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United States District Court,
D. New Jersey.

ASTRAZENECA PHARMACEUTICALS LP and Astrazeneca UK Limited, Plaintiffs,
v.
ANCHEN PHARMACEUTICALS, INC. Osmotica Pharmaceutical Corporation, Torrent Pharmaceuticals Limited and Torrent Pharma Inc., Mylan Pharmaceuticals Inc. and Mylan Inc., Defendants.

Civil Action Nos. 10–cv–1835 (JAP)(TJB), 10–cv–4203 (JAP)(TJB), 11–cv–2484 (JAP)(TJB), 10–cv–4205 (JAP)(TJB), 10–cv–4971 (JAP) (TJB), 10–cv–5519 (JAP)(TJB), 11–cv–2483 (JAP)(TJB).
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Attorneys and Law Firms

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OPINION

PISANO, District Judge.

I. INTRODUCTION

***1** 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]

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.

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).
- 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

***2** 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.

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

***3** 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.

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.

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

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.

***4** 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.

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

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.

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]

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.

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 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.

***5** 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]

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.

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, 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.

***6** 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

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