial. High dose was also better than low dose. The low dose did not work—it was indistinguishable from placebo at the end of the trial. Tr. 814:16-25, 816:3-6; JTX-181 at 11-12; JTX-187 at 8.

A physician or drug researcher would have understood from Study 8 that high doses of quetiapine should be targeted to achieve adequate efficacy. Tr. 816:18-25. Study 8 also revealed that the side effect of somnolence and sedation was experienced by patients at even low doses of quetiapine. Eighteen patients taking the "low dose" quetiapine (19% of the total on low dose) experienced somnolence, compared to 24 patients taking the "high dose" (25% of the total on high dose). JTX-187 at 11 tbl. 5.

Study 5 was an open-label, international, 6-week, multicenter trial in 118 patients more severely ill than in Study 4. The dose was increased from 50 mg/day to a maximum of 500 mg/day although, in the European and South African centers, a protocol amendment permitted a maximum daily dose of 750 mg. Such amendments occur where the trial physicians perceive that higher doses are needed for efficacy. Only 41% of patients were classified as treatment responders using a generous "soft measure" of efficacy. Study 5 indicates that higher doses are needed for efficacy. Tr. 817:9-819:23; JTX-181 at 7. Quetiapine was well tolerated in Study 5 and had little potential to induce EPS. JTX-181 at 8.

Study 7 compared quetiapine to chlorpromazine, a typical antipsychotic drug, in 201 patients hospitalized with acute exacerbation of schizophrenia (101 patients on quetiapine, 100 on chlorpromazine). The daily quetiapine dose was titrated upward from an initial 75 mg/day dose up to a maximum of 750 mg/day, with a mean dose of 407 mg/d (range, 50-750 mg). There were no statistically significant differences between the two groups at any time point; the study showed that quetiapine is at least as effective as chlorpromazine, with a "trend" towards superior efficacy with regard to both positive and negative symptoms of schizophrenia. Because the dose of chlorpromazine used in Study 7 was restricted, the trial was biased in favor of quetiapine; thus, the study was not instructive regarding the most effective dose of quetiapine to use in treating schizophrenia. Tr. 820:2-13, 821:8-16, 822:1-4; JTX-181.

Study 12, a Phase 3 trial, is described in the 1996 Casey paper as well as in an abstract by King & Link. JTX-181; PTX-1061. Study 12 was a 6-week, multicenter comparison of quetiapine at two total daily doses: 450 mg (administered in two or three divided doses) and a subtherapeutic low dose of 50 mg, in 622 moderately-ill hospitalized patients with acute

exacerbation of schizophrenia. By the end, patients given 450 mg per day (either in two or three divided doses) showed improvement over the 50 mg group. JTX-181; PTX-1061; Tr. 822:8-824:2; 1236:8-23, 1237:12-20. Study 12 indicated that quetiapine should preferably be dosed twice-daily, and that the higher dose was better than the lower dose; it said nothing about quetiapine's most effective dose. Tr. 823:10-22.

Study 13 was a 6-week trial in 361 moderately-ill hospitalized patients with acute symptoms of schizophrenia. After a one-week placebo phase, seven different groups of patients were treated with either one of five fixed doses of quetiapine (75, 150, 300, 600 or 750 mg), haloperidol or placebo. After 6 weeks of treatment, significant changes from baseline were identified between quetiapine (150-750 mg) or haloperidol and placebo. The maximum quetiapine clinical effect was reported to be 300 mg/day. Across all quetiapine dose groups, the incidence of EPS was no greater than in the group treated with placebo. Tr. 824:3-826:5; JTX-181 at 14-15. The study was not designed in such a way as to distinguish between the relative effectiveness of the different doses of quetiapine used in the trial. The size of the groups receiving those different doses was not large enough to show any differences between them. Tr. 824:23-825:11, 825:18-826:5.

In summary, these pre-May 1997 quetiapine clinical trial literature, which reported on trials of IR quetiapine, indicated that quetiapine's efficacy at the doses tested (150 to 750 mg/day) was weak and only moderate, that a number of the clinical trials failed, that higher doses of quetiapine provided better efficacy than lower doses, and that, to improve efficacy, the quetiapine dose needed to be raised to levels higher than the doses tested. Tr. 798:1-3; 801:21-802:8, 826:6-827:12; 1227:7-1228:2. These studies thus support the conclusion that, in May 1997, a POSA would not have been motivated to develop a sustained release form of

quetiapine; in fact, as the evidence at trial showed, such development would have been thought to be counterproductive. Instead, a POSA would have been motivated to proceed in a direction opposite to sustained release. The impression at that time from the pre-May 1997 quetiapine clinical trial literature was that the doses of quetiapine tested were too low and that higher doses of quetiapine were necessary to affect the important dopamine D2 receptor target and achieve improved efficacy. Tr. 798:12-799:5, 800:24-801:20.

*iii. Clinical Use - Treatment of Schizophrenia and Bipolar Disorder as of May 1997*

Bearing on the question of motivation, evidence relating to the clinical use of antipsychotics and, particularly, quetiapine, shows that in May 1997 the idea of treating an acutely-ill schizophrenic patient with a sustained release form of drug would be contraindicated. According to Plaintiffs' expert Dr. Calabrese, as of May 1997, in order to rapidly control the psychotic symptoms (*e.g.*, delusions) of acutely-ill psychotic patients, physicians used what Dr. Calabrese called the "sledgehammer" approach, also called rapid neuroleptization. This approach involves administering to the patient a well-tolerated dose of an antipsychotic drug, and rapidly increasing the dose. The goal is to gain rapid control over the symptoms because such acutely ill patients can be dangerous to themselves and the medical staff treating them. The key to this treatment is to achieve a high peak drug plasma level[11] as soon as possible. Tr. 1215:25-1217:21.

Dr. Calabrese testified that, compared to an immediate release form of a drug, a sustained release form takes longer to reach a peak drug blood level, and the peak is lower. In his 26 years of psychiatry practice, Dr. Calabrese has never used a sustained release preparation in the treatment of an acutely-ill psychotic patient. Tr. 1216:21-1218:2.

[11] Peak plasma level is the maximum amount of a drug in the blood after dosing. That is when the drug has its maximum clinical effect. Tr. 1229:11-22.

Defendants' expert Dr. Reist similarly testified that, if the goal was to obtain a higher peak drug blood level sooner, then an immediate release form of a drug would be preferred over a sustained release form. This is true for all drugs, including quetiapine. Tr. 1772:7-24. Like Dr. Calabrese, a goal in Dr. Reist's practice was to achieve fast action to address the symptoms of the acutely-ill patients. Efficacy was the primary goal; minimizing side effects was secondary. Tr. 1775:20-1776:15.

Given this, as of May 1997, no one in the field had ever suggested that an oral sustained release formulation of quetiapine would have offered any efficacy advantage in the treatment of schizophrenia. Tr. 834:17-21. At that time, there was no approved oral sustained release preparation of any antipsychotic drug. Tr. 1227:25-1228:2; 1802:3-6, 1811:24-1812:4. A POSA would not have been motivated to slow down release of quetiapine, as would be the case in a sustained release form, because that would have delayed the ability to rapidly control the symptoms of schizophrenia. Tr. 800:24-801:20, 834:22-835:7.

iv. Alleged General Motivations

Defendants assert that a POSA would have had a reason to make a sustained release formulation of quetiapine because of several known benefits allegedly possessed by all sustained release formulations over immediate release forms (*i.e.*, improved patient compliance, potential reduction in side effects, reduction in blood level fluctuations), and because of an alleged "marketplace" incentive (*i.e.*, the need to compete with, *e.g.*, existing once-daily products of other drugs). As discussed below, the Court finds that Defendants have not established the existence of any such motivations specifically existed as to quetiapine by clear and convincing evidence.

First, the Court finds that no specific motivation existed as of May 1997 to create a sustained-release formulation of quetiapine based on the general notion that sustained release improves patient compliance as compared to IR drug formulations. Defendants' three experts, Drs. Park, Kirsch and Reist, in support of their opinion that a POSA in May 1997 specifically would have been motivated to try sustained release quetiapine, all cited the general notion that patient compliance associated with IR drug forms would be improved by going to a sustained release form. Tr. 425:21-426:13; 589:15-590:5; Tr. 1712:3-11. These three witnesses proffered slightly different explanations of why improved compliance would have motivated a POSA to try sustained release quetiapine.

Defendants' formulation experts, Drs. Park and Kirsch, both testified that a benefit of every sustained release formulation known in May 1997 was improved patient compliance due to the fact that sustained release formulations required less frequent dosing in comparison to immediate release formulations. Tr. 425:21-426:13; 589:15-591:19. Dr. Reist testified that, in general, compliance would be improved with sustained release formulations because, in comparison with immediate release forms of drugs, a sustained release formulation would have a reduced frequency of dosing and one would expect that a sustained release formulation also would reduce side effects. Tr. 1712:23-1713:3, 1713:21-24; 1763:12-20.

Dr. Park's and Dr. Kirsch's opinions on improved patient compliance were general in nature, offered without reference to any specific illness or drug. Neither witness made any attempt to explain why a POSA in May 1997 would have believed that a general desire to improve patient compliance by reducing dosing frequency was specifically applicable to immediate release quetiapine.

In contrast, AstraZeneca's expert, Dr. Calabrese, a psychiatrist, testified that, in life-threatening illnesses like schizophrenia, it was not dosing frequency that drove noncompliance; rather, it was side effects and whether the medicines worked. That is, if the drug caused unpleasant side effects, patients would be more inclined to stop taking it. Dr. Calabrese also testified that the general motivation forming the bases for the opinions of Dr. Park and Dr. Kirsch does not hold true for quetiapine or other antipsychotic drugs. In Dr. Calabrese's opinion, it holds true only for other illnesses such as headache. Tr. 1238:19-1239:13.

In May 1997, quetiapine was not on the market in any form, and was not commercially available. Tr. 797:17-25; 1252:23-25. Consequently, except for the limited experience of physicians who participated in the few clinical trials of IR quetiapine discussed further below, practicing physicians generally had no clinical experience with quetiapine. They would have had no basis on which to know whether its side effects were problematical or whether the recommended twice-daily dosing of quetiapine presented any patient compliance problems.

By May 1997, the literature had described clinical trials of immediate release quetiapine in schizophrenia, and only for schizophrenia. Tr. 798:1-3; 1227:7-1228:2. According to this pre-May 1997 clinical trial literature, the recommended dosing for quetiapine IR was twice daily. Tr. 822:5-823:22; JTX-181 at 14-15. Other literature by May 1997, specifically the Greenberg reference, taught that there was no difference with respect to patient compliance between once-daily dosing of a drug and twice-daily dosing, but that there was a substantial difference between once-daily dosing and dosing three or more times per day. JTX-140 at 3; JTX-382 at 6; Tr. 833:15-834:12. Furthermore, Dr. Reist confirmed that,

from a compliance perspective, the literature showed that there was a much bigger difference between once-daily and three times-daily dosing than between once-daily and twice-daily. Reist Tr. 1737:21-1739:2, 1797:15-1798:2. Dr. Reist also stated that he had no reason to disagree with a statement in another publication (the Razali reference, JTX-382) saying that the authors' conclusion was "similar" to the conclusion in the Greenberg reference in that patients receiving daily or twice daily medication had significantly better compliance than those receiving medication three times a day or more. Tr. 1815:24-1816:15.

Dr. Calabrese testified that, in his personal clinical experience, it made no difference with respect to compliance whether a patient was dosed two times a day versus once a day. Tr. 1236:11-17. Confirming Dr. Calabrese's opinion that, in schizophrenia, compliance was driven by side effects and not by dosing frequency, the literature reported that patient noncompliance is linked principally to side effects. For example, a publication by Fenton reported that between one-quarter and two-thirds of patients who unilaterally discontinue prescribed medicines cite side effects as the primary reason. JTX-194 at 5. Dr. Reist did not disagree with that statement in Fenton, Tr. 1785:16-1787:5, and confirmed that if the Fenton statement is correct, it logically follows that reduced side effects would improve patient compliance. Tr. 1787:6-12.

Nor did Dr. Reist disagree with statements in another reference (the Young reference, JTX-381) to the effect that side effects are correlated with noncompliance. Tr. 1794:16-1795:21; JTX-381 at 9. Yet another publication, by Wirshing, states that EPS side effects have been linked with patient noncompliance. JTX-193 at 1. Dr. Reist agreed not only that Wirshing's statement is accurate, but that the statement comports with Dr. Reist's personal experience. Tr. 1784:19-1785:9.

It follows that if patient compliance is an issue as a result of the presence of side effects, compliance is less likely to be an issue for drugs that are relatively free of side effects. Tr. 1784:9-12. As of 1997, it was known that quetiapine did not cause significant EPS, a particularly problematic side effect of antipsychotic medicines; in the reported pre-1997 quetiapine clinical trials, EPS occurred only infrequently. Accordingly, the reduction in EPS side effects associated with IR quetiapine would lead to better compliance as compared to typical antipsychotic drugs. Tr. 1783:21-1784:8, 1787:13-23. In other words, compliance was less likely to be an issue for antipsychotic drugs, like IR quetiapine, which are relatively free of EPS side effects. Tr. Tr. 829:1-9; 1784:9-12.

Although quetiapine was known in May 1997 to have other side effects, such as sedation or somnolence, those side effects occurred at low dosages. As a result, a POSA would have had no reason to try a sustained release form of quetiapine, with its expected lower peak blood levels of drug, in an effort to reduce side effects, since these side effects already occurred at low doses. Tr. 829:1-830:14; Tr. 1233:10-1234:10; JTX-187 at 11 tbl. 5.

The Court finds that no specific motivation existed to try sustained release quetiapine based on the notion that sustained release formulations reduce side effects. As discussed above, Dr. Reist testified that a POSA in May 1997 would have been motivated to try a sustained release formulation of quetiapine because it would be expected to reduce side effects. Tr. 1712:3-11; 1712:23-1713:3, 1713:18-20. However, the Court notes that Dr. Reist has no personal experience to support his opinion that a sustained release quetiapine would necessarily reduce the side effects of the IR form and did Dr. Reist does not know if sustained release quetiapine has an improved somnolence profile as compared to IR quetiapine. Tr. 1765:24-1766:10, 1766:24-1767:2.

Similarly, Dr. Park testified that a reason why a POSA as of May 1997 would have been motivated to develop a sustained release form of quetiapine was that a sustained release formulation would, in comparison with an immediate release formulation, reduce the peak plasma concentration of the drug and, thus, reduce side effects. Tr. 532:10-533:8. However, when asked to identify the side effects of quetiapine known as of 1997, Dr. Park testified that he neither knew nor cared. Tr. 533:11-17. Clearly, Dr. Park did not know whether any side effect of IR quetiapine would be reduced by a sustained release form of quetiapine. None of Dr. Park's motivation testimony was specific to quetiapine.

As discussed above, because IR quetiapine was already essentially free of the most troublesome side effect, EPS, and because other side effects such as sedation or somnolence occurred at low doses of the IR form, a POSA would have had no reason to go to a sustained release form of quetiapine in an effort to reduce those side effects. It appears that such a form would have offered no advantage over the IR form with respect to side effects. Tr. 829:1-14; Tr. 1233:20-1234:15.

Also with respect to motivation, Defendants assert that a desire to have the ability to compete in the market with once-daily formulations and depot formulations of other drugs allegedly used to treat psychotic states would have motivated a POSA to develop a sustained release quetiapine formulation. The Court finds no clear and convincing evidence to support this assertion.

In support of his opinion that a POSA as of May 1997 would have been motivated to try a sustained release form of quetiapine because a number of extended release formulations of other drugs used in the treatment of psychiatric illnesses had been available and were in widespread use prior to that time, Dr. Reist cited to sustained release formulations of seven

drugs that existed prior to May 1997: lithium for bipolar disorder, two anticonvulsants (carbamazepine and Depakote), two antidepressants (bupropion and venlafaxine), a non-oral formulation of the typical antipsychotic fluphenazine, and a discontinued atypical antipsychotic (remoxipride). Tr. 1712:3-11, 1712:23-1713:17; *see also* Tr. 844:19-22 (discussing injectable fluphenazine)).

Dr. Reist testified that "slow release" carbamazepine had been used to treat the manic phase of bipolar disorder prior to May 1997, but that it was principally used to treat epilepsy. Tr. 1715:1-4, 1796:6-10, 1796:14-1797:1; JTX-385 at 1. According to Dr. Reist, the Persson reference (JTX-385) concluded that a "slow release" carbamazepine formulation could possibly reduce side effects associated with immediate release carbamazepine, and that "slow release" formulation was dosed twice-daily. Tr. 1716:2-17, 1796:11-13; JTX-385 at 1. Dr. Reist also noted that extended release Depakote was used to treat bipolar disorder prior to May 1997. Tr. 1717:11-1718:1, 1798:21-25.

According to Dr. Reist, a POSA knowing that both slow release carbamazepine and extended release Depakote were used to treat bipolar disorder would have provided motivation to try a sustained release form of a different antipsychotic drug, quetiapine, in the treatment of psychotic disorders. Tr. 1718:16-24. However, as Plaintiffs point out, even if that were true, then a POSA would have been motivated to try a sustained release form of literally any other known immediate release antipsychotic drug in the treatment of any psychotic disorder. Further, Dr. Reist conceded that widespread clinical trials were necessary in order to identify the side effect profile of the sustained release formulation of any new drug. Tr. 1801:15-24; DTX-2812 at 4.

Dr. Reist similarly testified that bupropion was useful to treat major depressive disorder, and that the Joseph reference (DTX-2812) taught a POSA that sustained release bupropion was expected to have provided lower peak blood levels of the drug and thus reduce seizures known to be a problem with immediate release bupropion. Tr. 1721:12-1723:10; DTX-2812 at 3. However, this is irrelevant to whether a POSA would have been motivated to try sustained release quetiapine for any psychotic disorder, since EPS side effects were known not to be a problem with IR quetiapine. Tr. 1784:3-12.

As of May 1997 none of the other orally-administered drugs relied on by defendants were approved for treating schizophrenia or bipolar depression. Since IR quetiapine was only used to treat schizophrenia at that time, a once-daily sustained release quetiapine logically would not be considered as a potential competitor of once- daily drugs used to treat other diseases.

Dr. Reist testified that the development of sustained release remoxipride, another atypical antipsychotic, as reported by Tench (JTX-185), would have motivated a POSA as of May 1997 to develop sustained release quetiapine, a drug that Dr. Reist claims has a number of features in common with remoxipride. Tr. 1724:9-1731:19; JTX-185. Prior to May 1997, however, IR remoxipride had already been withdrawn in Europe for toxicity when a number of patients died; it was never approved in the United States. Tr. 1725:7-10, 1794:2-4, 1794:8-12. As such, the Court cannot conclude that a POSA in 1997 would have been motivated to try sustained release quetiapine based on remoxipride's experience.

Last, a "depot" formulation was administered perhaps weekly or monthly, by injection. Tr. 845:4-21. There simply is no evidence that explains why such injectable

products would have motivated a POSA to develop a different, orally-administered once-daily product.

6. Prior Art Relied Upon by Defendants

As stated above, Dr. Park testified that asserted claims 1, 2 and 10-13 were obvious in light of the following five prior art references: the '288 patent, a 1987 Dow Brochure ("the Dow Brochure"), Published European Patent Application No. 0 661 045 A1 ("Sako"), a 1985 publication by Ford ("Ford"), and a 1991 publication by Skoug ("Skoug"), and further testified that asserted claims 11 and 12 were obvious in light of five prior art references: the '288 patent, the 1987 Dow Brochure, the Melia reference, Sako, and the 1994 Handbook of Pharmaceutical Excipients. Dr. Kirsch testified that asserted claims 3-9 and 13 were obvious in light of the '288 patent in combination with any one of several Dow Brochures (or International Patent Application Publication No. WO 94/04138 ("the '138 application"). A brief summary of these references is below:

The '288 Patent: In the 1980s, scientists at an AstraZeneca predecessor company discovered the quetiapine compound. Based on tests in animals, those scientists predicted that quetiapine would have antipsychotic properties with reduced tendency to cause EPS. In 1989, the USPTO issued the '288 patent, titled "Novel Dibenzothiazepine Antipsychotic." *See* JTX-423.

The '288 is prior art to the '437 patent. The '288 patent discloses the use of quetiapine to treat psychosis and hyperactivity, as well as discloses the hemifumarate salt of quetiapine. Tr. 436:2-7. It also discloses an effective daily dosing range. JTX 423 col. 6, lines 12-17.

Dow Brochures: Dow Chemical Company, a manufacturer of HPMC, published manuals containing formulation guidelines to teach a formulator how to use HPMC to create sustained release gel tablet.

Sako: European Patent Application No. 0 661 045 A1 teaches sustained release solid oral dosage formulations containing HPMC as a gelling agent and their use in a variety of medications.

Ford: Ford, *et al.*, "Formulation of Sustained Release Promethazine Hydrochloride Tablets Using Hydroxypropylmethylcellulose Matrices," discloses making and testing a series of sustained release hydrophilic gel matrix tablet using the freely soluble drug promethazine hydrochloride, various grades of HPMC in various amounts, and additional pharmaceutical excipients.

Skoug: Skoug, *et al.*, "In Vitro and in Vivo Evaluation of Whole and Half Tablets of Sustained-Release Adinazolam Mesylate," discloses sustained release gel matrix tablets of adinazolam, a highly soluble drug, using HPMC as the gelling agent.

Melia: Melia, "Hydrophilic Matrix Sustained Release Systems Based on Polysaccharide Carriers" describes the use of pH modifiers in gel matrix formulations and notes their use for drugs with pH-dependent solubility.

Handbook of Pharmaceutical Excipients (2d ed.): The Handbook discloses common excipients used in sustained release formulations.

The '138 Application: International Patent Application Publication No. WO 94/04138 discloses a sustained release formulation of bupropion hydrochloride using HPMC in combination with various excipients.

*a. Differences Between the Prior Art and the Claimed Invention*

Plaintiffs do not contest that every element of the asserted claims is disclosed in the prior art presented by Defendants. However, as Plaintiff point out, no single reference relied upon by Defendants describes a sustained release formulation of quetiapine or its use in treating psychotic states. Of the various prior art references that disclose sustained release formulations of pharmaceutically active agents, none specifically discloses quetiapine. Thus, no single prior art reference describes the subject matter claimed in asserted claims 1-13 of the ’437 patent.

The closest prior art reference is the ’288 patent. It discloses that the compound, quetiapine, is useful as an antipsychotic agent with a predicted reduced potential to cause EPS side effects observed with the use of other antipsychotic agents. The ’288 patent also discloses immediate release formulations of quetiapine and the use of such IR formulations to treat psychotic states by administering to psychotic patients an effective amount of quetiapine. The ’288 patent does not disclose a sustained release formulation of quetiapine. Tr. 540:18-20;1425:13-20; Kirsch Tr. 684:13-15; JTX-423.

*b. Motivation to Combine Prior Art and Reasonable Expectation of Success*

A number of prior art references disclose sustained release formulations of other pharmaceutically active ingredients. Defendants’ formulation experts, Drs. Park and Kirsch, and defendants’ psychiatrist expert, Dr. Reist, testified that a POSA as of May 1997 would have been motivated develop a sustained release formulation of quetiapine. Drs. Park and Kirsch testified that a POSA as of May 1997 would have combined the teachings of the prior art and would have had a reasonable expectation of being able to successfully make a sustained release formulation of quetiapine. Plaintiffs experts disputed these conclusions. The two issues of (1) whether a POSA as of May 1997 would have been motivated to make a

sustained release formulation of quetiapine by combining these references; and (2) whether a POSA at that time would have had a reasonable expectation of being able to successfully make such a formulation; are discussed below.

Drs. Park and Kirsch testified that claims 1-13 of the ’437 patent would have been obvious because, first, a POSA would have had a reason to combine, with the ’288 patent, various prior art references disclosing the use of HPMC gel matrix systems to achieve sustained release, and, second, based on those combinations of prior art, a POSA would have had more than a reasonable expectation of being able successfully to make a sustained release quetiapine formulation. Dr. Park testified that claims 1, 2, 10 and 13 of the ’437 patent would have been obvious to a POSA as of May 1997 based on the ’288 patent in combination with any one of four other prior art references: the 1987 Dow Brochure, Sako, Ford, and Skoug. Tr. 387:12-20, 416:18-417:16, 503:13-23. He testified that, based on those combinations of prior art, a POSA in May 1997 would have had more than a reasonable expectation of successfully making a sustained release form of quetiapine. Tr. 442:2-10, 452:12-17, 454:8-13, 455:25-456:4.

With respect to combining the ‘288 patent and Dow Brochure, Dr. Park testified that it would have been “natural” for any formulation scientist to make a sustained release quetiapine formulation by combining the ’288 patent with the 1987 Dow Brochure. He reasoned that the goal of sustained release is to slow down the drug release over an extended period of time, and that the Dow Brochure “clarified” the notion that, using HPMC, one can make a sustained release formulation “without any problem.” Tr. 429:8-18. Dr. Park also added that the Dow Brochure “disclose[s] all the information we need to know to make a formulation described in the ’437 patent.” Tr. 434:2-10.

The Court finds, however, that a POSA would not necessarily have been motivated to combine the '288 patent with the Dow Brochure, nor would a POSA have had any reasonable expectation of success. For example, the Dow Brochure itself states that the mechanism of sustained release with HPMC gels was dependent on many variables and "numerous" factors, none of which were considered by Dr. Park. Rather, it appears that Dr. Park used hindsight to justify his combination. Tr. 1426:12-1432:8.

Figure 3 of the 1987 Dow Brochure discloses that there are several different HPMC polymers that one can select to obtain different levels of sustained release. Tr. 1430:8-16; DTX-2980 at 8. Figure 3 involved a test system containing only a very small dose (5% of the tablet) of riboflavin, a hydrophobic compound that does not have pH-dependent solubility, whereas quetiapine is hydrophilic and has pH-dependent solubility. Tr. 1430:24-1431:7. A similarly-designed quetiapine tablet would be too large for commercial use. A tablet containing 5% drug dosed at 750mg of quetiapine (a typical dose) would be a 15 gram tablet, or thirty 500 milligram tablets. Tr. 1431:1-7. Thus, rather than motivate a POSA to try to make a sustained release formulation, the teaching of Figure 3 would teach away from combining '288 patent with the 1987 Dow Brochure. Tr. 1431:6-7.

Overall, the 1987 Dow Brochure teaches that "[o]bviously, the many variables involved in the formulation of hydrophilic matrix system can make the job a complex and time-consuming affair." Tr. 1429:8-1430:7; DTX-2980 at 27. That teaching is consistent with Dr. Prud'homme's opinion regarding the complexity and unpredictability of formulating a sustained release tablet. Tr. 1429:16-1430:7. That teaching in the Dow Brochure is inconsistent with Dr Park's opinion about the simplicity of making a sustained release formulation, however, the Court accords Dr. Park's opinion less weight. As Dr Prud'homme

testified, the 1987 Dow Brochure only provides general guidance for particular compounds, but quetiapine has a number of complex chemical and biological attributes complicating its use in a sustained release formulation. The Dow Brochure does not teach how to address a situation like with quetiapine in which multiple complicating factors are presented simultaneously. Tr. 1431:19-1432:8.

The Court finds that Defendants have not proven by clear and convincing evidence that a POSA would have been motivated to combined the ’288 patent with any of the Dow Brochures to obtain the subject matter of claims 1, 2, 10, and 13.

As to combining the teachings of the ‘288 patent and the Sako reference, Dr. Park testified that what led him to combine the ’288 patent and the Sako reference was that Sako “describes a number of important factors all in the same art.” Dr. Park stated that, although Sako discloses that “any drug” can be used, antipsychotic drugs are mentioned. He also testified that Sako discloses the use of HPMC as a gelling agent. Dr. Park then testified in a conclusory fashion that a POSA, having knowledge of the teachings of the ’288 patent and Sako, would have proceeded to develop the subject matter claimed in claims 1, 2, 10 and 13 of the ’437 patent with “more” than a reasonable expectation of success. Tr. 417:17-21, 444:1-452:17; JTX-434.

However, the Sako reference relates to a formulation that delays release of its active ingredient until reaching the colon, and it uses a “completely different approach” from sustained release. HPMC is but one of many release controlling agents disclosed; the reference, in fact, discloses over 100 different drug compounds—there is no emphasis on antipsychotics in Sako. Tr. 1440:4-1444:4. Dr. Park failed to recognize that there is no

emphasis on antipsychotics, that Sako is focused on a polymer other than HPMC, and that Sako is directed to completely different type of technology.

The Court gives more weight to Dr. Prud'homme's testimony and finds that a POSA would not have had any reason to combine the teachings of Sako with the '288 patent to develop a sustained release quetiapine formulation. To achieve the clinically-desired dosing of quetiapine at that time—an immediate high peak—one would not want to slow down the release. Tr. 1442:20-1443:2. Defendants have not proven by clear and convincing evidence that a POSA would have combined the '288 patent with Sako to obtain the subject matter of claims 1, 2, 10, and 13 or that a POSA would have had a reasonable expectation that such a combination would have been successful. *See* Tr. 1443:3-13.

Turning to the combination of the '288 patent and Ford, Dr. Park testified that Ford "teaches extensive use of HPMC, so anybody can easily combine '288 patent and Ford." Tr. 453:1-8. Ford teaches the formulation of a "very soluble" drug, promethazine hydrochloride, with HPMC, and that the ratio of drug to HPMC controls the drug release rate. Tr. 453:10-19). Dr. Park, however, never specifically explains why a POSA would be motivated to combine these references. Rather, he states generally that a POSA would have combined the '288 patent with the Ford reference because Ford "teaches extensive use of HPMC, so anybody can easily combine '288 patent and Ford" with "more" than a reasonable expectation "to come out with [an] oral solid sustained release formulation of quetiapine." Tr. 452:19-454:19.

It does not appear that a POSA would necessarily have been motivation to combine these teachings or would have had any reasonable expectation of success if they had. The active ingredient in Ford is much more soluble than quetiapine, and it has no pH-dependent

solubility, unlike quetiapine. Also, the Ford active ingredient is dosed at only 25 mg, whereas quetiapine requires much higher doses. Tr. 1444:5-1446:6. Furthermore, promethazine hydrochloride has very different properties from quetiapine and is used to treat a completely different condition. Tr. 1445:16-1446:6. Consequently, Defendants have not proven by clear and convincing evidence that a POSA would have combined the '288 patent with Ford to obtain the subject matter of claims 1, 2, 10, and 13 or that a POSA would have had a reasonable expectation that such a combination would have been successful. *See* Prud'homme Tr. 1445:16-1446:6.

With respect to combining the '288 patent with the Skoug reference, Dr. Park testified that a POSA would have combined the teachings of the two because Skoug "deals with HPMC formulation[s]" of a soluble drug, adinazolam mesylate. In a conclusory fashion, Dr. Park also testified that a POSA, aware of the "teachings" of the '288 patent and Skoug, would have proceeded to develop the subject matter of claims 1, 2, 10 and 13 of the '437 patent with "more" than a reasonable expectation of success in "making the oral sustained release formulation of quetiapine." Tr. 454:20-456:4.

There are several factors, however, that weigh against the finding that a POSA would have had reason to combine these references or would have had any reasonable expectation of success in doing so. For example, the active compound of Skoug is different from quetiapine, it is dosed differently, it has different solubility, and the disease state treated with it is different from what quetiapine is used to treat. Tr. 1446:7-1447:20. The Skoug reference itself evaluates biological properties of adinazolam to determine if it is suitable for an oral sustained release dosage form. JTX-327 at 7. This stands in contrast to Dr. Park's opinion that, in order to make a sustained release form of an existing drug, the only thing one needs to

know about the drug is its solubility. Tr. 412:5-20. Overall, the Court finds that Defendants have not proven by clear and convincing evidence that a POSA would have combined the '288 patent with Skoug to obtain the subject matter of claims 1, 2, 10, and 13 or that a POSA would have had a reasonable expectation that such a combination would have been successful. *See* Tr. 1445:16-1446:6.

Dr. Park also testified that '437 patent claims 11 and 12 would have been obvious in light of the '288 patent in combination with any one of four other prior art references: the Dow Brochure, Melia, the Handbook of Pharmaceutical Excipients, and Sako, each of which discloses the existence of pH-modifiers. Tr. 387:12-20, 505:17-21. However, Dr. Park did not explain how a POSA would decide whether to use a pH modifier, how to choose from a multitude of options, or why a POSA would have a reasonable expectation that any given pH modifier would provide an acceptable formulation. In particular, Dr. Park did not testify as to why the sodium citrate of claim 12 would have been selected. While Dr. Park testified that buffers are designed to "maintain a certain pH"; he did not explain why a POSA would choose a base like sodium citrate (found in claim 12) as opposed to a buffer.

The references asserted by Defendants--Dow, Melia, the Handbook of Pharmaceutical Excipients, and Sako--either generally describe the existence of pH modifiers or describe pH modifiers for particular compounds other than quetiapine. As to the former, the references provide no guidance as to whether and in what circumstances a pH modifier is needed or which one(s) to try. As to the latter, according to Dr. Prud'homme, the identified compounds do not have the "biological or chemical complexity of quetiapine" and, therefore, would not provide sufficient teaching as to whether a POSA would have expected success in using any of the pH modifiers with quetiapine. Tr. 1448:3-10.

For example, while the Dow Brochure discloses the existence of pH modifiers, it does not discuss pH modifiers for any particular compound and does not address which pH modifier(s), if any, should be used with a molecule that has the chemical and biological complexity of quetiapine. Tr. 1447:21-1448:10. Melia teaches the inclusion of succinic or tartaric acid to control the pH of the gel layer in HPMC matrices and enhance the release of weak bases. JTX-180 at 15. Melia also discusses the use of magnesium hydroxide, an alkali to suppress the initial surge of weakly basic drugs from HPMC capsules in gastric fluid. JTX-180 at 15. Because, however, Melia does not disclose a compound with the biological or chemical complexity of quetiapine, it does not provide a basis for expecting success in formulating quetiapine. Tr. 1448:3-10.

The Handbook of Pharmaceutical Excipients lists every pharmaceutical excipient that a formulator could possibly use. Tr. 494:2-5. The Handbook therefore provides many options, but no guidance. Like Melia, the Handbook does not disclose a compound with the complex biological or chemical properties of quetiapine and, therefore, the Handbook, provides be no basis for expecting success in formulating quetiapine. Tr. 1448:3-10.

The Sako patent application also describes the use of an organic acid such as citric acid or tartaric acid when a drug is a basic substance. Tr. 493:10-18. It, however, does not discuss the use of sodium citrate, which is claimed in claim 12. Sako, like previous references, does not disclose a compound with the biological or chemical complexity of quetiapine; based on Sako, there would be no basis for expecting success in formulating quetiapine. Tr. 1448:3-10.

The Court finds that Defendants have not proven by clear and convincing evidence that a POSA would have combined the ’288 patent with any of the references disclosing the

existence of pH modifiers to obtain the subject matter of claims 11 or 12. Defendants have not proven by clear and convincing evidence that a POSA would have had a reasonable expectation that such a combination would be successful.

Dr. Kirsch testified that claims 3-9 and 13 (as it incorporates claims 3-9) would have been obvious to a POSA as of May 1997 based on the '288 patent in combination with any one of four other prior art references: the 1982, 1987, or 1995 Dow Brochures and the '138 application. Tr. 578:21-579:10, 595:13-18. Dr. Kirsch noted that claim 3 recites four HPMC polymers and their characteristics. Tr. 597:15-19. According to Dr. Kirsch, all were commercially-available and well known, but only three of the four are identified in the Dow Brochures. Tr. 601:15-20). The fourth is found in the '138 application. Tr. 600:25-601:13.

Dr. Kirsch noted that the three HPMC polymer types disclosed in the Dow Brochures differed from the ranges in claim 3 (subparts (a) and (c)) in that Dow made HPMC grades with 7-12% hydroxypropoxy content but that those subparts of the claim set the upper part of the range at 9%. Tr. 601:15-602:12. As far as combining '288 patent with the Dow Brochures, Plaintiffs' expert Dr. Prud'homme disagreed with Dr. Kirsch's testimony for the same reasons as explained above with respect to Dr. Park's testimony. Tr. 1432:9-20.

Dr. Kirsch relied on the teaching of sustained release bupropion hydrochloride formulations comprising HPMC and pharmaceutically acceptable excipients in the '138 application. Tr. 596:6-12. Dr. Kirsch testified that he found Example 2 of the '138 application "particularly useful." Tr. 596:19-25. Dr. Kirsch focused on Example 2 because it discloses an example using 20% by weight Methocel E4M in a formulation, which Dr. Kirsch testified is an amount of E4M that falls within the ranges claims in claims 3-7. Tr. 607:3-15.

Dr. Kirsch testified that Example 2 also discloses the use of microcrystalline cellulose and magnesium stearate, which are mentioned as excipients in claims 8 and 9.

Absent the application of hindsight, however, it does not appear that a POSA would have had reason to combine the teachings of the ’138 application and the ’288 patent because the compounds in each are very different, bupropion has a solubility that is fifty times higher than that of quetiapine, with no pH-dependent solubility. Tr. 1450:7-15. Dr. Kirsch did not offer an opinion on the issue of why a POSA would have been motivated to combine these references. A POSA would also not have had a reasonable expectation that quetiapine could be successfully formulated in the same way that bupropion was formulated because of the different chemical and biological properties of the drug including the fact that bupropion is used to treat a different disease. Tr. 1450:22-1451:10.

Consequently, Defendants have not proven by clear and convincing evidence that a POSA would have combined the ’288 patent with either the Dow Brochure or the ’138 application to obtain the subject matter of claims 3-9 or 13 or that a POSA would have had a reasonable expectation that such a combination would have been successful. Tr. 1450:7-1451:10.

*c. Creating Sustained-Release Quetiapine --Reasonable Expectation of Success*

To prevail on obviousness, Defendants must establish by clear and convincing evidence that a POSA in May 1997 would have had at least a reasonable expectation of being able to make a sustained release formulation of quetiapine within the scope of the ‘437 patent claims (*i.e.*, a solid oral dosage form sustained release formulation where a gelling agent, preferably HPMC, provides the sustained release). The Court finds that Defendants have not met that burden. Defendants’ experts testified that a POSA easily would have been able to

make a HPMC-based gel system sustained release formulation of quetiapine in May 1997. However the Court finds that such a conclusion was based primarily upon hindsight and, further, failed to consider certain obstacles that a POSA would have faced in trying to develop any kind of sustained release form of a drug with the physical and biological properties of quetiapine.

If a POSA had decided to pursue sustained release quetiapine in May 1997, the POSA would have had a wide range of sophisticated technologies available to achieve sustained release, including transdermal patches, implantable systems, or orally-administered systems. Tr. 60:11-61:17, 1410:23-1411:6. The available orally-administered systems included liquid formulations, liposome formulations, and solid dosage forms. Tr. 1411:6-9.

Among solid oral dosage forms, there were a number of different technologies that one could have been tried to achieve sustained release. Tr. 1411:6-9. Those include osmotic pump technology, ion exchange resins, coated pellets, and inert (hydrophobic) matrix systems. PTX-1326 at 111-115; Tr. 1411:10-1412:6, 1415:4-15. These techniques were commonly used in May 1997 to achieve sustained release. Tr. 404:2-405:16. In developing a sustained release formulation, a POSA would need to consider the strengths and weaknesses of each type of formulation system relative to the chemical and biological properties of the active drug, in this case quetiapine. Tr. 1412:7-11.

Defendants' expert Dr. Park agreed that any formulation scientist understood that at least five formulation options for a solid sustained release oral dosage form were available in May 1997, although he testified only as to the gel matrix system approach employed in the '437 patent. In forming his opinion on obviousness, Dr. Park did not consider whether a

POSA would have even contemplated osmotic pumps, ion exchange resins, coated pellets or inert (hydrophobic) matrix systems. Tr. 520:8-521:18.

Dr. Park focused only on the gel matrix approach to sustained release. He justified his narrow focus by testifying that the gel matrix approach was the most commonly used, was the easiest, was safe and was foolproof. Tr. 405:17-23; 435:6-436:1. Yet even after focusing exclusively on the gel matrix systems, in conducting his obviousness analysis, Dr. Park did not consider all the complications identified in relevant references (discussed *infra*) except for solubility. Consequently, even if the Court had found that Defendants had proven by clear and convincing evidence that a POSA would have been motivated to try a sustained release formulation of quetiapine, Defendants have not proven by clear and convincing evidence that the POSA would have had a reasonable expectation of success in creating such a formulation because of (1) the vast number of formulation options and the unpredictable nature of formulation science and (2) the unique features of quetiapine. *See* Tr. 1409:14-19.

The evidence presented shows that formulation work can be unpredictable. Liu Dep. 419:18-420:8, 434:22-437:9. The prior art does not permit a POSA to predict the outcome of any given formulation approach. *See, e.g.*, Tr. 1419:5-9; PTX-1326 at 110. As one author states,

> What may be an effective type of dosage form design for one drug may be ineffective in promoting the sustained release of another drug because of peculiar physical, chemical, and biological qualities. To maintain the constant level of drug in the system, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. For each drug, this is a highly individualized quality.

Ansel, PTX-1326 at 110. Even if a POSA for some reason was directed to focus on HPMC, there is still a great deal of complexity and a non-finite number of possible solutions to the

problem of formulation. There would have been no expectation that any of the possible HPMC solutions would have worked. *See, e.g.*, Tr. 1419:5-9; PTX-1326 at 110.

It appears that it is only with hindsight would one focus on gelling agents without some teaching in the art directing a POSA to try gelling agents. Defendants have not articulated why gelling agents would have been selected for the development of a sustained release quetiapine formulation and why there would have been a reasonable expectation of success if a gelling agent was selected. The Court finds that Defendants have not carried their burden to show the obviousness of using a gelling agent by clear and convincing evidence. The evidence establishes that art of pharmaceutical formulation is significantly more complicated than defendants' experts suggest.

Defendants' expert Dr. Kirsch admitted that there exist physical, chemical, and biological properties of a drug that would caution against its use in a sustained release formulation. Tr. 623:20-624:1. Dr. Kirsch also acknowledged that certain literature, specifically the Robinson reference, PTX-1327, teaches that there are physical, chemical, and biological properties of a drug that may have an adverse influence on the production, design, and performance of a sustained release formulation of that drug. Tr. 624:14-20.

Dr. Park authored a prior art book chapter titled "Medical Applications of Controlled Release" that lists the following "Parameters Influencing the Design of Oral Sustained Release Dosage Forms": dose size, drug molecular weight, charge and pKa, aqueous solubility, partition coefficient, stability, absorption, metabolism, half-life, margin of safety (aka therapeutic index), side effects, and clinical response. PTX-1012 at 7-8; Tr. 538:21-540:5. Dr. Park specifically noted in his publication that a dose size of 0.5 grams (500 milligrams) "is an upper limit for the sustained release system" and that "[d]rugs with short

half-life will require too much amount for the sustained release." PTX-1012 at 7, 8. Yet, at trial Dr. Park opined that a POSA would only consider the solubility of quetiapine before deciding whether to combine various references or whether he or she had a reasonable expectation of success in obtaining a useful formulation. Park Tr. 540:7-13.

Other literature similarly teaches that a formulator would consider at least the following drug-related factors as influencing whether a sustained release formulation could be successfully made: solubility, pH dependent solubility, half-life, metabolism, and dose. Tr. 57:17-25, 58:2-15, 1400:19-1401:15; PTX-1327 at 10-11. For example, a book by Chang & Robinson, a standard reference in the field of pharmaceutical dosage forms, discloses that various properties of a drug adversely influence the ability to formulate a sustained release dosage form of that drug. PTX-1327 at 10-11; Tr. 1400:25 to 1401:7. Among those adverse influences are dose size, aqueous solubility, partition coefficient, drug stability, absorption, distribution, metabolism, duration of action, and therapeutic index. Tr. 1401:18-23; PTX-1327 at 10-11.

Dose size can adversely influence whether a sustained release dosage form could be made if the dose needed is greater than 500 mg. PTX-1327 at 10. If the dose needed is higher, it is a poor candidate for sustained release. The reason for this is that the additional materials needed in the tablet to provide the sustained release will make the tablet unacceptably large. Tr. 1403:1-18. Dr. Kirsch acknowledged that there is a tablet size beyond which a person could not swallow it. Tr. 626:12-17. The dose size believed to be effective for quetiapine as of May 1997 was not yet known, but the literature suggested the dose would be higher than 750 mg. Tr. 1404:1-15; *see also* Tr. 802:4-17, 826:9-17.

Aqueous solubility of a drug is another factor that can adversely influence whether a sustained release dosage form of a drug can be made. Chang & Robinson state that extremes in solubility, *i.e.* the drug is very or poorly soluble, would adversely impact whether a sustained release formulation could be made. Tr. 1404:16-24; PTX-1327 at 10.

A drug with pH-dependent solubility presents another problem that will adversely influence whether a sustained release dosage form could be made. PTX-1327 at 10; Tr. 1405:3-12; Bradley Dep. 84:22-85:7. A drug with pH-dependent solubility is one that dissolves differently depending on the pH (degree of acidity) of the surrounding environment – such a drug could dissolve more in the acidic environment of the stomach and less in the neutral environment of the GI tract. Tr. 1405:3-12; Park Tr. 490:10-15.

The partition coefficient of a drug – the degree to which it prefers to dissolve in water or in tissue – also can adversely influence whether a sustained release dosage form can be made. PTX-1327 at 10; Tr. 1406:3-15. A drug that too strongly prefers to dissolve in tissue or too strongly prefers to dissolve in water presents an undesirable situation. Tr. 1406:9-15. As of May 1997, the literature contained no information about the partition coefficient of quetiapine. Tr. 1406:16-18.

Drug stability also can adversely influence whether a sustained release dosage form can be made. PTX-1327 at 10. As of May 1997, the literature contained no information regarding the stability of quetiapine. Tr. 1406:19-23.

Metabolism of a drug also can adversely influence whether a sustained release dosage form can be made. PTX-1327 at 11. If a drug is extensively metabolized, it may be removed too quickly from the system. Tr. 1407:4-8). As of May 1997, the literature reported that quetiapine was extensively metabolized. Tr. 1407:19-1408:3; JTX-181 at 3. Contrary to the

teaching of Chang & Robinson and the opinion of Dr. Prud'homme, Dr. Park disagreed that the metabolism of a drug would be a factor to consider in making a sustained release dosage form. Tr. 415:2-15; Tr. 1407:9-17, 1408:18-22. However, the Court accords Dr. Park's testimony less weight.

The duration of action (related to the half-life) of the drug "obviously plays a major role in considering a drug for sustained-release systems" and can adversely influence a sustained release dosage form. PTX-1327 at 11; Tr. 1408:4-13. As of May 1997, there were conflicting reports in the literature regarding the half-life of quetiapine. Tr. 1408:14-17. Neither Dr. Park nor Dr. Kirsch considered this complicating factor associated with quetiapine in their obviousness analysis.

As Dr. Prud'homme testified, if a drug were to possess several of the properties listed by Chang and Robinson as adversely affecting whether a sustained release formulation could be made or if those properties were not known at the time, a POSA would not have had a reasonable expectation of success in making a sustained release formulation of that drug. Tr. 1408:23-1409:13. Based on a consideration of all the properties expected to adversely impact developing a sustained release formulation, quetiapine would not have been considered a good candidate for a sustained release dosage form as of May 1997. Tr. 1409:14-19.

7. Secondary Considerations

*a. Long-Felt Unmet Need*

Evidence that an invention satisfied a long-felt and unmet need that existed on the patent's filing date is a secondary consideration of nonobviousness. A long-felt but unmet need arises when there is " 'an articulated identified problem [as of the patent's filing date] and evidence of efforts to solve that problem.' " *Perfect Web Tech. v. InfoUSA, Inc.*, 587 F.3d

1324, 1332–33 (Fed. Cir. 2009) (quoting *Tex. Instruments v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993)). Plaintiffs' evidence shows that Seroquel XR, which embodies each of claims 1-12 of the '437 patent, unexpectedly satisfied a long-felt but unmet need that existed in May 1997 for the treatment of bipolar depression. Tr. 1242:17-23, 1250:21-1251:21.

In May 1997, there was a recognized but unmet medical need for an effective drug therapy for the treatment of bipolar depression. Tr. 1252:23-1253:16. Proven, effective drug therapy for the treatment of bipolar depression did not exist in May 1997. Tr. 1246:18-24. Seroquel XR satisfied that unmet need; in 2008, Seroquel XR received FDA approval for the treatment of bipolar depression. Tr. 1251:4-9; Stip. Fact 154.

Dr. Calabrese testified as to a number of studies that were undertaken after 1999 that showed quetiapine to be effective at treating bipolar depression. Tr. 1255-62. The drug used in the studies was Seroquel IR. *See id.* As it was unexpected at that time that Seroquel IR would have been effective for treating bipolar depression, a POSA would have also found it completely unexpected that quetiapine in a sustained release form would be effective in treating bipolar depression.

*b. Other Unexpected Benefits*

The Court finds that Plaintiffs have established that unexpected clinical advantages of Seroquel XR support a finding of nonobviousness.

First, Plaintiff assert that Seroquel XR has a unique an unexpected combination of FDA approvals, as it is, among other things, the only drug approved as monotherapy for the treatment of bipolar depression and as an adjunctive therapy for MDD. Seroquel XR has a unique and unexpected combination of FDA approvals that are, in turn, based on the

unexpected results of clinical trials conducted with the drug. Seroquel XR is the only drug ever approved for the treatment of both bipolar depression as monotherapy and major depressive disorder as adjunct therapy. JTX-449 at 1; Tr. 1080:2-6, 1084:3-12; Tr. 1277:15-20. Similarly, it is the only drug ever approved for the treatment of bipolar disorder, bipolar depression and major depressive disorder. Tr. 1220:3-6, 1277:15-20; Tr. 1942:12-15. Seroquel XR's approved FDA indications and the underlying clinical trials are evidence of unexpected clinical benefits. Tr. 1276:6-12. A POSA in May 1997 would not have expected that quetiapine in any form, including sustained release would be effective in treating bipolar depression or in patients with MDD. Tr. 1276:6-12.

Seroquel XR's set of approvals itself provides unexpected benefits. Dr. Calabrese noted that a bipolar disorder patient who has been misdiagnosed as suffering from MDD and treated with traditional antidepressants can become dangerously manic or fast-cycling. If the patient is treated with Seroquel XR, the risk of this potentially catastrophic problem is reduced. This is a particular benefit for family physicians who typically assess a patient in the course of ten minutes. Tr. 1276:6-23. Dr. Reist offered no opinion to rebut Dr. Calabrese's opinion that practicing physicians take comfort in the fact that Seroquel XR has proven efficacy in treating multiple conditions, which are often difficult to distinguish in their early stages and during brief office visits.

Second, Plaintiffs presented evidence at trial showing that Seroquel XR has a sedation profile that is unexpectedly superior as compared to the sedation profile of Seroquel IR. Even though Seroquel IR is effective in treating bipolar depression, the sedation and somnolence side effects associated with it are problematic for high-functioning patients who need to stay alert during the day. Tr. 1264:7-1265:8. In contrast to patients with schizophrenia, the

majority of patients with bipolar disorder function at a high level, are fully employed, and need to be functional throughout the day; side effects (such as somnolence and sedation) are major issues for this class of patient. Tr. 1264:18-1265:3. Due to job requirements or personal relationships, many patients find that they cannot tolerate Seroquel IR due to its sedation and somnolence profile. Tr. 1264:7-1265:8.

Another unexpected benefit of Seroquel XR is that it is better tolerated than Seroquel IR in the treatment of bipolar depression. Tr. 1263:20-1264:2; 1264:13-17. In particular, Seroquel XR is less sedating than Seroquel IR the following day after taking an evening dose. Nyberg Dep. 150:20-22, 151:13-20.

A POSA as of May 1997 had no reason to believe that a sustained release form of quetiapine would show reduced intensity of sedation as compared to an immediate release formulation. Calabrese Tr. 1269:6-14. Exactly why Seroquel XR is better tolerated is unclear but it relates to the extended release nature of the formulation; the prevalence of somnolence and sedation is the same between the two drugs, but those side effects are not as bothersome to Seroquel XR patients. Tr. 1264:7-12, 1265:4-8.

Dr. Calabrese testified that, based on his own clinical experience as well as the clinical experience of his colleagues in the field, the approval of Seroquel XR in 2008 provided a far better option for treating bipolar depression than Seroquel IR. The somnolence and sedation of Seroquel XR is less severe and, therefore, more tolerable than with Seroquel IR. Tr. 1265:4-14, 1266:8-15. Defendants' clinical expert, Dr. Reist, has never used Seroquel XR and could offer no contrary opinion. Tr. 1766:2-1767:2, 1815:4-7.

Dr. Calabrese testified that he started using Seroquel XR in bipolar depression in patients who were not tolerating Seroquel IR. Patients would be started with Seroquel IR;

they would complain of intolerable sedation; and Dr. Calabrese would switch them to Seroquel XR. Tr. 1265:15-1266:3. Those patients reported that Seroquel XR was better. Tr. 1265:23-1266:3. This would have been unexpected because the prevalence of the side effect (the percentage of patients reporting it) was the same between the two drugs, but the severity of the sedation in Seroquel XR was less. Tr. 1265:15-1266:7. Also, one might have expected that the somnolence would occur for a longer period of time with the sustained release quetiapine. Tr. 830:11-14.

According to Dr. Calabrese, Seroquel XR's better tolerability is important to high-functioning patients who need to be alert during the day. Calabrese Tr. 1264:18-1265:3. This improved tolerability makes Seroquel XR unexpectedly more effective in treating bipolar depression than Seroquel IR. Tr. 1253:7-16, 1265:4-8.

Dr. Calabrese's testimony regarding a reduction in sedation when using Seroquel XR is consistent with the results of two trials comparing Seroquel IR and Seroquel XR conducted by AstraZeneca. Clinical trials 33 and 40 studied differences in the intensity of somnolence and sedation between Seroquel IR and Seroquel XR. Tr. 1266:16-20. Trial 33 was a clinical trial to test the primary hypothesis regarding sedation one hour after the drug was administered. Tr. 1644:3-9. Trial 33 involved healthy volunteers, and Tr. 1267:1-8, healthy volunteers have an increased sensitivity to sedation and somnolence. Tr. 1267:4-8. In contrast, diseased patients may tolerate sedation and somnolence to some degree because it is therapeutic. Tr. 1267:4-8. Trial 33 concluded that there was a significant decrease in severity of sedation in Seroquel XR as compared to Seroquel IR at one hour after dosing. Tr. 1267:22-1268:3, Tr. 1644:3-13, 1644:24-1645:4; DTX-2665; JTX-176 at 5 fig.1.

Trial 40 was identical to Trial 33 except that it studied bipolar patients rather than healthy volunteers. Trial 40 concluded that there was a significant decrease in the severity of somnolence and sedation in Seroquel XR as compared to Seroquel IR at one hour after dosing. Tr. 1268:19-1269:5, 1646:14-18, 1647:14-19.

A third alleged unexpected benefit relates to dosing. Seroquel XR may be titrated up to the maximum approved dose more rapidly as compared to Seroquel IR. Titration refers to the process of ramping up a medication to the target dose over time. *See* Tr. 1273:24-1274:3. Often drugs need to be titrated slowly to avoid certain side effects. Tr. 1815:17-20. In practice, it is desirable to titrate a drug as quickly as possible to achieve the target dose. Tr. 1815:11-16. As compared to Seroquel IR, Seroquel XR shows a significant improvement in the speed with which it can be titrated according to the two drugs' FDA approved labels. Tr. 1273:15 to 1274:3 According to Plaintiffs expert Dr. Calabrese, this difference is surprising and unexpected because sustained release preparations take longer to achieve peak plasma concentration and would be expected to take longer to titrate. Tr. 1274:15-23, 1275:10-12. Accepting the testimony of Dr. Calabrese, the Court finds this to be an unexpected benefit weighing against obviousness.

Although Defendants' expert Dr. Reist testified that a POSA as of May 1997 would have expected Seroquel XR to be able to be titrated faster than Seroquel IR because of XR's reduced peak plasma levels, Dr. Reist appears to be speculating to a degree. Tr. 1763:5-8 (referring to side effects "likely" due to peak plasma levels). Moreover, Dr. Reist did not address Dr. Calabrese's opinion that the time to peak plasma was longer with XR and therefore one would expect titration to be longer.

*c. Commercial Success*

"[A] presumption arises that the patented invention is commercially successful 'when a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent.' " *Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1376 (Fed. Cir. 2000); *see also Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310-11 (Fed. Cir. 2010) ("A *prima facie* case of nexus is made when the patentee shows both that there is commercial success, and that the product that is commercially successful is the invention disclosed and claimed in the patent."). In other words, "commercial success or other secondary considerations may presumptively be attributed to the patented invention only where the marketed product embodies the claimed features and is coextensive with them." *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328 (Fed. Cir. 2008) (internal quotation marks omitted). Once the patentee demonstrates a *prima facie* nexus, the burden of coming forward with evidence in rebuttal shifts to the challenger. *Crocs*, 598 F.3d at 1310-11. As discussed below, the Court finds that Plaintiffs have established commercial success.

Seroquel XR was approved by the FDA for the treatment of schizophrenia on May 17, 2007. Stip. Fact 95, 152. In August 2007, AstraZeneca began selling those tablets under the name Seroquel XR Stip. Fact 95. Seroquel XR was approved by the FDA for the maintenance treatment of schizophrenia on November 15, 2007. Stip. Fact 153. On October 8, 2008, Seroquel XR was approved by the FDA as monotherapy in the treatment of bipolar depression; as monotherapy in the treatment of bipolar mania; and as adjunctive therapy in the treatment of bipolar mania. Stip. Fact 95, 154. Seroquel XR was approved by the FDA as adjunctive therapy for major depressive disorder ("MDD") on December 2, 2009. Stip. Fact

95. Seroquel XR is the only drug approved for the treatment of all of these diseases. Tr. 1220:3-6, 1277:15-20.

AstraZeneca heavily relies upon the combination of approved indications for Seroquel XR in its marketing of the drug. Pharmaceutical marketing is tightly regulated and must be tied to the contents of the FDA-approved label. Tr. 1933:5-8. Seroquel XR's unique combination of approvals in bipolar depression and MDD sets it apart from its competitors in the atypical antipsychotic drug market. Tr. 1541:3-9.

Seroquel XR was the fastest growing atypical antipsychotic drug in 2010. Tr. 1579:14-23. It has become the fifth best seller in the atypical antipsychotic drug class in just a little over three years. Tr. 1075:13-19; PTX-1009. During the period from 2008 to the first quarter of 2011, Seroquel XR's share of the atypical antipsychotic drug market, in terms of new prescriptions, grew from 1.2% to 6%. PTX-1008. Seroquel XR was also the lowest-priced branded atypical antipsychotic (other than Seroquel IR), and its price increases have been consistent with competitor products. Tr. 1609:24-1610:8.

Seroquel XR's sales growth (both dollars and prescriptions) and market share demonstrate its commercial success. Sales of Seroquel XR have grown considerably since its launch in 2007, with annual wholesale sales presently approaching $1 billion. AstraZeneca forecasts continued strong sales continuing in 2012, at which time competition is expected from generic immediate release quetiapine. Certain defendants agree with this forecast. Tr. 1072:12-1073:21.

Annual U.S. wholesale sales of Seroquel XR increased from $184.3 million in 2008 (its first full calendar year of sales) to $822 million in 2010, representing a cumulative annual growth rate of about 111 percent. Tr. 1069:17-1070:13; PTX-1004; PTX-1331. Seroquel

XR's cumulative wholesale sales since launch through March 2011 total $1.7 billion, "a very impressive growth in sales performance over a little more than a three-year period." Tr. 1069:17-1070:13; PTX-1004; PTX-1331.

According to AstraZeneca's records, net sales of Seroquel XR increased from about $70 million in 2007 to $120 million in 2008, the first full year of Seroquel XR sales, to about $341 million in 2009, and to over $640 million in 2010. JTX-100; Tr. 1071:9-25. Net sales are expected to increase to $873 million in 2011. JTX-100. Net sales are product sales minus customer discounts and rebates, principally managed market discounts. Tr. 1543:20-1544:3, 1545:23-1546:1. Managed market discounts are discounts given to AstraZeneca's customers based on usage and formulary access. Tr. 1546:2-10. These discounts are a standard practice in the pharmaceutical industry and are considered a cost of doing business. Tr. 1546:11-22. A disproportionately high share of Seroquel XR patients receive government-sponsored healthcare, which leads to correspondingly higher total discounts—the discounts given to the government (through, e.g., Medicaid) are, by law, the best available. Tr. 1546:23-1547: 8. Rebates to managed market customers also are standard practice in the pharmaceutical industry in general and in the antipsychotic drug market in particular. Tr. 1546:11-22.

Direct brand expenses are the expenses AstraZeneca incurs in marketing its products. Tr. 1547:9-14. Total marketing is the largest share of direct brand expenses, which includes marketing to physicians and consumers (e.g. television advertisements). Tr. 1547:15-1548:4. Product contribution after field force allocation (the allocation of expenses for the sales force used to market the drug, "FFA") is essentially the profit Seroquel XR contributes to the company. Tr. 1553:20-1554:2.

The total product contribution attributable to Seroquel XR after FFA, from launch through 2012, is expected to be about $1.6 billion. Tr. 1553:20-1554:6; JTX-100. AstraZeneca expects the total product contribution for Seroquel XR to be about $3 billion between 2013 and 2015. Tr. 1554:21-1555:1.

Since Seroquel XR's introduction in 2007, prescriptions for the product have also grown considerably. Quarterly new prescriptions (new prescriptions, not including refills) for Seroquel XR from launch through the first quarter of 2011 are illustrated in). Annual new prescriptions of Seroquel XR increased from 282,000 in 2008 to over 1.4 million in 2010 and achieved a total of over 3 million new prescriptions from market introduction through March 2011. The annualized growth rate for new prescriptions between 2008 and 2010 was over 128 percent. PTX-1005; Tr. 1063:3-14

New entrants such as Seroquel XR in the antipsychotic therapeutic area generally face physicians that are hesitant to switch medication for a patient that is responding reasonably well to his/her current medication, a result of the fact that the efficacy and tolerability of antipsychotic drugs vary widely at the individual patient level. Tr. 1074:15-1075:11, 1385:15-1386:1. Strong new prescription growth is evidence of commercial success given this challenge and is evidence of the fact that physicians are willing to switch patients from competing products and/or that Seroquel XR is serving a previously unmet need. Tr. 1075:12-1076:1.

Total prescriptions (all prescriptions, including refills) for Seroquel XR also have increased substantially as well. Total prescriptions of Seroquel XR increased from 439,000 in 2008 to almost 2.5 million in 2010 (an annualized growth rate of over 135 percent), and achieved a total of about 5 million prescriptions from launch through the first quarter of 2011.

PTX-1331; PTX-1006; Tr. 1070:14-1071:5. Data shows acceleration of the growth in Seroquel XR total prescriptions after it was approved to treat bipolar depression and again after it was approved to treat MDD. Tr. 1079:11-1080:1; PTX-1006; PTX-1331. These trends suggest that Seroquel XR provides a clinical benefit to the patient populations it treats. Tr. 1080:7-1081:1.

Commercial success is also shown by Seroquel XR's market share increase within the antipsychotic drug market. The antipsychotic drug market is a mature, crowded, highly competitive market. Many atypical antipsychotic drugs are prescribed as first-line treatment for psychotic disorders such as schizophrenia and bipolar mania. PTX-1003; Tr. 1061:14-24. Many of these drugs have been on the market since the late 1990s and early 2000s. Seroquel XR competes with products marketed by approximately seven other pharmaceutical companies in the atypical antipsychotic drug market, including many companies that are much larger companies than AstraZeneca. Tr. 1583:17-1584:3.

Being in a large, competitive market, AstraZeneca invests heavily in its promotional efforts for Seroquel XR Tr. 1584:4-21. As of 2010 Seroquel XR had higher total sales than the other new branded atypical antipsychotic drugs launched since 2003, all of which are sustained release atypical antipsychotic drugs. Seroquel XR's share of the total market rose from 1.2 percent in 2008 to 6 percent in the first quarter of 2011. PTX-1008; Tr. 1064:1-6. During that period, Seroquel XR gained more new prescription market share percentage points than any other branded atypical antipsychotic drug. PTX-1008. Seroquel XR's significant level of, and growth in, new prescription market share is further evidence of its commercial success.

Looking at the annual total prescriptions for atypical antipsychotic drugs from 1998 to 2010, PTX-1009; Tr. 1064:7-13, Seroquel XR has achieved higher total prescriptions than other branded drugs launched since 2003. PTX-1009; PTX-1331; Tr. 1078:1-1079:10. Since August 2007 (Seroquel XR's first full month on the market), Seroquel XR has grown more in the number of total prescriptions than any other branded drug except one (Abilify), and more than all of the other sustained release drugs. The results are similar when comparing the number of new prescriptions across drugs.

Turning to the relative shares of the atypical antipsychotic drugs, in terms of total prescriptions, for 2005 through the first quarter of 2011, Seroquel XR's total prescription share rose from 0.9 percent in 2008 to 5.3 percent in the first quarter of 2011, a greater increase than any other branded atypical antipsychotic drug during that time. PTX-1010; Tr. 1076:2-1077:1. Most of the other atypical antipsychotic drugs experienced a market share decline during this period. *Id.* Moreover, a competing generic atypical antipsychotic was introduced in the market in 2008, yet Seroquel XR continued to grow despite the fact that this generic competitor was available at a small fraction of the price of Seroquel XR. PTX-1010; Grabowski Tr. 1077:2-25.

The commercial success of Seroquel XR is primarily due to its unique combination of FDA approved indications and, therefore, there is the requisite nexus between the commercial success of Seroquel XR and the '437 patent. Contrary to Defendants' assertions, the Court finds that Seroquel XR's commercial success has not been due to other factors such as excessive promotion, Seroquel IR, and the '288 patent.

With respect to promotion, AstraZeneca's promotion of Seroquel XR has not been excessive. Testimony showed that it has been in line with what would have been expected for

a drug with Seroquel XR's pattern of approvals. Tr. 1095:14-22. The marketing-to-sales ratios for Seroquel XR were 50 percent for its first full year on the market, 33 percent for the second year, and 20 percent for the third. Tr. 1094:21-25. This is consistent with typical expenditures on marketing for the life cycle of a pharmaceutical product. Tr. 1093:21-1094:25. While Defendants' testified regarding, among other things, product lifecycle marketing and AstraZeneca's own goals for the product, the Court finds that Defendants failed to prove that the promotion, discounts, rebates or other expenditures associated with Seroquel XR were either excessive or primarily responsible for Seroquel XR's successful sales. Further, to the extent that AstraZeneca's internal marketing expenses are probative, they must be viewed in light of the fact that Seroquel XR was launched into a mature market with numerous atypical antipsychotics available and the need to promote the new and unique indications for bipolar depression and MDD. Tr. 1095:14-1096:7. In sum, promotion of Seroquel XR is not the primary reason for its commercial success. Tr. 1092:5-11.

Nor does the Court find Seroquel XR's commercial success to be attributable to Seroquel IR or the '288 patent. 589. In many ways, Seroquel IR appeared to be more "more of a barrier than a help" to Seroquel XR. Tr. 1132:19-2. Seroquel IR and Seroquel XR are differentiated products, with different indications, and Seroquel XR was treated as a new drug by the FDA. Although there can be some advantages from familiarity with the immediate release product, there also are burdens or barriers because Seroquel IR was on the market for more than a decade before Seroquel XR entered the market. . Tr. 1131:23-1132:12. As Dr. Grabowski testified, "[m]any patients were well controlled on the original formulation and on other competing alternatives in the marketplace. . . . [Seroquel] XR was coming into a marketplace . . . where many patients are already well controlled and physicians in this

marketplace are reluctant to switch individuals." Tr. 1132:13-18. It is significant that Dr. Grabowski had previously studied the economic effects of competition in the market between different products that had overlap in utility, and concluded "[t]hat it's difficult to switch patients that are already well controlled, particularly for diseases like mental health, oncology, [and] life-threatening or highly-disabling diseases." Tr. 1134:20-1135:6.

Further, the evidence shows that AstraZeneca did not rely on a strategy of switching the already-established patient base of Seroquel IR to Seroquel XR. Tr. 1564:10-16, 1575:17-25; PTX-1017 at 5. AstraZeneca's Seroquel XR 2009 Strategy and Launch Plans specifically stated that "[i]f a patient is doing well on SEROQUEL we are not asking to physicians to convert those patients to SEROQUEL XR unless the physician believes the patient should be switched." PTX-1017 at . Dr. Grabowski also independently concluded that AstraZeneca did not attempt to have doctors switch patients from immediate-release Seroquel IR to Seroquel XR. Tr. 1135:15-1137:7; PTX-1017 at 5.

Data shows that Seroquel XR did not gain market share primarily from Seroquel IR. Instead, during the period from September 2009 to November 2010, approximately half of Seroquel XR's growth came from new patients, about a quarter were either switches from other drugs or an addition to other therapy, and only about a quarter came as switches from Seroquel IR. Tr. 1139:9-17; JTX-225 at 7.

The evidence also established that the success of Seroquel XR was not directly attributable to the exclusivity granted by the '288 patent on the quetiapine molecule. Seroquel XR has its own set of unique indications, which is associated with economic trends Dr. Grabowski considered and is consistent with the physician perceptions reflected in the results of the Acumen survey, which was presented at trial. JTX-230; JTX-229; Tr. 1139:18-1140:4.

Further, AstraZeneca's own internal projections show that Seroquel XR's sales are expected to rise in 2012 even though the exclusivity associated with the '288 patent will expire in March 2012. JTX-100. Said another way, Seroquel XR's sales are expected to rise even though cheaper generic versions Seroquel IR are expected to be available. Tr. 1581:16-1582:3; JTX-100. According to Dr. Grabowski, if the sales of Seroquel XR were due to the exclusivity provided by the '288 patent, he would not expect to see increasing sales next year. Tr. 1144:16-1145:4.

## III. CONCLUSION

As set forth above, the Court finds that Anchen and Mylan have infringed of claims 1-13 of the '437 patent. Osmotica and Torrent have infringed claims 1-2 and 10-12. The Court further finds that Defendants have not established by clear and convincing evidence that any of the claims of the '437 patent are invalid. Consequently, judgment shall be entered in favor of Plaintiffs.

s/ JOEL A. PISANO
Joel A. Pisano, United States District Judge

Dated: March 28, 2012