UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., et al., Plaintiffs, v. SANDOZ, INC., et al., Defendants.	08 Civ. 7611 (BSJ)(AJP)
TEVA PHARMACEUTICALS USA, INC., et al., Plaintiffs, v. MYLAN PHARMACEUTICALS INC., et al., Defendants.	09 Civ. 8824 (BSJ)(AJP) **Opinion and Order**

BARBARA S. JONES
UNITED STATES DISTRICT JUDGE

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INTRODUCTION

This case involves the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified at 21 U.S.C. §§ 355, 360cc (2003); 35 U.S.C. §§ 156 (2002), 271 (2003)) (the "Hatch-Waxman Act"). Plaintiff Teva Pharmaceuticals USA, Inc. holds a patent on a glatiramer acetate product which it markets as Copaxone®, a medicine for treating multiple sclerosis ("MS"). The Defendants have filed abbreviated new drug applications ("ANDAs") with the FDA seeking to market a generic alterative to Copaxone® prior to the expiration of Teva's patents.

The Plaintiffs, Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., and Yeda Research and Development Co. Ltd. (collectively, "Teva") allege infringement. The Defendants, Sandoz Inc., Sandoz International GmbH, Novartis AG, and Momenta Pharmaceuticals, Inc. ("Momenta") (collectively, the "Sandoz" Defendants),[1] Mylan Pharmaceuticals Inc., Mylan Inc., and Natco Pharma Ltd. (collectively, the "Mylan" Defendants[2])

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[1] Teva voluntarily dismissed, without prejudice, their claims against Sandoz International GmbH and Novartis AG. (Dkt. 180 in 08 Civ. 7611(BSJ)(AJP).) Unless noted otherwise, all references to "Sandoz" are to the two remaining Sandoz Defendants—Sandoz Inc. and Momenta Pharmaceuticals, Inc.

[2] Unless noted otherwise, all references to "Mylan" are to all of the Defendants in 09 Civ. 8824.

(collectively, with the Sandoz Defendants, "Defendants") claim Teva's patents are invalid and unenforceable, among other defenses.

Specifically, Teva filed separate suits, first against the Sandoz Defendants, and second against the Mylan Defendants. The Court consolidated the cases on October 22, 2010. (Dkt. 200 in 08 Civ. 7611.)

Teva alleges Sandoz infringes four U.S. patents—No. 7,199,098, No. 6,939,539, No. 6,054,430, and No. 6,620,847—under 35 U.S.C. §§ 271(a), 271(b), 271(c), and 271(e)(2). Sandoz counterclaims and seeks a declaratory judgment of non-infringement, unenforceability, and invalidity of nine U.S. patents: No. 7,199,098, No. 6,939,539, No. 6,054,430, No. 6,620,847, No. 5,981,589, No. 6,342,476, No. 6,362,161, No. 5,800,808, and No. 6,048,898. With respect to Mylan, Teva alleges Mylan infringes seven U.S. patents under 35 U.S.C. § 271(e)(2): No. 7,199,098, No. 6,939,539, No. 6,054,430, No. 6,620,847, No. 5,981,589, No. 6,342,476, and No. 6,362,161. Mylan, in turn, counterclaims and seeks a declaratory judgment of non-infringement, unenforceability, and invalidity of the same nine U.S. patents as Sandoz.[3]

I. The Parties

[3] The Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202. Venue is proper pursuant to 28 U.S.C. §§ 1391(c) and 1400(b).

A. Teva

Teva Pharmaceuticals USA, Inc. ("Teva USA") is a Delaware corporation with its principal place of business in North Wales, Pennsylvania. (Joint Pretrial Order Stipulations ("JPO") ¶ 55.) Teva Pharmaceutical Industries Ltd. ("Teva Ltd.") is an Israeli company with its principal place of business in Israel. (JPO ¶ 56.) Teva Neuroscience, Inc. is a Delaware corporation with its principal place of business in Kansas City, Missouri. (JPO ¶ 57.) Yeda Research and Development Co. Ltd. markets and commercializes new developments from the laboratories of the Weizmann Institute of Science ("Weizmann"). (JPO ¶ 58.) Its principal place of business is in Israel. (JPO ¶ 58.)

B. Sandoz

Sandoz Inc. is a Colorado corporation with its principal place of business in Princeton, New Jersey. (JPO ¶ 62.) Sandoz Inc. does business in the State of New York, including in the Southern District of New York. (First Am. Compl.[4] ¶ 6.) Momenta is a Delaware corporation with its principal place of business in Cambridge, Massachusetts. (JPO ¶ 9.) Momenta does business in the State of New York, including in the Southern District of New York. (First Am. Compl. ¶ 9.)

C. Mylan

[4] Unless noted otherwise, all references to the First Amended Complaint are to the First Amended Complaint in Teva v. Sandoz, No. 08 Civ. 7611(BSJ)(AJP), and all references to the Complaint are to the Complaint in Teva v. Mylan, No. 09 Civ. 8824(BSJ)(AJP).

Mylan Pharmaceuticals Inc. is a West Virginia corporation with its principal place of business in Morgantown, West Virginia. (JPO ¶ 59.) Mylan Pharmaceuticals does business in the State of New York, including in the Southern District of New York. (Mylan Answer ¶ 8.) Mylan Inc. is a Pennsylvania corporation with its principal place of business in Canonsburg, Pennsylvania. (JPO ¶ 60.) Mylan Inc. does business in the State of New York, including in the Southern District of New York. (Mylan Answer ¶ 9.) Natco Pharma Ltd. ("Natco") is an Indian company with its principal place of business in India. (JPO ¶ 61.) Natco does business in the State of New York, including in the Southern District of New York. (Natco Answer ¶ 10.)

II. The Patents-in-Suit

A. Overview

The patents-in-suit are U.S. Patent Nos. 5,981,589 ("'589 Patent"), 6,054,430 ("'430 Patent"), 6,342,476 ("'476 Patent"), 6,362,161 ("'161 Patent"), 6,620,847 ("'847 Patent"), 6,939,539 ("'539 Patent") and 7,199,098 ("'098 Patent") (collectively, the "Orange Book Patents") and U.S. Patent Nos. 5,800,808 ("'808 Patent") and 6,048,898 ("'898 Patent") (collectively with the Orange Book Patents, the "patents-in-suit"). (JPO ¶ 64.) Each of the patents-in-suit is entitled "Copolymer-1 improvements in compositions of copolymers." (JPO ¶ 67.) The four inventors

named on the patents-in-suit are Eliezer Konfino, Michael Sela, Ruth Arnon, and Dvora Teitelbaum. (Plaintiffs' Trial Exhibits ("PTX") 1-9.) Eliezer Konfino worked for Teva and retired from the company in December 1991.[5] Michael Sela, Ruth Arnon, and Dvora Teitelbaum worked at Weizmann. (JPO ¶ 66.)

The patents-in-suit each claim priority to (i) U.S. Patent Application No. 08/248,037, filed May 24, 1994 ("'037 application"), abandoned, and (ii) Patent Application No. 08/344,248, filed November 23, 1994 ("'248 application"), also abandoned. (JPO ¶¶ 79-80.) The substantive portion of the patent specification is identical for each of the patents-in-suit. Accordingly, for ease of reference, unless noted otherwise, all citations to the specification are to the '808 patent specification.

The patents-in-suit are directed to improved compositions of copolymer-1. (PTX 1 at 1:1-2.) The patents explain that the improved compositions consist of a lower molecular weight form of copolymer-1 that may be used for the treatment of multiple sclerosis. (PTX 1 at 1: 43-53.)

The patent specification defines the molecular weight characteristics of the lower molecular weight copolymer-1 in several ways. The patent specification explains, for example, that the lower molecular weight copolymer-1 can be substantially

[5] The Stipulations do not specify for which Teva entity Konfino worked.

free of species over 40 kilodaltons ("kDa"), and it describes a preferred composition that has "less than 5% of species" having a molecular weight over 40 kDa. The patents also describe a more preferred composition having "less than 2.5% of species" having a molecular weight over 40 kDa. (PTX 1 at 1:64-2:4.)

In addition, the patents describe the claimed lower molecular weight copolymer-1 as "having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa." (PTX 1 at 2:5-7.) A "molar fraction" in this context refers to the proportion of molecules (as measured by the number of "moles" of molecules) between 2 kDa and 20 kDa, as compared to the total number (or "moles") of all of the molecules in the sample.

Finally, the lower molecular weight copolymer-1 is defined in the patents-in-suit by its average molecular weight. The patent specification provides various ranges for the average molecular weight values for the lower molecular weight copolymer-1. Those ranges are reflected in the asserted claims, which are discussed in further detail below. The patents also describe a synthetic process for making the claimed copolymer-1. (PTX 1 at 4:28-6:3.)

The patent specification describes two ways of producing a lower molecular weight copolymer-1. (PTX 1 at 2:14-41, 2:51-3:18, 4:28-6:3.) First, in Example 1, the patents describe

making copolymer-1 and then "fractionating"—or dividing into smaller portions—the resulting copolymer-1 to isolate a low molecular weight fraction. (PTX 1 at 2:57-3:2.) In addition, the patents provide examples describing processes for making copolymer-1 of varying molecular weights. (PTX 1 at 4:28-6:3.) Second, the patents describe the use of a particular reagent in the synthetic process—hydrobromic acid in the form of hydrogen bromide ("HBr") in acetic acid—to cleave an intermediate product called protected copolymer-1 polypeptides into smaller polypeptides. The patents-in-suit teach that the time and temperature of the HBr/acetic acid treatment step can be varied to control the amount of cleavage that occurs, and hence, the molecular weight of the resulting copolymer-1. (PTX 1 at 4:59-6:3.)

The patent specification describes the use of a calibrated size exclusion chromatography ("SEC") column, Superose 12, to measure the molecular weight distribution and average molecular weight of copolymer-1 samples. (PTX 1 at 3:6-13.)

Example 2, entitled "Toxicity Analysis," appears in the specification of each of the patents-in-suit and describes two different toxicity tests for copolymer-1: the in vivo mouse test and the in vitro rat basophilic leukemia ("RBL") degranulation test. (PTX 1 at 3:21-4:27.) Referring to the in vivo mouse test, Example 2 states that "[t]hree batches of copolymer-1

having an average molecular weight of 7.3 and 8.4 kDa (less than 2.5% copolymer-1 species over 40 kDa) and 22 kDa (more than 5% copolymer-1 species over 40 kDa) were subjected to the toxicity test" in which five mice in each experimental group were injected with the test solution. (PTX 1 at 3:23-40.) It goes on to state that "[if], at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated 'non-toxic'" and if "one or more of the mice had died or had shown adverse signs, then the batch was designated 'toxic'." (PTX 1 at 3:36-40.) In regard to the in vivo test, Example 2 concludes that "the batches with the average molecular weight of 7.3 and 8.4 kDa were both designated 'non-toxic', whereas in the batch with the average molecular weight of 22 kDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently designated 'toxic.'" (PTX 1 at 3:41-45.)

With respect to the RBL degranulation test, Example 2 explains that the purpose of this test was to "screen out those batches of copolymer-1 which invoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects." (PTX 1 at 3:63-67.) Example 2 reports that "[f]our batches of copolymer-1, with average molecular weight between 6,250-14,500, were analyzed for both % of the species with

molecular weight over 40 kDa and for degranulation of RBL's." (PTX 1 at 4:11-15.)

Example 2 sets forth the results of the RBL degranulation test in the following table:

Average M.W. (Daltons)	% of species with M.W. over 40 KDa	% Serotonin Release
6,250	<2.5	12.4
7,300	<2.5	21.0
13,000	>5	66.9
14,500	>5	67.8

(PTX 1 at 4:15-24.) In regard to the RBL test data, Example 2 concludes, "[a]s can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin indicative of toxicity is low, and vice versa." (PTX 1 at 4:25-27.)

The patent specification also describes pharmaceutical compositions comprising the lower molecular weight copolymer-1, as well as the treatment of multiple sclerosis using lower molecular weight copolymer-1. (PTX 1 at 1:51-53.)

B. Copaxone® - Teva NDA

Teva USA is the holder of New Drug Application ("NDA") No. 20-622, for glatiramer acetate, which was approved by the United States Food and Drug Administration ("FDA") on December 20, 1996. (JPO ¶¶ 82, 83.) The Teva entities market and sell

glatiramer acetate under the trade-name Copaxone® in the United States. (JPO ¶ 84.) Glatiramer acetate is a form of copolymer-1. (Sept. Tr. (Grant) 220:13-221:2; Sept. Tr. (Owens) 630:11-631:8; PTX 206 at SDZ00000031; PTX 320 at MYL0000236.) Copaxone® was first offered for sale in the United States on April 2, 1997. (Sept. Tr. (Congleton) 45:14-21.) It is approved for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis ("RRMS"), including patients who have experienced a first clinical episode and have magnetic resonance imaging features consistent with multiple sclerosis. (JPO ¶ 85.)

Each of the patents-in-suit is assigned to and owned by Yeda. (JPO ¶ 68.) Teva Ltd. is the exclusive licensee of each of the patents-in-suit. (JPO ¶ 69.) The Teva entities caused the Orange Book Patents to be listed in the FDA's publication, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book"). (JPO ¶ 65.)

C. Sandoz's and Momenta's ANDA

Momenta entered into a collaboration and license agreement with Sandoz AG on June 13, 2007, regarding, among other things, the development of a generic Copaxone® product. (PTX 957 (Brugger Dep.) at 105:12-106:08; PTX 175.) Sandoz Inc. submitted an ANDA, No. 90-218, on December 27, 2007, seeking approval from the FDA to manufacture and sell a generic

Copaxone® product before the expiration of the Orange Book Patents. (JPO ¶¶ 92, 93.)

[redacted] Sandoz Inc. submitted a major amendment to its ANDA. (Sept. Tr. (Grant) 221:8-164; PTX 351.) [redacted] Sandoz Inc. submitted a "Briefing Book" to the FDA, in advance of [redacted] meeting between Sandoz Inc. and the FDA regarding Sandoz's ANDA ("Briefing Book"). (Sept. Tr. (Gokel) 419:19-420:5; PTX 913.) The Briefing Book, among other things, described changes that Sandoz Inc. planned to make to its manufacturing process. (PTX 913.) Sandoz amended its ANDA [redacted] (Hagberg Reply Decl. Ex. A.)

Pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Sandoz Inc. filed a certification with the FDA, alleging that the claims of the Orange Book Patents are invalid, unenforceable, and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of Sandoz's ANDA proposed glatiramer acetate product ("Paragraph IV Certification"). (JPO ¶ 94.) Sandoz Inc. sent a letter ("the Notice Letter"), dated July 10, 2008, to Teva USA, Teva Ltd., Teva Neuroscience, and Yeda, notifying them that Sandoz Inc. filed an ANDA for glatiramer acetate and was providing information to Teva pursuant to 21 U.S.C. § 355(j)(2)(B)(i)-(ii). (JPO ¶ 95.)

On August 28, 2008, Teva sued Sandoz Inc. and Momenta for infringement of the Orange Book Patents. Teva Pharmaceuticals

USA, Inc., v. Sandoz Inc., No. 08 Civ. 7611 (BSJ)(AJP) (S.D.N.Y.). (JPO ¶ 97.) Sandoz Inc. and Momenta counterclaimed for, among other things, a declaratory judgment of non-infringement, invalidity, and unenforceability of all nine patents-in-suit. (Dkt. 14 at ¶¶ 89-116 in No. 08 Civ. 7611; Dkt. 16 at ¶¶ 89-116 in No. 08 Civ. 7611.)

D. Mylan and Natco ANDA

Mylan Inc. and Natco signed an agreement, dated June 7, 2008, relating to the development and marketing of a glatiramer acetate product in the United States. (JPO ¶ 87; PTX 245.) On June 29, 2009, Mylan Pharmaceuticals submitted an ANDA, No. 91-646, seeking approval to manufacture and sell Mylan's proposed glatiramer acetate product before the expiration of the Orange Book Patents. (JPO ¶¶ 86, 88.) [redacted] On April 19, 2011, the Mylan entities submitted a major amendment to the ANDA. (DTX 1411.) The major amendment did not make any changes to the manufacturing process.

Pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Mylan Pharmaceuticals filed a certification with the FDA, alleging that the claims of the Orange Book Patents are invalid, unenforceable, and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of Mylan's proposed

glatiramer acetate product ("Paragraph IV Certification"). (JPO ¶ 89.) Mylan Pharmaceuticals sent a notice letter, dated September 16, 2009, to Teva USA, Teva Ltd., Teva Neuroscience, and Yeda, notifying them that Mylan filed an ANDA for glatiramer acetate and was providing information to Teva pursuant to 21 U.S.C. § 355(j)(2)(B)(ii). (JPO ¶ 90.)

On October 16, 2009, Teva and Yeda sued the Mylan entities and Natco for infringement of the Orange Book Patents. Teva Pharmaceuticals USA, Inc., v. Mylan Pharmaceuticals, Inc., No. 09 Civ. 8824(BSJ)(AJP) (S.D.N.Y.). (JPO ¶ 91.) The Mylan Defendants counterclaimed for, among other things, a declaratory judgment of non-infringement and invalidity of all nine patents-in-suit. (Dkt. 8 at ¶¶ 82-117 in 09 Civ. 8824; Dkt. 34 at ¶¶ 187-224 in 09 Civ. 8824.)

III. Procedural History and Claim Construction

Teva and Sandoz submitted claim construction briefing in late 2009, and a claim construction hearing was held on January 20, 2010. (Dkts. 68-72, 76-82, 89-93, 96-97, 102, 104-05, 114-19 in 08 Civ. 7611.) Sandoz moved for summary judgment on the basis of indefiniteness on December 23, 2009. (Dkts. 120-22 in 08 Civ. 7611.) On September 7, 2010, the Court denied Sandoz's motion for summary judgment. (Dkt. 181 in 08 Civ. 7611.) Sandoz subsequently submitted supplemental claim construction

briefing regarding the term "average molecular weight." (Dkts. 192-93, 204-06 in 08 Civ. 7611.)

Teva and Mylan submitted claim construction briefing from April to July 2010. (Dkts. 38-39, 41, 43-45, 57-65 in 09 Civ. 8824.) Mylan moved for summary judgment on the basis of indefiniteness on November 15, 2010. (Dkt. 96-98 in 09 Civ. 8824.) On August 24, 2011, the Court issued a Memorandum and Order denying Mylan's motion for summary judgment and construing the disputed claim terms as follows:

- "Copolymer-1" is construed to mean "a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively, non-uniform with respect to molecular weight and sequence, which is synthesized by polymerization of suitably protected amino acid carboxyanhydrides." (Claim Construction Order ("CCO") at 12.)

- "Average molecular weight" is construed to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (Id. at 40.)[6]

- "Copolymer-1 having a molecular weight" is construed to mean "copolymer-1 having a peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (Id. at 40, n.10.)

- "Polypeptides composed of glutamic acid, lysine, alanine and tyrosine" is construed to mean "more than one polypeptide, each consisting essentially of glutamic

[6] There are different types of average molecular weights, including number average ("Mn"), weight average ("Mw"), z-average ("Mz"), and viscosity average ("Mv"), in addition to "peak average" ("Mp"). (Sept. Tr. 1195:6-19 (Scandella).)

acid, lysine, alanine and tyrosine residues." (Id. at 14-15.)

- "Copolymers of alanine, glutamic acid, lysine and tyrosine" is construed to mean "more than one polymer molecule, each consisting essentially of glutamic acid, lysine, alanine and tyrosine residues." (Id. at 15.)

- "Copolymer-1 fraction" is construed to mean "a portion of a copolymer-1 mixture having a narrower molecular weight distribution than the starting protected copolymer-1 mixture." (Id. at 16.)

- "Toxicity" is construed to mean "the degree to which a substance exhibits negative effects in mouse mortality or RBL degranulation test." (Id. at 44.)

- "Predetermined" is construed to mean "determined beforehand." (Id. at 47.)

- "Predetermined by a test reaction" is construed to mean "determined beforehand by a reaction carried out to determine results of varying reaction conditions." (Id. at 50.)

(Dkt. 273 in 08 Civ. 7611; Dkt. 194 in 09 Civ. 8824.)

A. July 2011 Inequitable Conduct Trial

After denying Teva's motion for a summary judgment finding of no inequitable conduct (Dkt. 232 in 08 Civ. 7611; Dkt. 141 in 09 Civ. 8824), the Court held a bench trial regarding Defendants' inequitable conduct defense in July 2011. The Court heard live testimony from the following witnesses:

i. Teva's Witnesses

Dr. Irit Pinchasi

Dr. Irit Pinchasi is a former Vice President for Innovative R&D at Teva.[7] (July Tr. (Pinchasi) 13:13-17.) Dr. Pinchasi testified regarding the research and development of Teva's Copaxone® product; the inventions described in the patents-in-suit; the technology related to those inventions; and Teva's initial patent application filed in May 1994.

Professor Ruth Arnon

Professor Ruth Arnon is a named inventor on the patents-in-suit. (PTX 1.) She is currently Professor Emeritus at Weizmann and President of the Israel Academy of Sciences and Humanities. (July Tr. (Arnon) 303:14-17.) She was formerly the Chair of the Department of Chemical Immunology, Dean of the Faculty of Biology, and Vice President of Weizmann. (July Trial Tr. (Arnon) 307:16-21.)

Professor Arnon testified regarding the discovery and development of copolymer-1; the inventions of the patents-in-suit; the technology related to those inventions; and the initial patent application filed in May 1994.

Dr. Barbara Baird

Dr. Barbara Baird is the Horace White Professor and Chair of the Department of Chemistry and Chemical Biology at Cornell University. (July Tr. (Baird) 569:7-11; PTX 768.) Dr. Baird is an expert in the RBL degranulation test, and has been using this

[7] At trial, Pinchasi did not specify for which Teva entity she worked.

test for over thirty years. (July Tr. (Baird) 572:7, 573:6-14, 576:10-12, 585:22-586:1.)

At trial, Dr. Baird testified regarding the RBL degranulation test and its use by Weizmann and Teva, including in the patents-in-suit.

ii. Defendants' Witnesses

Dr. Ian Kimber

Dr. Ian Kimber is Chair of the Department of Toxicology at the University of Manchester. His research has covered immunology and toxicology, with a particular focus on the regulation of immune responses and allergic disease. (July Tr. (Kimber) 368:17-20.) At trial, he testified regarding the toxicity testing described in the patents-in-suit.

Eugene Rzucidlo

Eugene Rzucidlo is an attorney at the law firm Hershkovitz & Associates who practices before the United States Patent and Trademark Office ("PTO"). He was previously a patent examiner at the PTO and a member of the Board of Patent Appeals. (July Tr. (Rzucidlo) 498:24-499:8.) He has practiced before the PTO continuously since 1985. (July Tr. (Rzucidlo) 499:16-500:11.)

At trial, Rzucidlo testified regarding the process of patent prosecution and the prosecution histories of the patents-in-suit.

B. September 2011 Infringement and Invalidity Trial

Starting on September 7, 2011, the Court held a bench trial regarding Plaintiffs' infringement claims and Defendants' remaining non-infringement and invalidity defenses. The Court heard testimony from Sandoz on its non-infringement, obviousness, lack of enablement, and indefiniteness defenses. The Court heard testimony from Mylan on its non-infringement, best mode, and obviousness defenses. During the trial, Mylan notified Plaintiffs and the Court that it was no longer asserting that the patents are invalid based on anticipation or public use. (Sept. Tr. 1349:9-1351:24.)

At the September trial, the Court heard live testimony from the following witnesses:

i. Teva's Witnesses

Jon Congleton

Jon Congleton is the Senior Vice President and General Manager of Teva Neuroscience. (Sept. Tr. (Congleton) 39:19-22.) He has been with Teva Neuroscience for over fifteen years. (Sept. Tr. (Congleton) 41:12-13.) Prior to becoming Senior Vice President, Congleton served as both product director and director of marketing for Copaxone®. (Sept. Tr. (Congleton) 42:1-13.)

At trial, Congleton testified regarding the nature of Teva's business, sales and marketing of Copaxone®, and the

history and state of the market for multiple sclerosis treatments.

Dr. Robert Lisak

Dr. Robert Lisak has been the Chairman of the Department of Neurology and Professor of Immunology and Microbiology at Wayne State University for the past twenty-five years. He is also Chief of Neurology at Harper University Hospital. (Sept. Tr. (Lisak) 78:6-79:7, 84:6-11; PTX 419.) He is an expert in multiple sclerosis and its treatment. (Sept. Tr. (Lisak) 87:24-88:6.)

Dr. Lisak testified regarding multiple sclerosis and its treatment; the long-felt need for a drug like Copaxone®; the failure of others to develop safe and effective multiple sclerosis treatments; and Defendants' infringement of claim limitations related to treating multiple sclerosis.

Dr. Gregory Grant

Dr. Gregory Grant is a Professor of Biochemistry in Medicine and Developmental Biology at the School of Medicine at Washington University School of Medicine. (Sept. Tr. (Grant) 178:9-13; PTX 760.) He is also Director of the Protein and Nucleic Acid Chemistry Laboratories of Washington University. (Sept. Tr. (Grant) 178:14-17; PTX 760.) He is an expert in the characterization of proteins and polypeptides using size exclusion chromatography. (Sept. Tr. (Grant) 188:11-17.)

Dr. Grant testified regarding the background of the chemistry and molecular weight measurement technique described in the patents-in-suit and Defendants' infringement with regard to the claim limitations relating to molecular weight. He also provided rebuttal testimony regarding the issues of non-obviousness, definiteness, and enablement.

Dr. George Gokel

Dr. George Gokel is a Distinguished Professor of Science and Associate Director of the Center for Nanoscience at the University of Missouri in St. Louis. (Sept. Tr. (Gokel) 334:3-8; PTX 774.) He is an expert in chemistry, including synthetic and peptide chemistry. (Sept. Tr. (Gokel) 340:4-10.)

Dr. Gokel testified regarding the chemistry described in the patents-in-suit; Defendants' infringement with regard to the claim limitations relating to copolymer-1 and the process for making copolymer-1; and provided an overall infringement opinion. He also provided rebuttal testimony regarding the issues of non-obviousness and best mode.

Dr. Nicole Sampson

Dr. Nicole Sampson is a Professor of Chemistry at Stony Brook University. (Sept. Tr. (Sampson) 536:6-10; PTX 436.) She is an expert in peptide and polymer chemistry. (Sept. Tr. (Sampson) 542:20-25.)

Dr. Sampson testified regarding Defendants' infringement with regard to the copolymer-1 claim limitations under the doctrine of equivalents and provided rebuttal testimony on the issue of non-obviousness.

ii. Mylan's Witnesses

Dr. Walter Owens

Dr. Walter Owens is the Vice President of Global Research and Development at Mylan Inc. (Sept. Tr. (Owens) 594:8-17.) He testified regarding the development of Mylan's generic Copaxone® product, including Mylan's use of universal calibration and the testing of its proposed product on the experimental autoimmune encephalomyelitis model.

Dr. Stephen Kent

Dr. Stephen Kent is a professor of chemistry, biochemistry, and molecular biology at the University of Chicago, where he has worked for the last ten years. He is an expert in the chemical synthesis and analysis of peptides and proteins. (Sept. Tr. (Kent) 651:10-16.)

At trial, he testified regarding, among other things, Mylan's best mode defense and provided rebuttal testimony regarding Mylan's infringement with regard to the copolymer-1 claim limitations.

Dr. Allen Zeiger

At the time of his retirement in 1998, Dr. Allen Zeiger was a professor of biochemistry and molecular biology at Jefferson Medical College at Thomas Jefferson University in Philadelphia. (Sept. Tr. (Zeiger) 785:2-12; DTX 1966; DTX 4030.) As a professor, he taught gel filtration chromatography (i.e., SEC) to graduate level students for 35 years. (Sept. Tr. (Zeiger) 870:23-871:3.)

Dr. Zeiger is an expert in the fields of biochemistry, immunochemistry, synthetic peptide chemistry, peptide polymer chemistry, and in the characterization of the properties of peptide polymers. (Sept. Tr. (Zeiger) 798:4-6, 799:7-8, 798:7-13, 799:7-8, 798:14-17, 799:7-8, 798:18-20, 799:7-8, 798:21-23, 799:10-23, 870:23-871:3.) At trial, he testified regarding, among other things, Mylan's obviousness defense.

Dr. Susan Rice

Dr. Susan Rice has her own consulting firm, Susan A. Rice and Associates, Inc. (Sept. Tr. (Rice) 995:23-996:10.) She testified regarding toxicity data disclosed in the patents-in-suit, and whether the data demonstrate that the claimed copolymer-1 has unexpected results over the prior art.

Dr. Ari Green

Dr. Ari Green received his M.D. in 2001 from the University of California San Francisco, where he is now an Assistant Professor of Neurology and the Assistant Director of the

Multiple Sclerosis Center. (Sept. Tr. (Green) 1354:16-23; PTX 1964.) He provided testimony regarding secondary considerations of non-obviousness.

iii. Sandoz's Witnesses

Dr. John Bishop

Dr. John Bishop is Senior Vice President, Pharmaceutical Sciences, at Momenta. (Sept. Tr. (Bishop) 1062:25-1063:5.) He testified regarding, among other things, the development of Momenta's generic Copaxone® product.

Dr. Trevor Laird

Dr. Trevor Laird is currently Owner and Senior Consultant for Scientific Update, a consultancy in the area of organic process chemistry. At trial, Dr. Laird testified regarding, among other things, Sandoz's obviousness defense and provided rebuttal testimony on Sandoz's infringement with regard to the "test reaction" claim limitations.

Dr. Carl Scandella

Since 1992, Dr. Carl Scandella has provided consulting services in the areas of biomolecule purification and analysis, process development, and manufacture of clinical lots, including the use of SEC. (Sept. Tr. (Scandella) 1169:15-18; DTX 3564.) During the course of his career, he has used a wide variety of analytical techniques for molecular weight measurement, including SEC, ultracentrifugation, MALDI-TOF mass spectrometry,

and light scattering, among others. (Sept. Tr. (Scandella) 1186:17-1187:12.) Dr. Scandella is an expert on SEC and the characterization of molecular weight. (Sept. Tr. (Scandella) 1191:9-15.) At trial, he testified regarding the Defendants' lack of enablement and indefiniteness defenses.

Dr. Randolph Wall

Dr. Randolph Wall is a Distinguished Professor in the Department of Microbiology, Immunology and Molecular Genetics at the UCLA School of Medicine and is the Associate Director of the UCLA Broad Stem Cell Center. (Sept. Tr. (Wall) 1747:15-18.) He has been a professor at UCLA since 1972. (Sept. Tr. (Wall) 1747:19-20.)

Dr. Wall is an expert in SEC. (Sept. Tr. (Wall) 1756:16-20; 1761:18.) At trial, he was a rebuttal witness for Sandoz regarding its lack of enablement and indefiniteness defenses.

iv. Witnesses Testifying by Deposition

The parties submitted designated deposition testimony from several witnesses including the following: Weizmann employees Professor Ruth Arnon and Dr. Michael Sela; current or former Teva employees Dr. Irit Pinchasi, Eliezer Konfino, Dr. Alexander Gad, and Dr. Haim Varkony; Mylan employees Dr. Stephen Wayne Talton and Dr. Ross Wallingford; Natco employees Dr. Bhujanga Rao, Dr. Duddhi Linga Rao, and Dr. Satyanarayana Kota; current or former Momenta employees Dr. Corinne Bauer, Dr. Steve

Brugger, Dr. Ganesh Venkataraman, and Dr. Mani Iyer; Sandoz employees Dr. Anup Ray and Shrinvasa Rao; and Defendants' expert witnesses Dr. Jerard Hurwitz (Mylan) and Dr. Frantisek Svec (Sandoz). None of these witnesses testified at the September trial.

IV. The Patents-in-Suit and the Patent Claims at Issue

Prior to the September trial, Plaintiffs voluntarily limited the number of asserted claims to narrow the issues for trial. The asserted claims of the patents-in-suit are claim 1 of the '808 patent; claim 1 of the '589 patent; claims 1, 2, and 3 of the '898 patent; claims 1, 2, and 3 of the '430 patent; claim 1 of the '476 patent; claim 1 of the '161 patent; claims 1 and 6 of the '847 patent; claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent; and claims 1 and 8 of the '098 patent. Plaintiffs assert claim 3 of the '430 patent and claim 3 of the '898 patent against Mylan only.

The asserted claims claim, among other things, copolymer-1 with lower molecular weight characteristics, methods of making lower molecular weight copolymer-1, pharmaceutical compositions comprising lower molecular weight copolymer-1, as well as methods of treating multiple sclerosis using the claimed lower molecular weight copolymer-1. The asserted claims contain limitations relating generally to one or more of the molecular weight attributes of the claimed copolymer-1, the process for

making the claimed copolymer-1, and the use of the claimed copolymer-1 for treating multiple sclerosis.

A. Molecular Weight Claim Limitations

All but three of the 22 asserted claims of the patents-in-suit include numerical limitations directed to molecular weight attributes of either the copolymer-1 end product and/or an intermediate product called trifluoroacetyl ("TFA") copolymer-1. The molecular weight limitations can be categorized as "average molecular weight" and "molar fraction" limitations. (PTX 1-2; PTX 4-9.) In addition, three of the asserted claims are directed to a "predetermined molecular weight profile" and have no numerical limitations. (PTX 3.)

i. Average Molecular Weight Limitations

Claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1 and 6 of the '847 patent and claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent are directed to copolymer-1 having an "average molecular weight" falling within a particular numeric range. (PTX 1; PTX 2; PTX 7; PTX 8.) For example, claim 1 of the '539 patent provides:

> A copolymer-1 composition comprising a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has **an average molecular weight of about 4 to about 9 kilodaltons,** wherein the mixture of polypeptides is non-uniform with respect to molecular weight and sequence, and wherein the composition is suitable for treating multiple sclerosis.

(PTX 8 at 5:18-24 (emphasis added).)

The asserted claims containing "average molecular weight" limitations require copolymer-1 having an average molecular weight of "about 5 to 9 kilodaltons" (claim 1 of the '808 patent and claim 1 of the '589 patent), "about 4 to about 9 kilodaltons" (claims 1 and 6 of the '847 patent and claims 1, 8, 9, 12, 23, 30, and 31 of the '539 patent), and "6.25 to 8.4 kilodaltons" (claim 10 of the '539 patent). (PTX 1; PTX 2; PTX 7; PTX 8.)

ii. Molar Fraction Limitations

Several of the asserted claims include limitations relating to the molecular weight distribution of a sample of copolymer-1 or the intermediate TFA copolymer-1. These "molar fraction" limitations are expressed as a certain percentage of the copolymer-1 polypeptides (or TFA copolymer-1 molecules) having molecular weights falling within a molecular weight range or above a particular molecular weight value. (PTX 4; PTX 5; PTX 6; PTX 8; PTX 9.) Claim 1 of the '430 patent exemplifies the copolymer-1 molar fraction and TFA copolymer-1 molar fraction limitations:

> Copolymer-1 having **over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa**, prepared by a process comprising the steps of:
>
> reacting protected copolymer-1 with hydrobromic acid to form **trifluoroacetyl copolymer-1 having over 75% of**

> **its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa**, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and treating said trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa with aqueous piperidine solution to form copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa.

(PTX 4 at 5:21-6:8 (emphasis added).)

The copolymer-1 "molar fraction" limitations include "over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa" (claims 1, 2, and 3 of the '430 patent); "less than 2.5% . . . over 40 kilodaltons" (claims 8 and 30 of the '539 patent); "less than 5% . . . over 40 kilodaltons; and . . . over 75% . . . within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons" (claim 1 of the '476 patent; claim 1 of the '161 patent; claim 1 of the '098 patent); and "less than 2.5% . . . above 40 kDa" (claims 9, 10, and 31 of the '539 patent and claim 8 of the '098 patent). (PTX 4; PTX 5; PTX 6; PTX8; PTX9.)

All of the TFA copolymer-1 molar fraction limitations require "trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa" (claims 1, 2, and 3 of the '430 patent; claim 1 of the '476 patent; claim 1 of the '161 patent). (PTX 4; PTX 5; PTX 6.)

iii. Predetermined Molecular Weight Profile Limitations

Claims 1, 2 and 3 of the '898 patent do not include any numerical molecular weight limitations. Instead, they require that the copolymer-1 have a "predetermined molecular weight profile." (PTX 3.) For example, claim 1 of the '898 patent provides:

> A method of manufacturing **copolymer-1 of a predetermined molecular weight profile**, comprising the steps of: selecting a predetermined molecular weight profile, reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having the predetermined molecular weight profile, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and treating said trifiuoroacetyl copolymer-1 having the predetermined molecular weight profile with aqueous piperidine solution to form copolymer-1 having the predetermined molecular weight profile.

(PTX 3 at 5:35-6:11 (emphasis added).)

B. Process Limitations

Twelve of the asserted claims are directed either to a method of manufacturing copolymer-1 having the desired molecular weight characteristics or to copolymer-1 that is made by a particular process. Although the details of each claim may vary, claim 1 of the '589 patent is illustrative of the claims directed to a process for making the claimed copolymer-1:

> Copolymer-1 having a molecular weight of about 5 to 9 kilodaltons, **made by a process** comprising the steps of:

> reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1, treating said trifluoroacetyl copolymer-1 with aqueous piperidine solution to form copolymer-1, and purifying said copolymer-1, to result in copolymer-1 having a molecular weight of about 5 to 9 kilodaltons.

(PTX 2 at 6:4-13 (emphasis added).)

The asserted process for making and product-by-process claims are claim 1 of the '808 patent; claim 1 of the '589 patent; claims 1, 2, and 3 of the '898 patent; claims 1, 2, and 3 of the '430 patent; claim 1 of the '476 patent; claim 1 of the '161 patent; and claims 1 and 6 of the '847 patent. Claims 1, 2, and 3 of the '898 patent; claims 1, 2, and 3 of the '430 patent; claim 1 of the '476 patent and claim 1 of the '161 patent also require that the hydrogen bromide ("HBr") treatment step "take[] place for a time and at a temperature predetermined by test reaction." (PTX 3; PTX 4; PTX 5; PTX 6.)

C. Treatment of Multiple Sclerosis

Ten of the asserted claims include limitations relating to the treatment of multiple sclerosis. Claim 1 of the '476 patent and claims 23, 30, and 31 of the '539 patent are directed to methods for treating multiple sclerosis. Claim 1 of the '161 is directed to "[a] composition for the treatment of multiple sclerosis." Claims 1, 8, 9, and 10 of the '539 patent recite "wherein the composition is suitable for treating multiple sclerosis." Claim 12 of the '539 patent recites "a dose

therapeutically effective to treat multiple sclerosis of a copolymer-1 composition." (PTX 5; PTX 6; PTX 8.)

D. Pharmaceutical Composition

Four of the asserted claims include limitations relating to the use of the lower molecular weight copolymer-1 as a pharmaceutical composition. Claims 12, 23, 30, and 31 of the '539 patent are directed to the use of lower molecular weight copolymer-1 as a pharmaceutical composition. (PTX 8.) For example, claim 12 of the '539 provides:

> A pharmaceutical composition comprising:
>
> a dose therapeutically effective to treat multiple sclerosis of a copolymer-1 composition, wherein the copolymer-1 composition comprises a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of about 4 to about 9 kilodaltons, wherein the mixture of polypeptides is non-uniform with respect to molecular weight and sequence; and a pharmaceutically acceptable excipient.

(PTX 8 at 5:54-63.)

V. Copolymer-1 and Multiple Sclerosis

A. Multiple Sclerosis: The Disease

Multiple sclerosis is an inflammatory disease of the central nervous system first recognized in the 1860s by the French neurologist Jean-Martin Charcout. (See Sept. Tr. (Lisak) 88:8-89:18.) It is an unpredictable disease involving two of the most complex systems in the body—the immune system and the central nervous system. (Sept. Tr. (Lisak) 136:3-10.) In

persons afflicted with multiple sclerosis, autoimmune cells attack myelin, a protective sheath wrapped around nerves found in the brain and the spinal cord. (Sept. Tr. (Lisak) 88:8-89:4.) This leads to the degeneration of myelin and, eventually, the degeneration or death of underlying nerve cells. (Sept. Tr. (Lisak) 90:4-92:11.)

This degeneration process eventually prevents the central nervous system from functioning properly as the brain loses the ability to send or receive messages to and from various parts of the body and as other functions of the brain or spinal cord become impaired. (Sept. Tr. (Lisak) 90:4-92:11.) As multiple sclerosis progresses, the immune system's attack on myelin causes multiple lesions or scars to form on the brain and the spinal cord. (Sept. Tr. (Lisak) 89:11-15.) The appearance of these multiple scars or scleroses accounts for the disease name "multiple sclerosis." (Sept. Tr. (Lisak) 89:11-15.)

The most common form of multiple sclerosis is RRMS. (Sept. Tr. (Lisak) 96:17-19.) Approximately 85% of all multiple sclerosis patients have this form of the disease. (Sept. Tr. (Lisak) 89:11-15.) Patients with RRMS experience periodic relapses or attacks which are accompanied by steadily worsening disability as the functioning of the nervous system becomes more impaired over time. (Sept. Tr. (Lisak) 95:16-96:25.) The symptoms of RRMS include blurred and double vision, loss of

balance and coordination, tremors, fatigue, bladder and bowel dysfunction, paralysis, and even death in some patients. (Sept. Tr. (Lisak) 92:20-93:21.) Patients may exhibit different neurologic symptoms at various times and many patients become permanently disabled. (Sept. Tr. (Lisak) 92:20-93:21.)

The initial onset of multiple sclerosis typically occurs early in life—between the ages of twenty and forty. (Sept. Tr. (Lisak) 94:10-18.) Dr. Lisak testified that the disease strikes patients in the "prime of life"—when they are beginning their careers, finishing school, or beginning to raise a family. (Sept. Tr. (Lisak) 94:10-18.) There is no way to predict when relapses associated with multiple sclerosis will occur and thus the disease acts like a "hanging sword," threatening sufferers with future attacks of unknown length that may result in increased or complete disability. (Sept. Tr. (Lisak) 97:1-9.)

Prior to the 1990s, there were no treatments available to prevent relapses or slow the progression of disability associated with the disease. (Sept. Tr. (Lisak) 102:2-9; Sept. Tr. (Green) 1391:21-1392:4.) The only option for a physician was to treat a patient's symptoms and to try to shorten the duration of a relapse. (Sept. Tr. (Lisak) 102:2-9; Sept. Tr. (Green) 1391:21-1392:4.)

B. The Weismann Scientists' Discovery of Copolymer-1

Professor Arnon, Professor Sela, and Dr. Teitelbaum are Ph.D. immunologists who worked together at Weizmann, a world-renowned research institute located in Israel. (July Tr. (Pinchasi) 9:12-20; 16:11-17:5; July Tr. (Arnon) 302:23-303:13, 304:11-17; 304:18-305:14.) In about 1966, Professor Arnon and her colleagues became interested in studying an autoimmune disease called experimental autoimmune encephalomyelitis ("EAE"), which is an animal model for multiple sclerosis. (July Tr. (Arnon) 309:11-310:10.) It was already understood by that time that EAE was induced by a single protein called myelin basic protein ("MBP"), but nothing was known about the mechanism of the disease. (July Tr. (Arnon) 309:11-310:10.) Professor Arnon and her colleagues theorized that if they could produce a synthetic polymer that mimicked MBP, it could be used as a research tool to study the mechanism of EAE. (July Tr. (Arnon) 309:11-311:8.)

Professor Arnon and her colleagues synthesized three synthetic polymers, which they called copolymer-1, copolymer-2, and copolymer-3. The copolymers differed in their amino acid composition, but were all targeted to have a molecular weight of 23,000 daltons, which was the molecular weight of MBP. (July Tr. (Arnon) 310:11-311:8.) Professor Arnon and her colleagues tried without success for over a year to use the synthetic copolymers to induce EAE in animals. (July Tr. (Arnon) 310:11-

23.) Eventually, it occurred to them that the synthetic copolymers they made were not similar enough to MBP to induce EAE, but might be similar enough to MBP to compete with it and prevent its activity. (July Tr. (Arnon) 310:11-23.) The experiments they set up to test their hypothesis were successful. (July Tr. (Arnon) 310:11-23.) Instead of inducing EAE, copolymer-1 proved to be effective in suppressing EAE. (July Tr. (Arnon) 310:24-311:13.) The other two copolymers were much less effective. (July Tr. (Arnon) 311:9-13.)

At the time Professor Arnon and her colleagues discovered that copolymer-1 was effective in suppressing EAE, there were practically no treatments available for multiple sclerosis. (July Tr. (Arnon) 311:14-23.) The only options for patients were immunosuppressive drugs, but these had very severe side effects and were not routinely used. (July Tr. (Arnon) 311:14-23.)

Professor Arnon and her colleagues published their initial findings in 1971 in the European Journal of Immunology ("1971 Teitelbaum article"). (PTX 499.) The article described copolymer-1 as having a molecular weight of 23,000 daltons. (July Tr. (Arnon) 311:24-312:22; PTX 499 at 242.)

In 1974, the PTO granted U.S. Patent No. 3,849,550 (the '550 Patent") to Yeda. (DTX 1219.) The patent named Professor Arnon, Professor Sela, Dr. Teitelbaum, and their co-workers as

inventors, and disclosed and claimed the copolymers that they discovered could treat EAE. (DTX 1219.)

The first placebo controlled clinical study of copolymer-1 for the treatment of multiple sclerosis was conducted by Professor Murray Bornstein of the Albert Einstein College of Medicine in New York ("Bornstein trial"). (July Tr. (Arnon) 316:6-15; July Tr. (Pinchasi) 22:4-24; Sept. Tr. (Lisak) 108:25-104:13.) Fifty patients were enrolled in the pilot trial, 25 of whom received copolymer-1. (Sept. Tr. (Lisak) 109:24-110:4; PTX 31 at 408.) Professor Arnon and her colleagues at Weizmann participated in the basic design of the Bornstein trial and supplied Dr. Bornstein with copolymer-1 for use in the trial. (July Tr. (Arnon) 316:16-21.) The copolymer-1 they supplied was intended to have a molecular weight of 23,000 daltons in order to match the molecular weight of MBP. (July Tr. (Arnon) 316:22-317:11.) In fact, however, the batches ranged from 14,000 to 23,000 daltons. (July Tr. (Arnon) 317:12-15; Sept. Tr. (Lisak) 110:11-21; PTX 31 at 408.)

The results of the Bornstein trial were published in 1987 in the New England Journal of Medicine ("1987 Bornstein article"). (July Tr. (Arnon) 327:22-328:9; Sept. Tr. (Lisak) 108:25-109:13; PTX 31.) While the results from the study were encouraging, they did not definitively establish whether the copolymer-1 composition studied was a safe and effective

treatment for RRMS. (PTX 31 at 408; Sept. Tr. (Lisak) 108:25-111:22.)

During the Bornstein trial, Dr. Bornstein notified Professor Arnon and her colleagues that some of the patients experienced local injection site reactions and that, on rare occasions, some patients experienced systemic side effects that included difficulty breathing, palpitations, severe flush, sweating, and severe anxiety. (July Tr. (Arnon) 317:16-320:6; July Tr. (Pinchasi) 23:17-24:23; PTX 28.) His report of these side effects was of grave concern to Professor Arnon. (July Tr. (Arnon) 320:7-16.) She knew copolymer-1 was to be given to patients on a daily basis and, as a result, that any side effects would be a severe issue. (July Tr. (Arnon) 320:7-16.) At that time, however, neither Professor Arnon nor her colleagues had any idea what was causing the side effects or how they could get rid of them. (July Tr. (Arnon) 320:7-16.)

Based on Dr. Bornstein's reports, Professor Arnon and her colleagues looked for screening assays that could be used to differentiate between batches that would cause side effects and those that would not. (July Tr. (Arnon) 320:17-25.) They eventually utilized the in vitro RBL degranulation test. (July Tr. (Arnon) 320:17-25; DTX 3114.) In the RBL degranulation test, RBL cells are preloaded with radio-labeled serotonin and then exposed to copolymer-1. (July Tr. (Arnon) 327:8-21; July

Tr. (Baird) 587:3-589:20.) The amount of serotonin released, or degranulated, by the cells is then measured. (July Tr. (Arnon) 327:8-21; July Tr. (Pinchasi) 25:11-26:1; July Tr. (Baird) 587:3-589:20; DTX 3114.) The RBL test was and still is used as a model for allergic-type reactions, because the degranulation it exhibits in the presence of a stimulant mimics the immune response of human mast cells—a central cell in the allergic immune response system—in responding to allergens or other substances. (July Tr. (Arnon) 321:8-18, 322:21-323:4; July Tr. (Baird) 576:24-577:7, 578:16-582:16, 585:9-21; PTX 522.)

The Weizmann scientists adopted the term "toxicity" to refer to the results of the RBL degranulation test. (July Tr. (Arnon) 327:8-21.) If 30% or more serotonin was released upon exposure to copolymer-1, the batch was designated "toxic" and discarded. (July Tr. (Arnon) 327:8-330:18; PTX 31 at 409.)

One of Professor Arnon's colleagues at Weizmann who was very experienced with the RBL degranulation test suggested the test. (July Tr. (Arnon) 321:8-18.) Before making the decision to go forward with the RBL degranulation test, Professor Arnon personally read all of the literature about the test, including articles by Dr. Reuben Siraganian's group at NIH. (July Tr. (Arnon) 321:8-18, 322:21-323:4; July Tr. (Baird) 576:24-577:7, 578:16-582:16, 585:9-21; PTX 522.)

C. Teva's Agreement with Weizmann

In November 1987, Teva and Yeda, the commercial arm of Weizmann, entered into an agreement for the development of copolymer-1. (DTX 1232.) Teva's goal was to take the invention made by the Weizmann scientists and translate it into a useful pharmaceutical product that could be given to multiple sclerosis patients. (July Tr. (Pinchasi) 12:10-16.) The copolymer-1 project at Teva was divided into chemical, analytical, pharmaceutical, and biological development teams, which were responsible for different aspects of the project. (July Tr. (Pinchasi) 15:4-18.)

Dr. Pinchasi served as project manager of the copolymer-1 project at Teva and was responsible for coordinating all development work. (July Tr. (Pinchasi) 11:6-12, 14:12-15:3.) At trial, Dr. Pinchasi testified that because she is not a chemist, she had only high-level managerial responsibility for the chemical, analytical, and pharmaceutical aspects of the project. (July Tr. (Pinchasi) 15:4-16:3.) She had more substantive input into the biological aspects of the project. (July Tr. (Pinchasi) 14:12-16:3.)

The biology team consisted of Dr. Pinchasi, and Professor Arnon and Dr. Teitelbaum from Weizmann. (July Tr. (Pinchasi) 16:4-18.) Dr. Pinchasi met frequently with both Professor Arnon and Dr. Teitelbaum, and worked in Dr. Teitelbaum's laboratory for several months. (July Tr. (Pinchasi) 16:19-17:5.) Although

Professor Arnon was involved at a higher level, she was consulted on all significant decisions. (July Tr. (Pinchasi) 16:19-17:5.)

When Dr. Pinchasi began working on the project, she understood from Weizmann scientists that copolymer-1 needed to have a molecular weight in the range of MBP, which was about 20,000 daltons. (July Tr. (Pinchasi) 18:6-19:1, 33:12-14 ("They were actually aiming at 23,000 daltons, which is the molecular weight of myelin basic protein, the endogenous protein copolymer-1 was designed to mimic.").) In fact, in 1974, Professor Arnon and her colleagues published an abstract in the Israeli Journal of Medical Sciences ("1974 Teitelbaum abstract") that reported that copolymers having the same composition as copolymer-1 but with molecular weights lower than 17,000 or higher than 50,000 daltons proved ineffective for suppression of EAE. (July Tr. (Arnon) 312:23-313:18; Sept. Tr. (Grant) 1442:8-1444:4; PTX 509 at 1172-73.) Dr. Pinchasi also learned that the molecular weight of the copolymer-1 used in the Bornstein trial ranged from 14,000 to 23,000 daltons. (July Tr. (Pinchasi) 22:4-21, 33:21-34:5.)

For these reasons, at the beginning of the copolymer-1 project, Teva aimed to produce a high molecular weight copolymer-1, in the range of 20,000 daltons. (July Tr. (Pinchasi) 18:6-19:1, 33:6-34:5.)

Early on in the copolymer-1 project, Dr. Pinchasi and her team were informed about the local and systemic side effects Dr. Bornstein observed in his clinical trial. (July Tr. (Pinchasi) 24:2-23.) They learned that Weizmann scientists concluded that these side effects were caused by something "toxic" in the copolymer-1 batches, but that Professor Arnon and her colleagues had no idea what that toxic element was. (July Tr. (Pinchasi) 24:24-25:10.) Dr. Pinchasi and her team also learned Weizmann scientists had developed the RBL degranulation test in order to screen batches for "toxicity." (July Tr. (Pinchasi) 25:11-26:18.)

Solving the toxicity problem was one of the initial major challenges the Teva and Weizmann scientists faced in developing copolymer-1 into a pharmaceutical product. Much of their development work was focused on this issue. (July Tr. (Pinchasi) 26:19-27:6; July Tr. (Arnon) 331:7-333:6.) The Teva and Weizmann scientists studied the literature for clues as to what might be causing the toxicity and investigated many different possibilities. (July Tr. (Pinchasi) 26:19-27:6.) In the end, the literature did not provide an answer. (July Tr. (Pinchasi) 26:19-27:19.)

Finally, the Teva and Weizmann scientists discovered that toxicity—the cause of the side effects Dr. Bornstein observed during his clinical trial—was related to the molecular weight

of the product. (July Tr. (Pinchasi) 27:25–28:25.) The higher the average molecular weight of a copolymer-1 batch, the higher the probability that the batch would be toxic. (July Tr. (Pinchasi) 27:25-28:25; July Tr. (Arnon) 332:8-333:6; DTX 3567 (Konfino Dep. Tr. Vol. 1) at 62:24-63:9.) In particular, they discovered that there was a narrow molecular weight range between 5,000 and 9,000 daltons in which there is a high probability that a copolymer-1 batch will be both active and non-toxic. (July Tr. (Arnon) 333:7-17; July Tr. (Pinchasi) 34:6-35:5.)

Teva initially determined toxicity using Weizmann's RBL degranulation test. (July Tr. (Pinchasi) 29:1-5.) It later added an in vivo toxicity test in which copolymer-1 is injected into mice. (July Tr. (Pinchasi) 29:1-13.)

The correlation between molecular weight and toxicity that was discovered by the Teva and Weizmann scientists was unexpected. (July Tr. (Pinchasi) 32:1-6, 34:19-35:5; July Tr. (Arnon) 333:23-334:2.) There was nothing in the literature that indicated such a correlation. (July Tr. (Pinchasi) 32:1-6.) It was also unexpected that copolymer-1 in the range of 5,000 to 9,000 daltons would be both non-toxic and active. The Teva and Weizmann scientists believed that a much higher molecular weight was needed for copolymer-1 to have activity because copolymer-1 was meant to mimic MBP, with a molecular weight in the range of

20,000 daltons, and because Weizmann's previous testing showed lower molecular weight copolymer-1 to be ineffective. (July Tr. (Pinchasi) 33:6-34:5, 34:19-35:5; July Tr. (Arnon) 312:23-313:18, 316:25-317:11, 333:18-22.)

To obtain regulatory approval to market copolymer-1 in the United States, Teva needed to submit two pivotal studies on copolymer-1 to the FDA. The two pivotal studies are supposed to be performed with exactly the same product, having exactly the same characteristics. (July Tr. (Pinchasi) 35:12-36:20, 37:18-38:4.) Teva planned to rely on the Bornstein trial as one of its two pivotal studies. As explained earlier, however, the Bornstein trial used copolymer-1 having a molecular weight between 14,000 and 23,000 daltons. (July Tr. (Pinchasi) 35:18-21, 37:2-14.) Because of the toxicity issues that had been discovered, Teva knew it would have to perform its second pivotal study with much lower molecular weight copolymer-1. Teva understood that the FDA might not accept the Bornstein trial as one of the two pivotal studies if it switched to the lower molecular weight copolymer-1, and that it might therefore have to perform a second trial before copolymer-1 would be approved. (July Tr. (Pinchasi) 37:15-38:4.) For these reasons, Teva had an "up front" meeting with the FDA, where they shared "the data that was available for copolymer-1." (July Tr. (Pinchasi) 37:5-8, 38:3-4.)

In addition to its regulatory concern, from a practical perspective, Teva understood it would be a challenge to reproducibly produce copolymer-1 having a molecular weight of 5,000 to 9,000 daltons because the Teva and Weizmann scientists had not yet developed a manufacturing process that could sufficiently control the molecular weight of the final product. (July Tr. (Pinchasi) 38:14-39:4.)

To avoid marketing a product that had a chance of being toxic, Teva targeted a molecular weight for copolymer-1 of about 7,000 daltons. (July Tr. (Pinchasi) 38:5-39:4, 81:13-82:19; PTX 708 at TEV000324552.) Teva's second pivotal trial began in October 1991. (Sept. Tr. (Lisak) 106:24-108:17; PTX 597 at 1271.) This clinical trial, named the Johnson Study after principal investigator Kenneth Johnson, was a Phase III large-scale, multicenter, placebo-controlled, double-blinded study. (Sept. Tr. (Lisak) 106:24-108:17; PTX 597 at 1268.) A total of 251 patients participated in the two-year trial. (Sept. Tr. (Lisak) 106:24-108:17; PTX 597.)

The study demonstrated, for the first time, that copolymer-1 was a safe and effective treatment for patients with RRMS. (Sept. Tr. (Lisak) 110:22-111:22.) It also demonstrated, among other things, that daily injections of copolymer-1 resulted in a statistically significant reduction in relapse rates for patients with RRMS. (Sept. Tr. (Lisak) 107:25-108:4; PTX 597 at

1268.) The study concluded in 1994 and the results were published in 1995 in the Journal of Neurology. (PTX 597.)

On June 14, 1995, Teva submitted its NDA, relying on both the 1987 Bornstein trial and the Johnson Study to demonstrate the safety and efficacy of copolymer-1. (PTX 81 at TEV000002326.) While Teva represented to the FDA that the safety of the copolymer-1 compositions studied in the Johnson Study and the Bornstein trial were comparable, Teva did not draw any comparisons between the tolerability of the compositions or their propensity to cause injection site reactions. (PTX 881 (Green Dep.) at 111:11-18; PTX 81.)

Although Teva's NDA set an average molecular weight specification of 4,700 to 13,000 daltons, Teva actually targeted an average molecular weight of 7,000 ± 1,000 daltons for the batches of copolymer-1 that were to be marketed. (July Tr. (Pinchasi) 85:23-89:22.) Teva informed the FDA of this 7,000 ± 1,000 daltons average molecular weight target as part of its NDA submission. (July Tr. (Pinchasi) 85:23-89:22; DTX 1023 at TEV000000455; see also July Tr. (Pinchasi) 81:23-85:13; PTX 723 at TEV000599260.) Teva set the formal specification at 4,700 to 13,000 daltons originally to maintain a larger margin for average molecular weight in light of potential manufacturing changes that might be necessary to market the product. (July Tr. (Pinchasi) 86:4-86:24.) Batches within the 4,700 to 13,000

daltons specification were still tested for toxicity on the RBL screen and in vivo mouse test, and rejected if they failed on either of those screens. (July Tr. (Pinchasi) 86:4-24.)

D. Discovery of the Process for Achieving Low Molecular Weight Copolymer-1

Teva was able to reproducibly achieve the narrow molecular weight range of about 7,000 daltons because of a discovery made by Teva chemist Eliezer Konfino. When Teva scientists began working on the copolymer-1 project, they found that the same starting materials and what they believed to be the same reaction conditions produced copolymer-1 of varying molecular weights. (July Tr. (Pinchasi) 38:14-39:4.) Konfino discovered that the second step of the process for making copolymer-1, which involves the addition of HBr/acetic acid, cleaves, or cuts up, the polypeptide copolymer-1 chains, and therefore lowers the average molecular weight of the product. (July Tr. (Pinchasi) 68:5-25, 76:13-77:18, 81:23-85:13; PTX 36; PTX 36-T; PTX 42.)

Konfino found that he could control the average molecular weight of the final copolymer-1 product by controlling the time and temperature of the second step of the process. The longer the reaction is run, and the higher the temperature, the more cleavage occurs and the lower the average molecular weight of the product. (July Tr. (Pinchasi) 68:5-25, 76:13-77:18, 81:23-85:13; PTX 36; PTX 36-T; PTX 42.) Konfino also discovered that

the time and temperature for the Step 2 reaction that would provide copolymer-1 of approximately 7,000 daltons could be determined by running a test reaction. (July Tr. (Pinchasi) 81:23-82:19.)

VI. Background on Polypeptide Chemistry, Synthesis, Analytical Testing

A. Polypeptide Chemistry

A polymer is a molecule composed of smaller subparts called monomers. (Sept. Tr. (Grant) 191:9-16; PTX 986 at 4.) A copolymer is a polymer composed of more than one type of monomer. (Sept. Tr. (Grant) 191:19-192:1; PTX 986 at 4.) The monomers that make up copolymer-1 are amino acids. (Sept. Tr. (Grant) 192:2-3.) An amino acid is a molecule that contains an amino group, a carboxylic acid group, and a side chain. (Sept. Tr. (Grant) 192:4-19; Sept. Tr. (Gokel) 341:6-25; PTX 986 at 5; PTX 987 at 4.)

A polypeptide is a molecule made up of amino acid monomers that are joined together by peptide bonds. (Sept. Tr. (Grant) 180:17-21; Sept. Tr. (Gokel) 344:11-22.) Copolymer-1 is a mixture of polypeptides. (PTX 1 at 1:32.) The polypeptides comprising copolymer-1 are synthetic (i.e., they are made in a laboratory) and they are composed of four amino acids: glutamic acid, lysine, alanine, and tyrosine. (Sept. Tr. (Grant) 180:22-

23, 183:13-19, 192:20-193:23; Sept. Tr. (Gokel) 342:12-344:10, 344:23-345:12; PTX 986 at 6-7; PTX 987 at 6, 8-11.)

The individual polypeptide molecules, or "species," in copolymer-1 have different lengths and sequences. For that reason, the molecular weight of a sample of copolymer-1 can best be described either as an average molecular weight or as a molecular weight distribution. (Sept. Tr. (Grant) 194:14-195:2, 195:7-10, 1544:23-1545:11; Sept. Tr. (Scandella) 1193:24-1194:2; PTX 986 at 8.) The molecular weight of an individual polypeptide molecule is the sum of the atomic weights of the atoms comprising the molecule. (Sept. Tr. (Grant) 193:24-194:13.) A molecular weight distribution, by contrast, is a description of the molecular weights of the polypeptides that make up a mixture of polypeptide molecules. (Sept. Tr. (Grant) 198:9-13.)

B. Synthesis of Copolymer-1

The varying lengths and sequences of the polypeptide chains in a sample of copolymer-1 are a result of the method of its synthesis. (Sept. Tr. (Grant) 195:11-197:10.) The patents-in-suit teach that copolymer-1 is synthesized using a four-step process in a "batch" method of synthesis. (Sept. Tr. (Gokel) 352:2-354:15; Sept. Tr. (Grant) 1401:19-1402:4; PTX 1 at 4:30-6:3; PTX 987 at 22.)

In Step 1, the N-carboxyanhydrides, or activated versions, of the amino acids glutamic acid, lysine, alanine, and tyrosine are combined in the presence of a chemical called an initiator. The initiator starts the reaction of the amino acids by joining with one of the activated amino acids, which removes the N-carboxyanhydride group and allows the first amino acid to join to a second amino acid, which in turn allows the second amino acid to react with a third amino acid, and so forth. Each initiator molecule starts a new polypeptide chain. This sequence of reactions results in polymerization of the amino acids into polypeptide chains. (Sept. Tr. (Grant) 195:17-197:16; Sept. Tr. (Gokel) 349:3; PTX 986 at 9; PTX 987 at 14.)

Glutamic acid and lysine each have two sites that can form bonds with other amino acids. In order to ensure that the amino acids combine with each other in a straight chain and do not become branched during the polymerization step, protecting groups are used to block the reactive sites on the side chain of each of these amino acids. Benzyl groups are used to protect the glutamic acid and TFA groups are used to protect the lysine. (Sept. Tr. (Gokel) 342:16-343:23, 345:5-346:25; PTX 987 at 7, 12-13.) The result of the Step 1 polymerization is called "protected copolymer-1" because the side chains of glutamic acid and lysine are protected by the benzyl and TFA protecting groups, respectively. Protected copolymer-1 is a mixture of

polypeptides that have different lengths and amino acid sequences. (Sept. Tr. (Grant) 195:17-197:16; Sept. Tr. (Gokel) 347:1-349:8, 353:4-16; PTX 987 at 15, 22.)

In Step 2, the protected copolymer-1 is treated with HBr/acetic acid to remove the benzyl protecting groups from glutamic acids ("deprotection"). During the deprotection process, the polypeptide chains are also cleaved ("depolymerized"), which results in shorter polypeptide chains. (Sept. Tr. (Gokel) 347:1-350:5, 353:17-25; PTX 987 at 16-18, 22.) The resulting product of the Step 2 deprotection/depolymerization process is called TFA copolymer-1 because the TFA protecting groups remain on the lysine residues. (Sept. Tr. (Gokel) 350:11-18.)

The time and temperature of the HBr/acetic acid reaction of Step 2 determines the extent of cleavage of the polypeptide chains and the resulting average molecular weight of the copolymer-1 product. (PTX 1 at 4:59-65.) The longer the reaction is run or the higher the temperature, the more cleavage occurs and the lower the average molecular weight of the product. As a result, this step is used to control the molecular weight of the resulting copolymer-1. (Sept. Tr. (Sampson) 1641:6-1642:8; PTX 992 at 6-7; July Tr. (Pinchasi) 81:23-82:19; DTX 1023 at TEV000000455.)

In Step 3 of the synthetic process, the TFA copolymer-1 is treated with piperidine to remove the TFA protecting groups from the lysines, resulting in copolymer-1. (Sept. Tr. (Gokel) 350:19-22, 351:3-12, 354:1-9; PTX 987 at 15, 22.) The chain lengths of the polypeptides are not affected in the TFA deprotection step. (Sept. Tr. (Gokel) 350:23-351:2.)

In Step 4 of the synthetic process, the copolymer-1 can be purified by dialysis. In one method of dialysis, acetic acid is used. (Sept. Tr. (Gokel) 350:23-351:2; PTX 1 at 5:12-6:2; PTX 987 at 22.)

C. Size Exclusion Chromatography

The patents-in-suit explicitly identify SEC as the method to be used for determining the molecular weight of copolymer-1. (Sept. Tr. (Grant) 186:16-20, 197:17-25, 326:15-18; Sept. Tr. (Scandella) 1227:5-10; PTX 1 at 3:6-7.) SEC—also known as "gel filtration" or "gel permeation chromatography"—is a separation and analytical technique that separates molecules based upon their size in solution. SEC can be used to determine the molecular weights of samples, such as polypeptides, as well as their molecular weight distributions. (Sept. Tr. (Grant) 186:5-15, 186:21-187:4, 198:1-3, 198:14-20, 329:14-20, 1411:2-5, 1415:8-17; PTX 553 at 63-64; PTX 566 at 2.)

SEC was first described in the literature in the late 1950s or early 1960s, and the first commercial SEC instrument was

marketed in 1964. (Sept. Tr. (Grant) 1409:17-19; PTX 553 at 63-64; PTX 514 at 199.) By 1994, there was a considerable amount of scientific literature describing the use of SEC. (Sept. Tr. (Grant) 1409:17-23; Sept. Tr. (Scandella) 1314:15-25.) This literature included textbooks, individual book chapters, and numerous scientific articles. (Sept. Tr. (Grant) 1409:24-1410:2.) For example, N.C. Billingham, Molar Mass Measurements in Polymer Science (John Wiley & Sons 1977) ("Billingham 1977"), contains a chapter entitled "Gel Permeation Chromatography," which states that "[t]he idea of producing separation of discrete molecular species on the basis of differences in molecular size has been familiar to the biochemist for many years." (PTX 514 at 199.)

Polypeptides were some of the first substances studied by SEC, and by 1994, the prior art with respect to using SEC to determine the molecular weight of polypeptides was extensive. (Sept. Tr. (Grant) 1410:3-9.) By 1994, all aspects of the SEC process—including its theory and practice, and the interpretation of results—had been described in numerous book chapters such as Billingham 1977, the "Gel Filtration" chapter in Protein Purification - Principles, High Resolution Methods and Applications (Jan-Christer Janson and Lars Ryden eds., 1989) ("Janson 1989"), and the "Characterization of Complex Polymers by Size Exclusion Chromatography and High-Performance Liquid

Chromatography" chapter from Modern Methods of Polymer Characterization (Howard G. Barth and Jimmy W. Mays, 1991) ("Barth 1991"). (Sept. Tr. (Grant) 1410:10-1412:5, 1414:8-21, 1418:19-1419:21; PTX 514; PTX 553; PTX 566.)

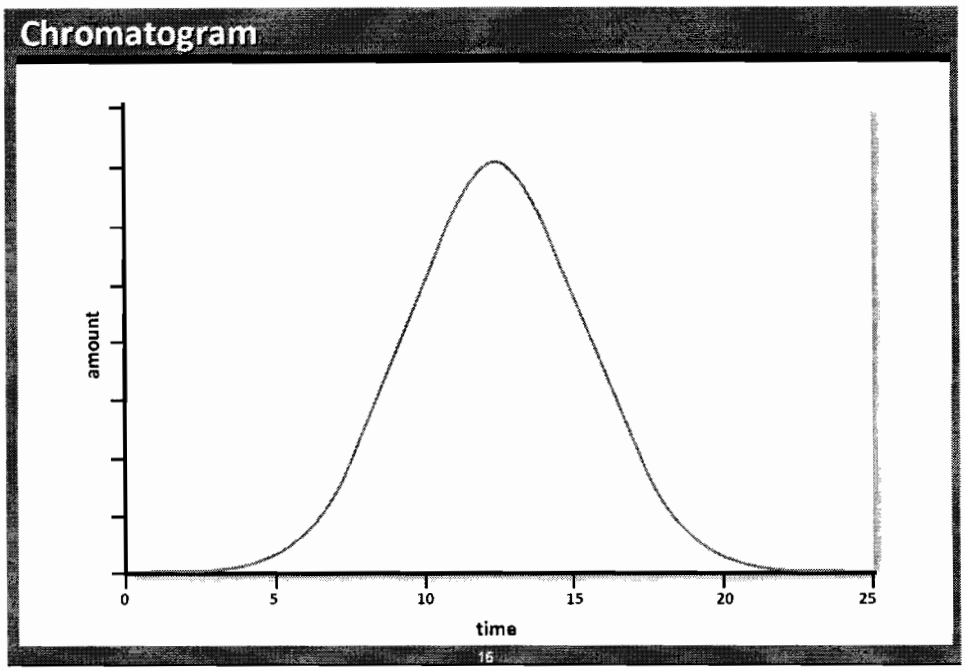
In 1994 (and to this day), SEC was the best method for determining the molecular weight distribution of a mixture of polypeptides like copolymer-1. Barth 1991, for example, describes SEC as "a well-recognized technique for the determination of polymer molecular weight distributions." (PTX 566 at 2.) Similarly, Billingham 1977 explains that SEC is "used as a matter of routine in very many polymer laboratories" to characterize the molecular weight of polydisperse polymers. (Sept. Tr. (Grant) 198:14-20, 329:14-20; PTX 514 at 200.)

SEC analysis utilizes a size exclusion (or gel filtration) column, which is a gel-filled glass or metal cylinder where the separation of molecules takes place. (Sept. Tr. (Grant) 198:4-8, 198:24-199:25; PTX 986 at 10-11.) The sample to be analyzed is introduced into the top of the column along with liquid which carries the sample down through the gel. (Sept. Tr. (Grant) 200:1-13; PTX 986 at 12-13.) The individual beads making up the separation gel have many pores of varying sizes. Size exclusion takes place because large molecules cannot get into the pores, and therefore pass through quickly, while smaller molecules can go into the pores to various extents, and they therefore travel

a longer path through the column and come out later than the larger molecules. (Sept. Tr. (Grant) 199:12-25, 200:14-201:7; PTX 986 at 14-15.) For this reason, molecules of different sizes are separated from one another as they travel through the column.

The bottom of the column is connected through a tube to a detector. The detector detects the presence and the quantity (amount) of molecules exiting the column. (Sept. Tr. (Grant) 201:8-24.) The output of the detector is a graph, called a chromatogram, which is plotted on the x-axis as time and on the y-axis as the amount of the material passing the detector at each point in time. (Sept. Tr. (Grant) 201:25-203:19; PTX 986 at 16; see Figure 1 below.) Larger molecules exit the column first due to the size exclusion. (Sept. Tr. (Grant) 200:23-201:7; PTX 986 at 13.) The highest point, or peak, of the chromatogram, represents the time at which the species of molecules present in the highest abundance passes by the detector. (Sept. Tr. (Grant) 1404:23-1405:9; PTX 969 (Svec Dep.) at 9:19-23; PTX 982.)

Figure 1



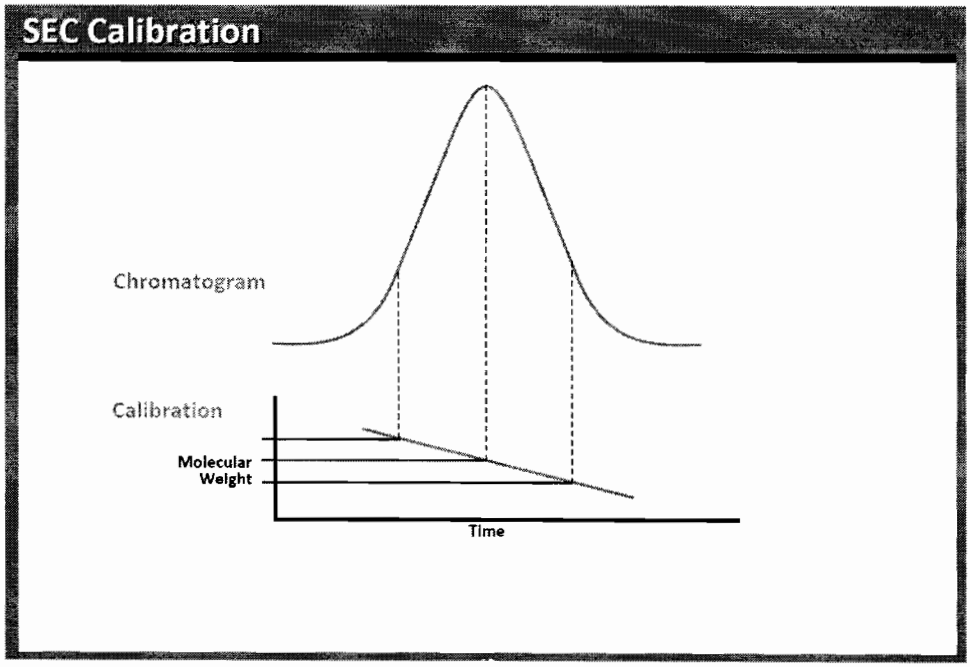
(PTX 986 at 16.)

To determine the molecular weight of the molecules exiting the column at each point (or time) along the chromatogram, it is necessary to have a calibration curve, which correlates the time at each point along the chromatogram's x-axis with the molecular weight of material exiting the column at that particular time. (Sept. Tr. (Grant) 203:20-204:3.) SEC calibration was well-understood in 1994. (Sept. Tr. (Grant) 204:4-5.) By that time, it was well-known that to create a calibration curve, calibration standards—molecules of known molecular weights—had to be run through the column to determine the time that they exited the SEC apparatus. The molecular weight of each standard, which can be determined by a number of independent (non-SEC) methods, is plotted against the time at which the

standard comes out of the column. (Sept. Tr. (Grant) 204:6-205:10; PTX 986 at 17.)

To determine the molecular weight at any point on the chromatogram—the peak, for example—one can match the time from the x-axis to the corresponding time on the calibration curve and read the molecular weight from the y-axis of the calibration curve. (Sept. Tr. (Grant) 205:11-206:2; PTX 986 at 18; see Figure 2 below.)

Figure 2



In 1994, it was known that there were at least two options for calibrating an SEC column to get accurate molecular weights for a polypeptide mixture like copolymer-1. The conventional way was to use calibration standards that have the same relationship between size and shape in solution (also known as

"hydrodynamic volume")[8] and molecular weight as the sample being measured. The other alternative was to use "universal calibration." (Sept. Tr. (Grant) 206:3-208:20, 1399:18-1400:13; PTX 969 (Svec Dep.) at 94:21-95:5; PTX 990 at 2.)

With respect to the first method, the necessity of matching the hydrodynamic characteristics of the sample and the calibration standards in conventional SEC calibration was well-known to those skilled in the art and well-described in the literature in 1994. (Sept. Tr. (Grant) 1412:6-1413:16; Sept. Tr. (Scandella) 1314:15-1316:24; PTX 961 (Kota Dep.) at 18:3-14; PTX 962 (B. Rao Dep.) at 75:6-76:10, 78:14-80:5; PTX 973 (Venkataraman Dep) at 108:20-109:23; PTX 974 (Wallingford Dep.) at 146:9-149:7; PTX 317 at MYL0000111; PTX 553 at 72.) For example, Janson 1989 states that "[t]he relationship between size and molecular weight of solutes is strongly dependent upon solute shape. . . . It is readily seen that calibration versus molecular weight is only meaningful for solutes of similar shape." (PTX 553 at 72.)

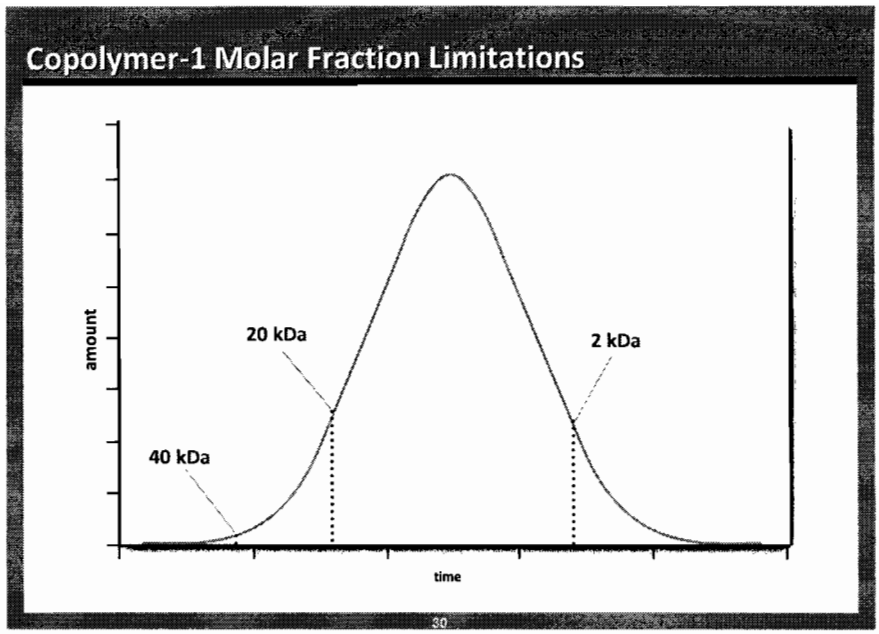
With respect to the second method, if standards that match the hydrodynamic volume to molecular weight characteristics of the sample were unavailable, it was well-known that universal calibration could be used to determine an accurate molecular weight for a sample. (Sept. Tr. (Grant) 208:14-20, 1399:18-

[8] At trial, this method was commonly referred to as "self-standards."

1400:13, 1401:12-18, 1413:17-23; PTX 970 (Svec Dep.) at 320:2-321:10, 326:14-327:10.) Universal calibration does not require the standards to have the same hydrodynamic volume to molecular weight relationship as the sample, because it uses a different physical property (intrinsic viscosity) to allow a correlation of the size of molecules exiting the column to their molecular weight. (Sept. Tr. (Grant) 208:14-20, 1400:6-15.)

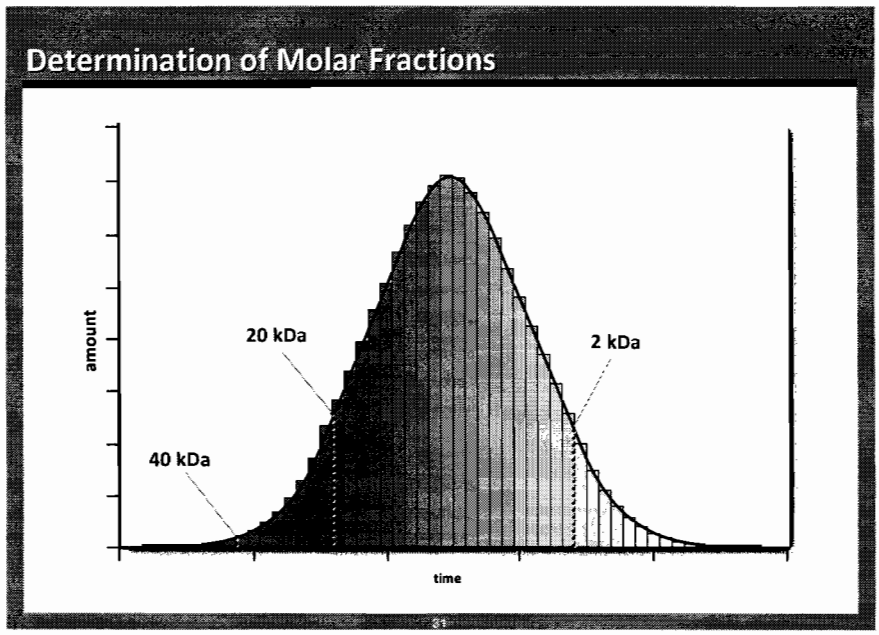
In addition to allowing determination of an average molecular weight, SEC allows the separation of molecules and the determination of the percentage of molecules having molecular weights falling within any given molecular weight range. (Sept. Tr. (Grant) 209:17-25, 227:8-22; PTX 986 at 33.) A chromatogram represents the amount of material that is exiting the size exclusion column at any particular time (as reflected on the x-axis). It also represents the entirety of the molecules in the sample. (Sept. Tr. (Grant) 203:14-19.) On the illustrative chromatogram shown below (Figure 3), the molecular weights of 40 kDa, 20 kDa, and 2kDa are depicted from left to right because large molecules come out of the size exclusion column earlier than smaller molecules. (Sept. Tr. (Grant) 227:8-22; PTX 986 at 30.)

Figure 3



In order to calculate the percentage of species having a molecular weight within a certain range, the chromatogram is divided into slices, which can be represented by small rectangles, as shown in Figure 4 below. A molecular weight is assigned to each slice through the use of a calibration curve. The number of moles of the material, which represents the number of molecules in each slice, can be calculated by dividing the amount of the material in the slice by the molecular weight that has been assigned to that slice. (Sept. Tr. (Grant) 228:11-229:11, 230:8-12; PTX 986 at 31.)

Figure 4



The number of moles of all of the molecules falling within a molecular weight range—between 2 kDa and 20 kDa, for example—can be added together and divided by the total number of moles of all of the molecules present in the sample, as represented by the entire chromatogram. Multiplying this fraction by 100 gives the percentage (on a "molar fraction" basis) of molecules within the molecular weight range. Similarly, the molar percentage of molecules having molecular weights above 40 kDa can be calculated by dividing the number of moles of material having molecular weight above 40 kDa by the total number of moles of the materials represented by the entire chromatogram. (Sept. Tr. (Grant) 229:12-230:7; PTX 986 at 32.)

When using this method, it is not necessary to know how many different molecular weights are in each slice. It is

acceptable to assign a single molecular weight to each slice. (Sept. Tr. (Grant) 298:11-299:3, 329:6-330:7; PTX 986 at 31.)

D. Level of Ordinary Skill in the Art

The level of ordinary skill in the art in this case is very high. Dr. Grant defined a person of ordinary skill in the art as having an "advanced degree or equivalent in a chemical or biological discipline and significant experience in the synthesis or characterization of polymers, including proteins or synthetic peptides." The person of ordinary skill in the art would also have "access to and the ability to consult with other scientists having related and/or complementary knowledge and experience in the areas of polymer chemistry, biochemistry, analytical chemistry, separation technology, medicine, and toxicology." (Sept. Tr. (Grant) 189:19-190:6, 1398:11-17; PTX 986 at 3.)

Defendants' expert witnesses also defined the level of skill in the art as high. (Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9; Sept. Tr. (Wall) 1756:2-12; Sept. Tr. (Zeiger) 809:10-811:15; DTX 4030 at 4.) Sandoz's expert, Dr. Scandella, for example, defined a person of ordinary skill in the art as having a Ph.D. in chemistry, biochemistry, or a related field with a minimum of three years of experience in chromatography, and specifically in SEC of macromolecules. (Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9.) Sandoz's other expert,

Dr. Wall, defined a person of ordinary skill in the art as having a Ph.D. in chemistry, biochemistry, or a related field, with three years of experience in chromatography or a person who has supervised or directed a research lab that conducts chromatography. (Sept. Tr. (Wall) 1756:2-12.)

Mylan's expert Dr. Zeiger defined a person of ordinary skill: "A person of ordinary skill in fields of biochemistry and immunology in 1994 would have had an advanced degree in a chemical or biological discipline, and extensive experience in the synthesis, fractionation, and characterization of polymers, such as their hydrodynamic and structural properties, as applied to proteins, synthetic peptides and/or polydisperse peptide mixtures, as well as experience in the determination of the molecular weight distribution and average molecular weights of such polymers by methods such as size exclusion chromatography (SEC), and an understanding of how the standards and conditions used in the molecular weight determination affect the results obtained." (Sept. Tr. (Zeiger) 809:10-811:15; DTX 4030 at 4.) He also testified that he has "no problem" with Dr. Grant's definition of a person of ordinary skill in the art. (Sept. Tr. (Zeiger) 811:15.)

The Court accepts Dr. Grant's testimony and adopts his definition of the level of ordinary skill in the art.[9] In light of the nearly identical view of the level of ordinary skill in the art put forward by the parties' experts, the Court notes that its analysis of the legal and factual issues is the same regardless of which expert's definition is used.

DISCUSSION

I. Infringement[10]

A. General Principles

A finding of patent infringement involves a two-step process. First, the claims must be construed.[11] Then, the construed claims must be compared to the accused products or processes to determine whether all of the limitations of at least one claim are present—literally or by a substantial equivalent. E.g., Acumed LLC v. Stryker Corp., 483 F.3d 800, 804 (Fed. Cir. 2007) (citations omitted). "To establish literal infringement, 'every limitation set forth in a claim must be found in an accused product, exactly.'" Becton, Dickinson & Co.

[9] The Court accepts Dr. Grant's definition with the caveat, which is not part of Dr. Grant's quoted testimony above, that the relevant time period is May 24, 1994—the day the '037 application was filed. See PC Connector Solutions LLC v. SmartDisk Corp., 406 F.3d 1359, 1363 (Fed. Cir. 2005) (explaining, in context of claim construction, that a claim's "meaning must be interpreted as of its effective filing date") (citations omitted).

[10] With respect to all claims and defenses, the Court separately states its findings of fact and conclusions of law pursuant to Rule 52(a) of the Federal Rules of Civil Procedure. Fed. R. Civ. P. 52(a).

[11] The Court issued its claim construction decision, construing the disputed claim terms, on August 29, 2011. (Dkt. 273 in 08 Civ. 7611; Dkt. 194 in 09 Civ. 8824.)

v. Tyco Healthcare Grp., LP, 616 F.3d 1249, 1253 (Fed. Cir. 2010) (citation omitted). "For process patent or method patent claims, infringement occurs when a party performs all of the steps of the process." BMC Res., Inc. v. Paymentech, L.P., 498 F.3d 1373, 1379 (Fed. Cir. 2007) (citation omitted).

"The doctrine of equivalents prevents an accused infringer from avoiding liability for infringement by changing only minor or insubstantial details of a claimed invention while retaining the invention's essential identity. The doctrine of equivalents is utilized '[t]o temper unsparing logic and prevent an infringer from stealing the benefit of the invention.'" Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd., 234 F.3d 558, 564 (Fed. Cir. 2000) (alteration in original) (citations and internal quotation marks omitted), vacated on other grounds by 535 U.S. 722 (2002). "Under the doctrine of equivalents, a claim limitation not literally met may be satisfied by an element of the accused product if the differences between the two are 'insubstantial' to one of ordinary skill in the art." Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1351 (Fed. Cir. 2003) (citations omitted). "[T]he insubstantial differences inquiry may be guided by determining whether the element in the accused device performs substantially the same function in substantially the same way to

obtain the same result as the claim limitation." Id. (internal quotation marks omitted).

"'The patentee bears the burden of proving infringement by a preponderance of the evidence.'" Creative Compounds, LLC v. Starmark Labs., 651 F.3d 1303, 1314 (Fed. Cir. 2011) (citation omitted). The same preponderance of the evidence burden applies to patentees, such as Teva, asserting infringement under 35 U.S.C. § 271(e)(2). See Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1365-66 (Fed. Cir. 2003). In Abbott Laboratories v. TorPharm, Inc., the Federal Circuit explained that "[a]n infringement inquiry provoked by an ANDA filing under 35 U.S.C. § 271(e)(2)(A) is focused on the product that is likely to be sold following FDA approval." 300 F.3d 1367, 1373 (Fed. Cir. 2002) (citation omitted); see also Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1569 (Fed. Cir. 1997) (explaining that "the question of infringement[,]" under 35 U.S.C. § 271(e)(2), "must focus on what the ANDA applicant will likely market if its application is approved"). "Because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." Abbott Labs., 300 F.3d at 1373 (citation omitted).

Lastly, pursuant to 35 U.S.C. § 271(b), "[w]hoever actively induces infringement of a patent shall be liable as an infringer." AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042, 1056 (Fed. Cir. 2010). To establish induced infringement, a patentee must show by a preponderance of the evidence "'the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement.'" AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042, 1056 (Fed. Cir. 2010) (citation omitted).

B. Findings of Fact as to Mylan

i. Mylan's ANDA Product

The active ingredient in Mylan's proposed product is described as glatiramer acetate. (Sept. Tr. (Owens) 629:1-12; PTX 319 at MYL0000143; PTX 320 at MYL0000235-36; PTX 962 (B. Rao Dep. 06/09/2010) at 37:14-2; PTX 984 at 1.) Mylan's ANDA makes clear that glatiramer acetate was formerly known as, and is synonymous with, "copolymer-1." For example, copolymer-1 is listed in the Nomenclature section of the ANDA as a "synonym" for glatiramer acetate. (Sept. Tr. (Grant) 250:7-9; Sept. Tr. (Owens) 630:11-631:8; PTX 320 at MYL0000236.) The Manufacturing section of the ANDA refers to the product of Mylan's manufacturing process as "copolymer-1." (PTX 321 at MYL0000253, 622.) Mylan's proposed labeling also states that glatiramer acetate was "formerly known as copolymer-1." (Sept. Tr. (Gokel)

369:21-370:3; 372:14-18; 373:14-18; PTX 321 at MYL 0000253; PTX 734 at MYL0004956; PTX 962 (B. Rao Dep. 06/09/2010) at 192:6-10; PTX 987 at 55.)

Natco scientists also acknowledged that Mylan's proposed product is copolymer-1. Dr. Bhujanga Rao, Natco's President of Research & Development and 30(b)(6) witness, testified that the Mylan/Natco proposed product is a "copolymer-1 composition" and that Mylan's scientists understood that the terms "glatiramer acetate" and "copolymer-1" are "used interchangeably." (PTX 962 (B. Rao Dep. 06/09/2010) at 11:13-19, 23:20-24:2, 259:21-260:3.) Dr. Satyanarayana Kota, the general manager of Research & Development at Natco and the scientist responsible for starting its peptide group, testified similarly that glatiramer acetate and copolymer-1 are "the same." (PTX 961 (Kota Dep.) at 28:1-16, 52:17-53:8, 202:15-25.)

ii. Amino Acid Composition

The glatiramer acetate in Mylan's proposed product is composed of the following four amino acids: glutamic acid, alanine, lysine, and tyrosine. (Sept. Tr. (Gokel) 378:6-14; 394:17-395:2; PTX 320 at MYL0000237, 615-17.) Mylan's ANDA provides the molar fractions for these four amino acids, which represent the relative proportions of the four amino acids in Mylan's product. (Sept. Tr. (Gokel) 380:21-381:14, 394:17-395:22; PTX 325 at MYL0001050, 68, 79; PTX 961 (Kota Dep.) at

71:5-15, 111:25-112:16.) According to its ANDA, Mylan's glatiramer acetate lots have the following molar fractions of glutamic acid, alanine, tyrosine and lysine, respectively: Drug substance lot GMA/001/09, 0.144: 0.427: 0.092: 0.336; Drug substance lot GMA/002/09, 0.148: 0.432: 0.092: 0.328; Drug Substance lot GMA/003/09, 0.142: 0.440: 0.092: 0.327; Drug product lot WV901, 0.137: 0.462: 0.090: 0.311; Drug product lot WV902, 0.146: 0.463: 0.088: 0.304; and Drug product lot WV903, 0.144: 0.464: 0.088: 0.305. (Sept. Tr. (Gokel) 394:17-395:16, 399:20-400:1, 400:4-6; PTX 300 at MYL0002927; PTX 312 at MYL0002929; PTX 313 at MYL0002931; PTX 325 at MYL0001050, 68, 79; PTX 961 (Kota Dep.) at 111:25-112:16.)

iii. Molecular Weight

Mylan's specification for the peak average molecular weight of its proposed product is between 5,000 and 9,000 daltons. (Sept. Tr. (Grant) 249:21-251:20, 253:25-254:8, 312:1-22, 313:12-22, 314:21-315:3; PTX 300 at MYL0002928; PTX 312 at MYL0002930; PTX 313 at MYL0002932; PTX 318 at MYL00000107, 117; PTX 325 at MYL0001050, 68, 79; PTX 330 at MYL0000752, 765, 766; PTX 986 at 42, 43.) As set forth in Figure 5 below, the data in Mylan's ANDA demonstrates that each of its lots falls within the specified 5,000-9,000 daltons range. (Sept. Tr. (Grant) 249:17-251:20, 255:13-257:11, 257:18-258:3, 258:9-19, 258:25-259:23; PTX 300 at MYL0002928; PTX 312 at MYL0002930; PTX 313 at

MYL0002932; PTX 318 at MYL00000107, 117; PTX 325 at MYL0001050, 1068, 179; PTX 986 at 42-44.)

Figure 5

Drug Substance

Lot	Peak Average Molecular Weight (Da)
GMA/001/09	6445
GMA/002/09	6431
GMA/003/09	6718

Drug Product

Batch	Peak Average Molecular Weight (Da)
WV901	6280
WV902	6358
WV903	6036

Source: PTX 300, 312, 313, 325

Mylan determined the peak molecular weight values in its ANDA using SEC with a Superose 12 column. (Sept. Tr. (Grant) 252:2-8, 254:12-20; PTX 323 at MYL0000765-66.) Mylan calibrated its SEC column using peptide standards that (i) had amino acid compositions consistent with the composition of copolymer-1 and (ii) had the same size-to-molecular weight relationship as copolymer-1. (Sept. Tr. (Grant) 250:23-251:7; PTX 323 at MYL0000765-66.) In addition to having a specified peak molecular weight, Mylan's proposed product also has particular molecular weight distribution characteristics, some of which are shown in Figure 6 below. (Sept. Tr. (Grant) 260:23-263:9; PTX 421; PTX 986 at 46.)

Dr. Grant used electronic molecular weight data generated by Mylan, during its SEC measurements of three Mylan drug substance lots, to calculate the percentage (on a molar fraction basis) of the copolymer-1 molecules in each lot having a molecular weight between 2 and 20 kilodaltons and the percentage having a molecular weight above 40 kilodaltons. (Sept. Tr. (Grant) 260:23-263:9; PTX 421; PTX 986 at 46.) Those percentages are listed in Figure 6 below:

Figure 6

	% molar fraction between 2 and 20 kilodaltons (%)	% molar fraction above 40 kilodaltons (%)
GMA-001-09	≥ 83.13%	≤ 0.03%
GMA-002-09	≥ 81.70%	≤ 0.05%
GMA-003-09	≥ 80.95%	≤ 0.04%

Source: PTX 421

Using the electronic molecular weight data for the same three Mylan drug substance lots, Dr. Grant also calculated the molar fraction percentage of molecules having molecular weights between 2 and 20 kilodaltons in the TFA copolymer-1 intermediate that corresponds to each lot.[12] (Sept. Tr. (Grant) 263:22-265:9;

[12] Mylan criticized Dr. Grant's use of the electronic molecular weight data because it was generated using Mylan's original set of peptide standards as calibration markers. Mylan's critique is unfounded. Mylan argued that due to the limited number of standards, the calibration could not be extrapolated beyond the molecular weights of the peptide standards. But as Dr. Grant explained, Mylan's molecular weight software applied the calibration across the entire distribution. (Sept. Tr. (Grant) 318:17-321:5.) Moreover, using the same data, Mylan itself analyzed the molecular weight distribution of its

PTX 421; PTX 986 at 50.) Those percentages are listed in Figure 7 below:

Figure 7

Trifluoroacetyl copolymer-1 corresponding to sample	% TFA molar fraction between 2 and 20 kilodaltons (%)
GMA-001-09	≥ 87.45
GMA-002-09	≥ 86.09
GMA-003-09	≥ 84.52

Source: PTX 421

During trial, Mylan produced to Teva additional electronic data for its proposed product generated using SEC with universal calibration. Using this newly-produced data, Dr. Grant performed another set of calculations of the molar fraction percentages for Mylan's lots. (Sept. Tr. (Grant) 1464:8-1468:4.) Consistent with his previous calculations, Dr. Grant found that, in each of Mylan's lots, greater than 90% of the copolymer-1 molecules on a molar fraction basis had molecular weights between 2 and 20 kilodaltons. (Sept. Tr. (Grant) 1465:16-25.) He also found that, in all lots, less than or equal to 2.5% by molar fraction of the copolymer-1 molecules had

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proposed product and calculated the percentage of molecules having molecular weights between 2 and 20 kDa. Finally, Mylan calculated the weight average and number average molecular weights for its product. All of these calculations required Mylan to extrapolate its calibration beyond the molecular weights of the peptide standards to cover the entire molecular weight distribution. Demonstrating that extrapolation is appropriate, Mylan reported all of this information to the FDA based on its original set of peptide standards. (Sept. Tr. (Grant) 318:12-321:51; PTX 25 at 1057.)

molecular weights above 40 kilodaltons. (Sept. Tr. (Grant) 1466:9-19.)

Dr. Grant also calculated the molar fraction percentage of molecules having molecular weights between 2 and 20 kilodaltons in the TFA copolymer-1 intermediate that corresponds to each of Mylan's lots based on the universal calibration data produced during trial. (Sept. Tr. (Grant) 1466:1-19.) He found the percentage to be greater than or equal to 90% for all lots. (Sept. Tr. (Grant) 1466:1-8.)

iv. Mylan's Manufacturing Process

Natco scientist Dr. Kota was part of the team responsible for developing Natco's proposed generic product. (PTX 962 (Rao Dep. 06/09/2010) at 26:8-27:4, 35:4-8; PTX 963 (Rao Dep. 09/30/2010) at 27:20-28:23.) When he began working on the project, he consulted the scientific literature regarding copolymer-1, including at least some of the patents-in-suit. (PTX 961 (Kota Dep.) at 31:7-14, 31:24-32:16, 40:15-42:22, 42:24-51:19; PTX 962 (Rao Dep. 06/09/2010) at 26:8-27:4; PTX 963 (B. Rao Dep. 09/30/2010) at 19:11-21:22.) [redacted] (Sept. Tr. (Gokel) 374:14-375:5; PTX 270 at NAT0121552; PTX 961 (Kota Dep.) at 80:6-82:8, 82:23-84:25, 85:2-3.)

[redacted] (PTX 270 at NAT0121552; PTX 728 at NAT0028763; PTX 961 (Kota Dep.) at 77:18-23, 77:25-78:7, 80:6-82:8, 82:23-84:25, 85:2-3, 191:16-192:22, 194:18-195:21, 197:22-200:16.) [redacted] (PTX 728 at NAT0028763; PTX 961 (Kota Dep.) at 197:22-200:16.) [redacted] (PTX 961 at 78:1-7.)

[redacted] (PTX 192; PTX 961 (Kota Dep.) at 184:15-185:14; PTX 962 (B. Rao 06/09/2010 Dep.) at 165:20-166:16, 168:5-11; 168:14-169:15.) [redacted]

[redacted] (PTX 1 at 6:5-12; PTX 728 at NAT0028763; PTX 961 (Kota Dep.) at 200:17-201:12, 202:15-203:5, 203:16-25.) [redacted] (PTX 270 at NAT0121552; PTX 961 (Kota Dep.) at 80:6-82:8, 82:23-84:25, 85:2-3), [redacted]

[redacted] (PTX 963 (B. Rao 09/30/2010 Dep.) at 42:11-44:7, 44:9-45:12, 45:14-46:15, 46:17-25.)

v. ANDA Process

Section 3.2.S.2 of Mylan's ANDA, entitled "Manufacture," sets forth the manufacturing process for Mylan's proposed glatiramer acetate product. (PTX 321.) Although Mylan has filed amendments to its ANDA, it has not revised its manufacturing process or produced any new exhibit batches since its original ANDA filing.

Mylan uses the same four-step process to make its glatiramer acetate active ingredient set forth in the patents-in-suit (the "patent process"), which is described above. In Step 1 of the Mylan ANDA process, like in Step 1 of the patent process, the N-carboxyanhydrides of the amino acids alanine, glutamic acid, lysine, and tyrosine are combined with the initiator diethylamine to form long chains. (Sept. Tr. (Gokel) 348:13-22, 370:7-371:17; PTX 321 at MYL0000251, MYL0000260.) Like the patent process, the glutamic acids and lysines used in Step 1 of the Mylan process must have benzyl and TFA protecting groups, respectively. (Sept. Tr. (Gokel) 342:16-343:23, 345:5-346:10; PTX 987 at 12-13.) Step 1 results in a mixture of

polypeptide chains that are referred to in Mylan's ANDA as GMA F1 or protected copolymer-1. (Sept. Tr. (Gokel) 371:18-21; PTX 321 at MYL0000251, MYL0000254; PTX 987 at 47-52.) Protected copolymer-1 still has the benzyl protecting groups on the glutamic acids and the TFA protecting groups on the lysines. (Sept. Tr. (Gokel) 371:18-372:18; PTX 321 at MYL0000251.)

In Step 2 of Mylan's process, as in the patent process, protected copolymer-1 is reacted with HBr/acetic acid. (Sept. Tr. (Gokel) 371:22-372:6; PTX 321 at MYL0000252; PTX 987 at 53-54.) Like in the patent process, the addition of HBr/acetic acid serves two purposes. First, it removes the benzyl protecting groups from the glutamic acids. Second, it cleaves, or cuts, the polypeptide chains. (Sept. Tr. (Gokel) 371:22-372:6; Sept. Tr. (Sampson) 1641:8-17; PTX 987 at 16-18.) The process of cleaving the polypeptide chains is known as depolymerization. (Sept. Tr. (Gokel) 349:11-18; PTX 987 at 16-18, 53-54.) The product of Mylan's Step 2 reaction is TFA-copolymer-1. (Sept. Tr. (Gokel) 371:22-372:18; PTX 987 at 53.)

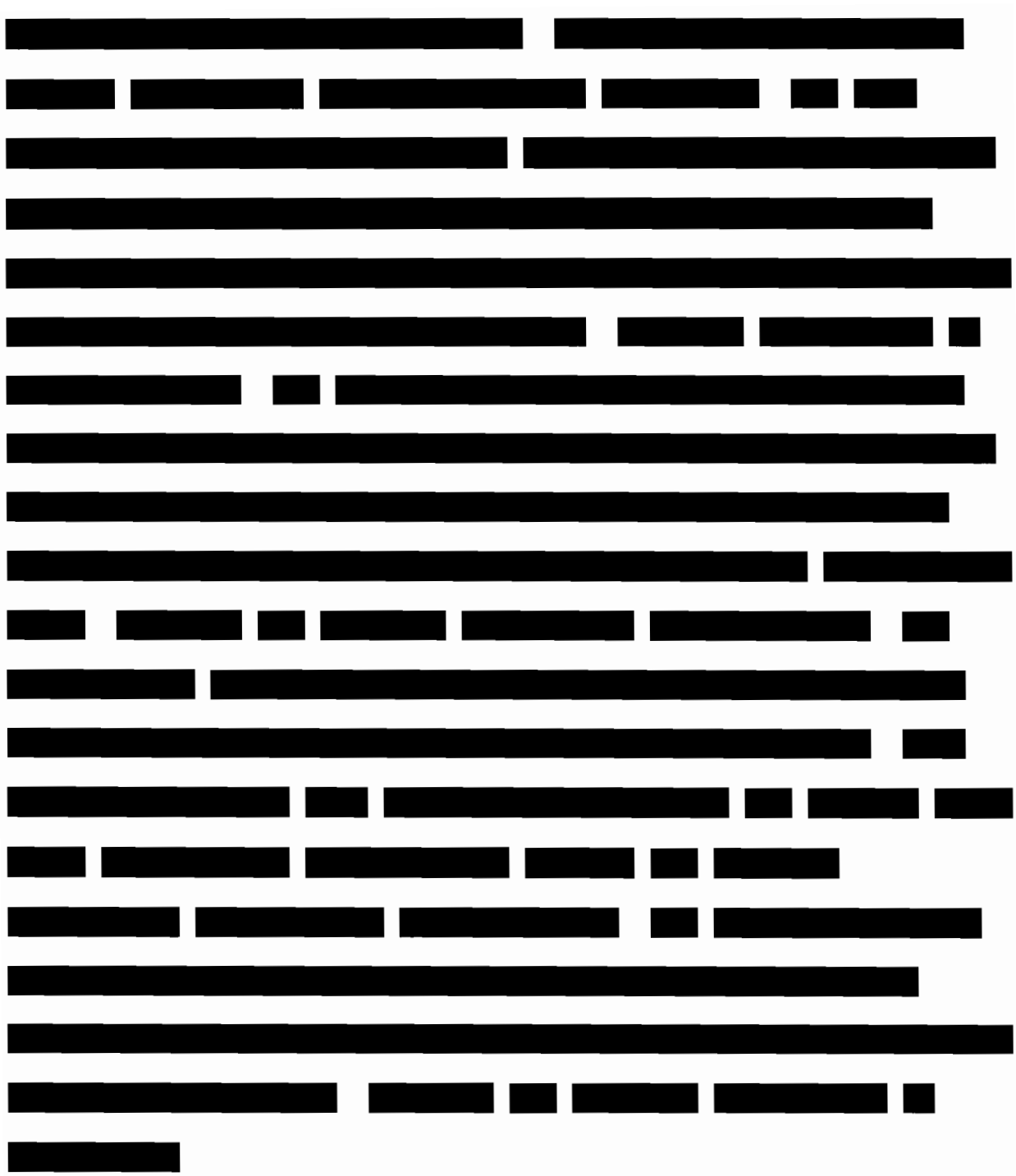
As in the patent process, Step 2 is used to control the molecular weight of Mylan's product so that it meets the specification of 5,000 to 9,000 daltons. (Sept. Tr. (Gokel) 349:12-350:10, 371:22-372:6, 444:13-447:5; Sept. Tr. (Sampson) 1641:8-1642:8; PTX 321 at MYL0000645-51.) In order to determine the time and temperature at which to run Step 2 so that the

final copolymer-1 product has the targeted average molecular weight of between 5,000 and 9,000 daltons, Mylan ran a series of test reactions. (Sept. Tr. (Gokel) 445:4-447:11; PTX 321 at MYL0000645-49; PTX 961 (Kota Dep.) at 124:4-127:11.) [redacted]

[redacted]

Mylan applied these time and temperature determinations, based on the test reactions, to its ANDA process. (Sept. Tr. (Gokel) 447:2-6; PTX 320 at MYL0000272-73; PTX 321 at MYL0000647, MYL0000649; PTX 964 at 120:23-122:9, 125:10-126:20.)

[redacted]



In Step 3 of Mylan's process, TFA-copolymer-1 is treated with piperidine, which removes the TFA protecting groups from the lysines. (Sept. Tr. (Gokel) 372:14-18; PTX 321 at

MYL0000253; PTX 987 at 55.) The patent process also employs this step.

In Step 4 of Mylan's process, as in the patent process, the resulting product from Step 3 is purified by diafiltration using acetic acid. (Sept. Tr. (Gokel) 372:14-23, 373:8-17; PTX 321 at MYL0000253, 267.) The product of Step 4 is glatiramer acetate, or copolymer-1. (Sept. Tr. (Gokel) 372:14-18, 373:3-5; PTX 321 at MYL0000621; PTX 987 at 55.)

vi. Mylan's ANDA Product Label

The proposed label for Mylan's proposed product has the same indication and dosage information as Teva's label for Copaxone®. (Sept. Tr. (Lisak) at 141:13-145:6; PTX 697; PTX 734 at MYL0004949.) Mylan's proposed product label states that the product is "indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis." (Sept. Tr. (Lisak) at 141:13-145:6; PTX 734 at MYL0004949.) If Mylan's product is approved by the FDA, its use would comprise a method of treating multiple sclerosis (Sept. Tr. (Lisak) at 145:21-146:1; 146:23-147:1), and Mylan's proposed label would encourage physicians to use the ANDA product to treat patients with multiple sclerosis (Sept. Tr. (Lisak) 147:16-19; PTX 963 (B. Rao 09/30/2010 Dep.) at 226:17-22; PTX 971 (Talton Dep.) at 85:17-21.)

C. Conclusions of Law as to Mylan's Product

i. Mylan's Proposed Product Infringes Each of the Asserted Claims because Mylan's Product is Copolymer-1

The Court construed "copolymer-1" to mean "a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively, non-uniform with respect to molecular weight and sequence, which is synthesized by polymerization of suitably protected amino acid carboxyanhydrides." (CCO at 12.) Mylan does not contest that its product is a "mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine;" that it is "non-uniform with respect to molecular weight and sequence;" and is "synthesized by polymerization of suitably protected amino acid carboxyanhydrides." Moreover, the evidence at trial established that Mylan's proposed product, in fact, meets those limitations. (Sept. Tr. (Grant) 250:7-12; Sept. Tr. (Gokel) 377:5-378:10; 413:22-415:9.)

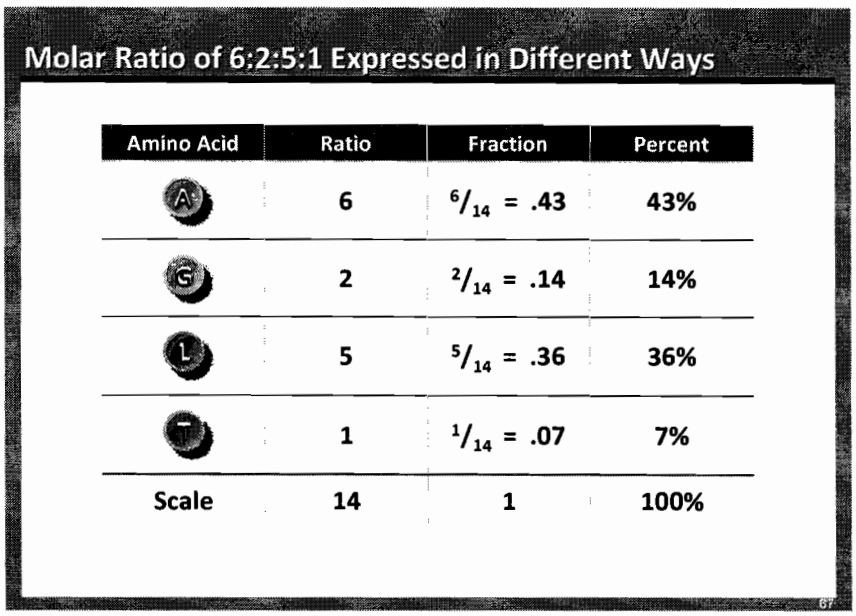
Mylan nevertheless argues its product is not copolymer-1 because the molar ratio of the amino acids in its product is not approximately 6:2:5:1. The evidence at trial was to the contrary, however. It showed that Mylan's proposed product has a molar ratio of approximately 6:2:5:1 and, thus, is copolymer-1 within the meaning of the claims of the patents-in-suit.

A "molar ratio" is a means of expressing the relative proportions of each of the components in a mixture. (Sept. Tr.

(Gokel) 378:20-379:11.) The molar ratio of "approximately 6:2:5:1" describes the relative proportions of the four amino acids alanine, glutamic acid, lysine, and tyrosine in copolymer-1. (Sept. Tr. (Gokel) 411:21-412:1.) For every 14 amino acids, approximately 6 will be alanine, approximately 2 will be glutamic acid, approximately 5 will be lysine, and approximately 1 will be tyrosine. (Sept. Tr. (Gokel) 381:6-14; PTX 987 at 67.) Because the sum of 6 + 2 + 5 + 1 is 14, the molar ratio 6:2:5:1 is expressed on a scale of 14. (Sept. Tr. (Gokel) 411:24-412:1.)

As shown below in Figure 8, the molar ratio of 6:2:5:1 can be expressed in different ways:

Figure 8



(PTX 987 at 67.) For example, approximately 6:2:5:1 can be expressed as the percentages of the four amino acids in a

copolymer-1 mixture, which, by definition, must add up to 100%: approximately 6 out of 14, or approximately 43%, are alanine; approximately 2 out of 14, or approximately 14%, are glutamic acid; approximately 5 out of 14, or approximately 36%, are lysine; and approximately 1 out of 14, or approximately 7%, are tyrosine. (Sept. Tr. (Gokel) 381:24-382:3; PTX 987 at 67.)

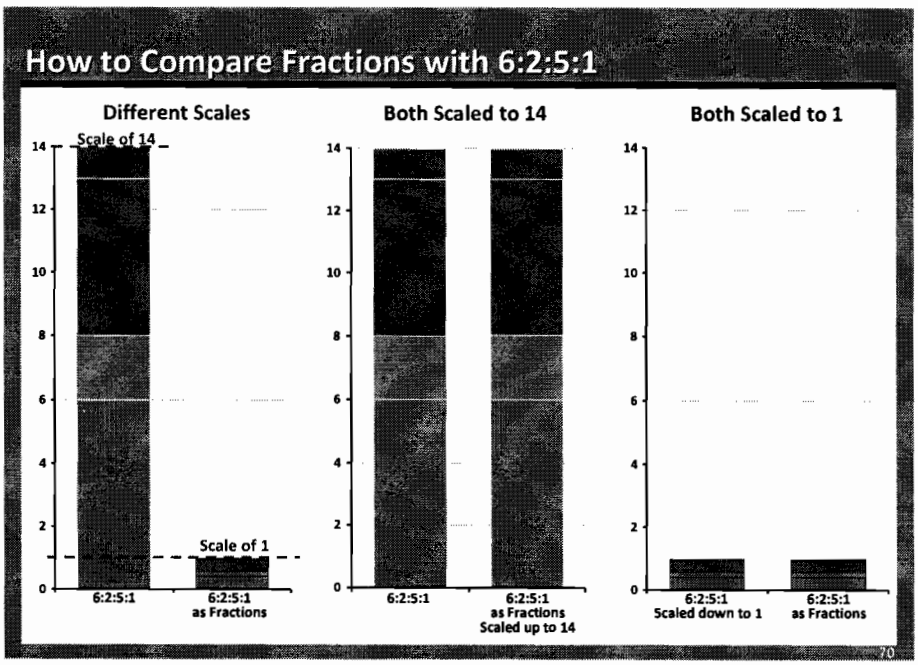
The molar ratio of approximately 6:2:5:1 can also be expressed in terms of molar fractions, which, by definition, must add up to 1. Expressed in this manner, the molar fraction of alanine would be approximately 0.43; the molar fraction of glutamic acid would be approximately 0.14; the molar fraction of lysine would be approximately 0.36; and the molar fraction of tyrosine would be approximately 0.07. (Sept. Tr. (Gokel) 381:6-14; PTX 987 at 67.)

Whether expressed as (1) "approximately 6:2:5:1;" (2) approximately 43% alanine, 14% glutamic acid, 36% lysine, and 7% tyrosine; or (3) approximate molar fractions of 0.43 alanine, 0.14 glutamic acid, 0.36 lysine, and 0.07 tyrosine, the molar fractions all represent the same copolymer-1 compositions with the same relative proportions of the same four amino acids. (Sept. Tr. (Gokel) 381:6-382:15; PTX 987 at 67.)

To determine whether a sample has a molar ratio of "approximately 6:2:5:1," one can compare the sample using the 6:2:5:1 scale of 14, the percentages of the amino acids scale of

100%, or the molar fraction scale of 1. For the comparison to be accurate, the amino acid composition of the sample and 6:2:5:1 must be expressed on the same scale. (Sept. Tr. (Gokel) 382:23-383:15.). Failure to put the two on the same scale will give skewed and fallacious results, as demonstrated below in Figure 9.

Figure 9



(PTX 987 at 70.)

In its ANDA, Mylan provides the molar ratios for its proposed product in terms of molar fractions. (Sept. Tr. (Owens 629:19-21; Sept. Tr. (Gokel) 394:17-396:21, 399:20-400:1, 400:4-6; Sept. Tr. (Owens) 629:19-21; PTX 300 at MYL0002927; PTX 312 at MYL0002929; PTX 313 at MYL0002931; PTX 325 at MYL0001050; PTX 961 (Kota Dep.) at 111:25-112:16; PTX 987 at 74, 77, 78.) To

determine whether Mylan's product meets the "approximately 6:2:5:1" limitation, "6:2:5:1" can be converted to molar fractions and then compared directly to the molar fractions in Mylan's ANDA. Alternatively, Mylan's molar fraction data can be converted to a scale of 14 and then compared directly to 6:2:5:1. (Sept. Tr. (Gokel) 395:17-387:25; PTX 987 at 74-75.) The crucial thing, again, is that the comparison be performed on the same scale. The data for Mylan's Drug Substance Lot GMA/001/009 are compared both ways in Figure 10 below:

Figure 10

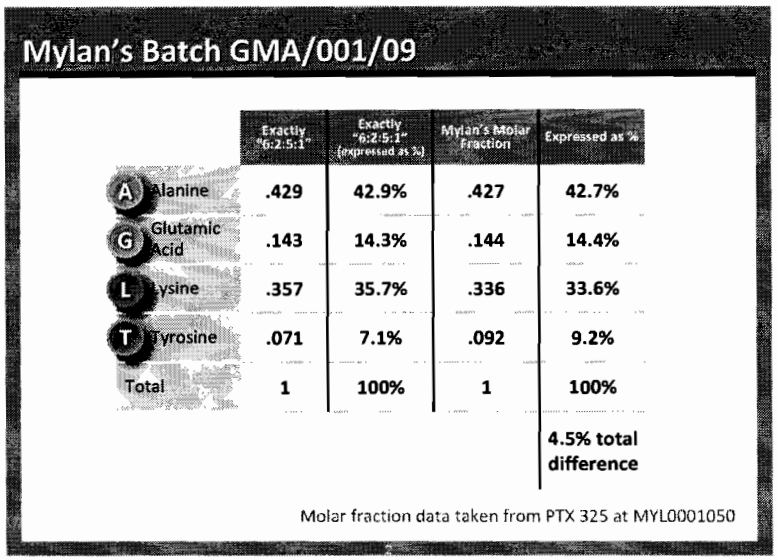
Mylan Drug Substance Lot GMA/001/09

Amino Acid	6:2:5:1	6:2:5:1 (Scale = 1)	Lot GMA/001/09 (Scale = 1)		Scale = 14	
A	6	.43	.427	x 14	5.98	6
G	2	.14	.144	x 14	2.02	2
L	5	.36	.336	x 14	4.70	5
T	1	.07	.092	x 14	1.29	1
Scale	14	1	1		14	14

(Sept. Tr. (Gokel) 396:3-397:9; PTX 987 at 74.)

Mylan's molar fraction data and 6:2:5:1 could also be converted to percentages and then compared directly. That comparison is shown in Figure 11 below:

Figure 11



(Sept. Tr. (Sampson) 543:1-544:17; PTX 988 at 2.)

As shown above, copolymer-1 with a molar ratio of exactly 6:2:5:1 would have 42.9% alanine, 14.3% glutamic acid, 35.7% lysine, and 7.1% tyrosine. Using the molar fractions reported for GMA/001/09 in Mylan's ANDA, the percentages of each amino acid in the batch are 42.7% alanine, 14.4% glutamic acid, 33.6% lysine, and 9.2% tyrosine. (PTX 988 at 2; Sept. Trial (Sampson) 543:22-545:4; PTX 988 at 2.) The percent differences in alanine, glutamic acid, lysine and tyrosine are therefore 0.2, 0.1, 2.1, and 2.1 percentage points, respectively, resulting in a total difference of 4.5% between the molar ratio of Mylan's product and exactly 6:2:5:1. (Sept. Trial (Sampson) 543:14-545:4; PTX 988 at 2.)

At trial, Mylan's expert, Dr. Kent, testified that the difference in the molar fraction of tyrosine between Mylan's

product and a product with a molar ratio of exactly 6:2:5:1 is 30%. (E.g., Sept. Trial (Kent) 715:3-9.) This is incorrect. Although there is a 30% difference, as a matter of arithmetic, between the numbers .071 (molar fraction of tyrosine in a product of exactly 6:2:5:1) and .092 (molar fraction of tyrosine in Mylan's product), that does not mean that the molar ratios differ by 30%. Dr. Sampson explained that in order to properly compare the molar fractions, one has to look at the compositions of the two copolymers in their entirety and not simply focus on a single amino acid. Looking at the compositions as a whole, there is a 2.1% difference in the tyrosine content, since one batch has 7.1% and the other has 9.2%. (Sept. Tr. (Sampson) 545:23-546:20.)

To determine whether the 4.5% total molar ratio difference between Mylan's product and exactly 6:2:5:1 falls within the scope of "approximately"—including the 2.1% difference in tyrosine content—the Court looks to the specification of the patents-in-suit and the prosecution history. See Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1056 (Fed. Cir. 1988) ("We note that the height and position limitation in the claim are modified by the terms 'substantially' and 'approximately.' These terms must be interpreted in light of the specification and prosecution history to determine the literal coverage of the claims with respect to height and position.").

Turning to the specification first, the person of ordinary skill in the art would understand that the molar ratio of 6:2:5:1 is reported in one significant figure. In plain terms, this means that the molar ratio is reported as 6:2:5:1 as opposed to 6.0: 2.0: 5.0: 1.0, for example. Because 6, 2, 5, and 1 are whole numbers and not precise, a person of ordinary skill in the art would understand that each of these numbers—6, 2, 5, and 1—encompasses its rounding range. (Sept. Tr. (Gokel) 384:4-385:8.)

The person of ordinary skill in the art would also understand that the specification of the patents-in-suit cites to Teitelbaum 1971 in connection with the description of copolymer-1. One of ordinary skill would, thus, look to that article in order to gain an understanding of the scope of "approximately 6:2:5:1." (PTX 1 at 23-26; Sept. Tr. (Gokel) 387:25-389:8; PTX 499.) Table 1 of Teitelbaum 1971 is entitled "Composition of copolymer 1." It provides, among other things, the molar ratios for two batches that are expressly defined as "copolymer-1." Copolymer-1 Batch 1 is reported as having a molar ratio for alanine, glutamic acid, lysine, and tyrosine of 6.0: 1.9: 4.7: 1.0, respectively. Copolymer-1 Batch 2 is reported as having a molar ratio for alanine, glutamic acid, lysine, and tyrosine of 6.7: 2.1: 4.2: 1.0, respectively.

(Sept. Tr. (Gokel) 390:16-25; Sept. Tr. (Sampson) 550:18-551:2; PTX 499 at 243; Sept. Tr. (Kent) 726:16-24.)

The authors of the article report that they considered the amino acid compositions of the two batches to be the same. (PTX 499 at 247; Sept. Tr. (Sampson) 552:12-18.) The total percent difference between the molar ratio of Teitelbaum 1971 Batch 2 and the molar ratio of exactly 6:2:5:1 is 12%. One of ordinary skill in the art would understand that the scope of "approximately 6:2:5:1" must be broad enough to include the molar ratio of Teitelbaum 1971 Batch 2, which was expressly defined as copolymer-1. Accordingly, the scope of "approximately 6:2:5:1" must, at a minimum, include total amino acid content differences of up to 12% from exactly 6:2:5:1. (Sept. Tr. (Gokel) 391:1-392:15; Sept. Tr. (Sampson) 551:3-21; PTX 987 at 71; PTX 499 at 243; PTX 988 at 5.)

The prosecution history of the '539 patent also provides guidance on the scope of "approximately 6:2:5:1." In a December 1, 2004 submission to the PTO during the prosecution of the '539 patent, Teva amended the claims to recite "copolymer-1" and explained to the PTO the meaning of that term as used in the claims. (PTX 20-A at TEV000304802.) Teva told the PTO that "the term 'copolymer-1' is not limited to a specific molar ratio of amino acids." Teva explained that "[t]he molar ratio of the polypeptides of 'copolymer-1' varies slightly based on the

particular batch and the particular analytical methodology used." Teva pointed, as an example, to the two batches of copolymer-1 in Teitelbaum 1971 discussed above. (PTX 20-A at TEV000304802; Sept. Tr. (Kent) 736:17-737:10; PTX 20-A at TEV000304802.)

Teva also directed the PTO to three batches of copolymer-1 used in the Bornstein trial that had molar ratios of "1.9: 4.0: 6.0: 1.0," "1.8: 3.9: 5.7: 1.0," and "1.9: 4.0: 6.3: 1.0." (PTX 20-A at TEV000304802; Sept. Trial. Tr. (Kent) 737:11-22.) These molar ratios, rearranged and expressed as ratios of alanine to glutamic acid to lysine to tyrosine, are 6.0: 1.9: 4.0: 1.0, 5.7: 1.8: 3.9: 1.0, and 6.3: 1.9: 4.0: 1.0.

Based on the prosecution history, the term "approximately 6:2:5:1" must be broad enough to include the molar ratios of the Teitelbaum 1971 batches, as well as the three Bornstein batches —all of which were expressly defined as copolymer-1. See Monsanto Co. v. Bayer BioScience N.V., 363 F.3d 1235, 1244-45 (Fed. Cir. 2004) (finding improper the limitation of claims to a particular class of plants where the specification and prosecution history contained express statements that applicants had not limited claims in such a manner). Since the amino acid molar ratio of Mylan's proposed product differs from exactly "6:2:5:1" by only 4.5%, it is closer to exactly 6:2:5:1 than both the amino acid molar ratios of Teitelbaum Batch 2 and the

Bornstein batches referred to during the prosecution history. The Court thus finds that Mylan's product falls within the scope of "approximately 6:2:5:1."

Mylan's argument for why its product does not meet the "approximately 6:2:5:1" limitation, and therefore is not copolymer-1, rests in large part on the testimony of its expert Dr. Kent. In Dr. Kent's opinion, in order to determine whether Mylan's copolymer-1 meets the "approximately 6:2:5:1" requirement, the molar fractions for each of the four amino acids provided in Mylan's ANDA must first be divided by the molar fraction for tyrosine. (Sept. Tr. (Kent) 701:6-23.) This mathematical procedure is referred to as "normalizing" to tyrosine. (Sept. Tr. (Gokel) 400:21-401:20; Sept. Tr. (Kent) 712:1-8.) The resulting values for glutamic acid, lysine, alanine and tyrosine must then be compared directly to 6, 2, 5, and 1, respectively. (Sept. Tr. (Kent) 701:6-702:13.) If the value of any single amino acid differs by more than 10%, according to Dr. Kent, the composition cannot be copolymer-1. (Sept. Tr. (Kent) 703:5-704:8.) In regard to how he arrived at 10%, at trial, Dr. Kent testified that, in 1994, a person of ordinary skill in the art would expect to obtain reproducible amino acid results with less than 5% uncertainty and that the "common cutoff" for comparing samples is two standard deviations—10%. (Sept. Tr. (Kent) 703:5-704:5.)

Dr. Kent's opinion about the meaning and scope of approximately 6:2:5:1 is wrong for several reasons. First, Dr. Kent's opinion on the scope of "approximately 6:2:5:1" would exclude from the definition of copolymer-1 batches that the inventors themselves identified as copolymer-1 and batches that Teva expressly represented to the PTO were copolymer-1. See Liebel-Flarsheim Co. v. Medrad, Inc., 358 F.3d 898, 909 (Fed. Cir. 2004) (district court erred in construing claim term narrowly where prosecution history showed that patentee intended a broader scope).

Specifically, Dr. Kent testified that using his definition of "approximately 6:2:5:1," Teitelbaum 1971 Batch 2 is not copolymer-1 despite the fact that the inventors themselves defined it as copolymer-1. (Sept. Tr. (Kent) 726:16-24, 728:18-24.) Dr. Kent attempted to explain away this flaw in his opinion by asserting that the molar ratio of Batch 2 never appeared in the literature after Teitelbaum 1971. As he was forced to eventually concede, however, the molar ratio of Batch 2 was reported in at least two later publications. (Sept. Tr. (Kent) 731:4-22; PTX 508 at 280; Sept. Tr. (Kent) 732:6-733:4; PTX 976 at 285.) Dr. Kent testified similarly that the three Bornstein batches that Teva expressly identified as copolymer-1 during the prosecution of the '539 patent were also not copolymer-1 using his definition of "approximately 6:2:5:1."

(Sept. Tr. (Kent) 741:3-18.) The Court rejects this opinion because it is "squarely contrary" to the prosecution history. See Liebel-Flarsheim Co., 358 F.3d at 909.

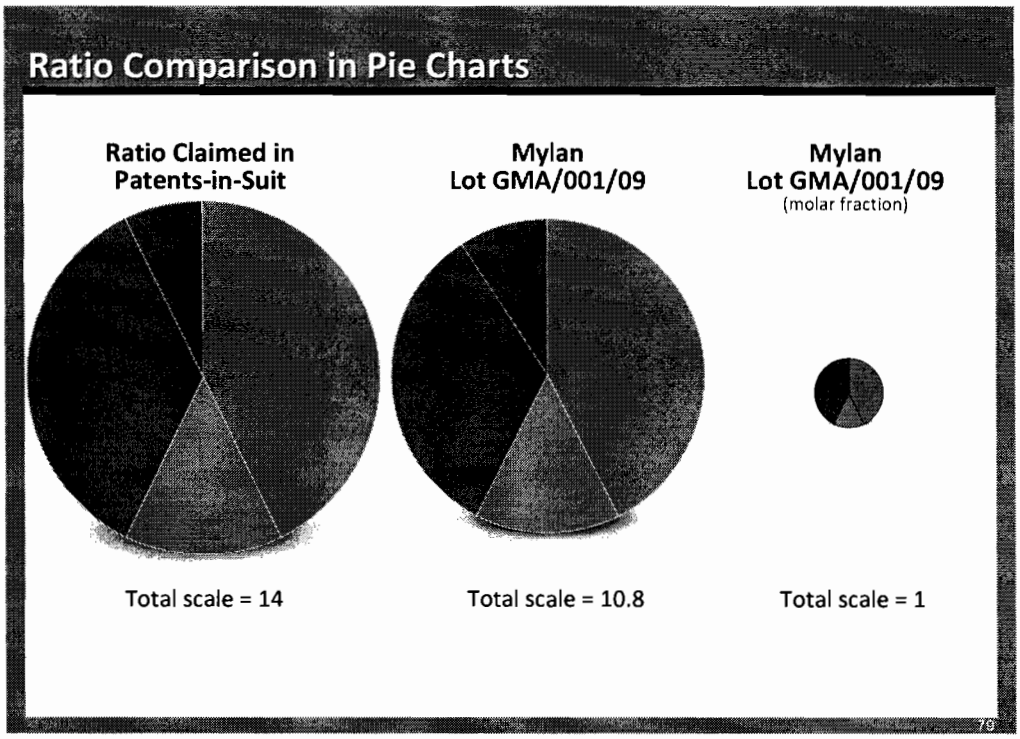
Second, nothing requires that Mylan's molar fraction data be normalized to tyrosine before comparing it to 6:2:5:1, as Dr. Kent suggests. The patents-in-suit make no mention of normalizing to tyrosine. (Sept. Tr. (Kent) 749:3-6.) And despite testifying that it is common practice to normalize to the least abundant species, Dr. Kent conceded he does not do so in his own work outside the context of this litigation. (Sept. Tr. (Kent) 747:22-748:16.)

Significantly, Dr. Kent admitted, during cross-examination, that the best way to compare the amino acid compositions of samples is by comparing their molar fractions, not their molar ratios. (Sept. Tr. (Kent) 743:10-15; 744:1-13.) Dr. Kent also acknowledged that either molar ratios or molar fractions could be used to determine whether a sample has a molar ratio of approximately 6:2:5:1. (Sept. Tr. (Kent) 743:16-21.)

Moreover, as explained above, the molar ratio of Mylan's product cannot be directly compared to 6:2:5:1 unless both numbers are on the same scale. (Sept. Tr. (Gokel) 382:23-383:15, 401:21-402:9; PTX 987 at 68.) As set forth above, "approximately 6:2:5:1" is expressed on a scale of 14. Mylan's molar ratio data in its ANDA is expressed as molar fractions on

a scale of 1. Normalizing this molar fraction data to tyrosine, as Dr. Kent requires, converts Mylan's molar ratio to a scale of 10.8. As shown in Figure 12 below, this puts the numbers on different scales and leads to an invalid comparison. (Sept. Tr. (Gokel) 400:21-402:9, 411:14-412:19; Sept. Tr. (Sampson) 555:24-556:11; PTX 987 at 79.)

Figure 12



Third, in regard to Dr. Kent's 10% "common cutoff" (Sept. Tr. (Kent) 703:15-704:5), Dr. Kent offered nothing to support this opinion. Dr. Gokel, by contrast, whom the Court credits, testified that the level of uncertainty in amino acid analysis, as of 1994, was in the range of 10-20%, and supported his opinion by pointing to Crabb et. al., "A Collaborative Amino

Acid Analysis Study From The Association of Biomolecular Resource Facilities," Current Research in Protein Chemistry, 49-61 (1990) ("Crabb 1990"). As Dr. Gokel testified, Crabb 1990 reports that the precision of amino acid analysis varied from 11.4% to 26.4%. (Sept. Tr. (Gokel) 385:16-386:20; PTX 558 at 54-55.)

Dr. Gokel explained that the molar ratio "approximately 6:2:5:1" cannot be more precise than the experiments used to determine the molar fractions of each amino acid. (Sept. Tr. (Gokel) 386:21-25.) Thus, the scope of "approximately 6:2:5:1" would have to include, at a minimum, the 10-20% uncertainty in amino acid analysis. Using Dr. Kent's formula of two standard deviations, this would translate to a 20-40% "cutoff" when comparing samples to exactly 6:2:5:1.

Thus, even if Dr. Kent were correct that the term "approximately" should include only those samples within two standard deviations of exactly 6:2:5:1, that would include samples in which any of the amino acids differed by as much as 20-40% from exactly 6:2:5:1.

Finally, Dr. Kent testified that a copolymer-1 molar ratio of approximately 6:2:5:1 requires the presence of a bromotyrosine impurity. (Sept. Tr. (Kent) 756:9-757:18.) Following this view to its logical end, pure copolymer-1 with no impurities would not fall within the Court's construction of

copolymer-1. Indeed, Dr. Kent testified that if a person of ordinary skill in the art followed the exact procedure for making copolymer-1 described in the patents-in-suit and used high quality HBr with no free bromine in it, the resulting product would not be copolymer-1. (Sept. Tr. (Kent) 758:10-24.) This cannot be the case.

ii. The Reason for Mylan's Molar Ratio is Irrelevant to the Infringement Analysis.

The crux of Mylan's non-infringement argument is that its manufacturing process is different from the one set forth in the patents-in-suit. This difference, according to Mylan, affects the molar ratios of copolymer-1. The reason Mylan's product has a particular molar ratio is irrelevant, however, to the infringement analysis. The only question with respect to infringement is whether Mylan's product has a molar ratio of "approximately 6:2:5:1" and therefore is copolymer-1 within the meaning of the claims. See Acumed LLC, 483 F.3d at 804 ("A finding of patent infringement requires a two-step process: first, the court determines the meaning of the disputed claim terms, then the accused device is compared to the claims as construed to determine infringement.") (citation omitted).

Even if Mylan's argument were relevant, which it is not, it is contrary to the evidence. According to Mylan, making copolymer-1 pursuant to the process described in the patents-in-

suit leads to an undisclosed side reaction. This side reaction occurs during the first deprotection step, in which the HBr/acetic acid solution is used to remove the benzyl protecting groups from the glutamic acid residues. The undisclosed side reaction results in the formation of a fifth amino acid—bromotyrosine. (Sept. Tr. (Kent) at 657:9-658:6.)

As Dr. Kent acknowledged at trial, however, this side reaction does not necessarily occur when practicing the process in the patents-in-suit:

> Q. If you had HBr that was very pure and didn't contain any free bromine, then you wouldn't have bromotyrosine formation, right?
>
> A. That's correct.
>
> Q. So one way of controlling the formation of bromotyrosine would be to use high quality HBr that didn't have free bromine, right.
>
> A. Yes, that's absolutely correct.

(Sept. Tr. (Kent) at 754:3-10.) Thus, in 1994, a person of ordinary skill in the art could have followed the process for making copolymer-1 found in the patents-in-suit without forming any bromotyrosine. (Sept. Tr. (Kent) 754:3-10, 755:16-22.)

Mylan's argument that its product, made with phenol, has about 30% more tyrosine than a copolymer-1 composition made without phenol is also belied by the evidence. At trial, Mylan's Vice-President of Global Research and Development, acknowledged that at least some of Mylan's copolymer-1 batches

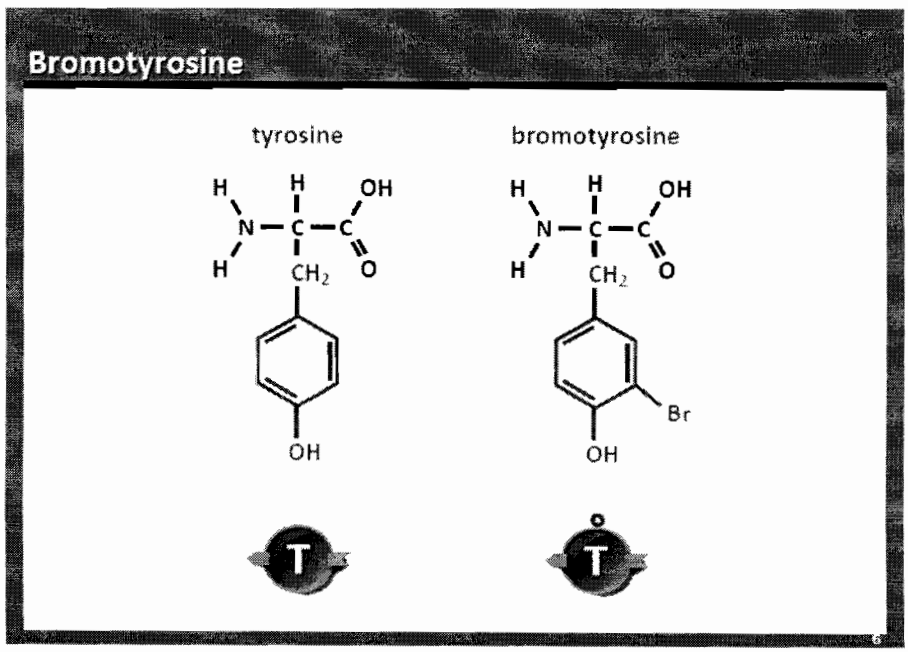
made using phenol had a lower tyrosine content than batches made without phenol. (Sept. Tr. (Owens) at 639:6-8.)

The Court also finds that Mylan's characterization of bromotyrosine as a "fifth amino acid" in copolymer-1 is misleading. As an initial matter, tyrosine and bromotyrosine are not two unrelated molecules. Referring to Figure 13 below, Dr. Kent conceded the similarities between the two:

> Q. Okay. In any event, bromotyrosine is the tyrosine molecule exactly the same except one position on the molecule has a bromine added, correct?
>
> A. It is exactly the same. If you take the compound on the left and replace one proton with a bromine on the aromatic ring, then you have bromotyrosine, that's correct.

(Sept. Tr. (Kent) 759:15-20.)

Figure 13



(PTX 989 at 6.)

The Court notes that outside the context of this litigation, Mylan does not refer to bromotyrosine as a "fifth amino acid" in copolymer-1. In its ANDA, Mylan represented to the FDA that there are four—not five—amino acids in copolymer-1: alanine, glutamic acid, lysine, and tyrosine. The ANDA discusses the presence of bromotyrosine, but only as an impurity. It is never referred to as a possible fifth amino acid in the copolymer-1 composition.[13] (Sept. Tr. (Kent) 771:24-772:3; Sept. Tr. (Owens) 632:4-6, 632:11-633:6; Sept. Tr. (Gokel) 1597:24-1598:2; PTX 320 at MYL0000685-86.)

Finally, if the impurity bromotyrosine were to be considered a "fifth amino acid" in copolymer-1, then there would also be "sixth" and "seventh" amino acids—the impurities benzyl glutamic acid and TFA-lysine. (Sept. Tr. (Gokel) 1597:24-1600:23; Sept. Tr. (Kent) 772:11-25; PTX 987 at 4, 13.) Mylan has made no such claim.[14]

iii. The Doctrine of Equivalents

Even if Mylan's proposed product did not literally meet the requirement of a molar ratio of "approximately 6:2:5:1," it

[13] Sandoz also represented to the FDA that bromotyrosine may be an impurity in copolymer-1. It likewise never referred to bromotyrosine as a possible "fifth amino acid" in the copolymer-1 composition. (Sept. Tr. (Gokel) 1603:13-1606:16; PTX 349 at SDZ00017963, SDZ00018149.)

[14] To the extent Mylan argues that Copaxone® does not have a molar ratio of 6:2:5:1 because it is manufactured using phenol, the Court need not consider this argument. The molar ratio of Copaxone® is not the issue here. The issue is whether Mylan's proposed product infringes the patents-in-suit.

infringes under the doctrine of equivalents. See Boehringer Ingelheim Vetmedica, Inc., 320 F.3d at 1351 ("Under the doctrine of equivalents, a claim limitation not literally met may be satisfied by an element of the accused product if the differences between the two are 'insubstantial' to one of ordinary skill in the art.") (citations omitted).

At trial, Dr. Sampson testified that the difference between the molar ratio of Mylan's proposed product and "approximately 6:2:5:1" is insubstantial and, therefore, is equivalent to "approximately 6:2:5:1." (Sept. Tr. (Sampson) 543:14-545:4, 552:24-553:15; 557:20-23.) In support of her opinion, Dr. Sampson pointed to, among other things, the data in Teitelbaum 1971. As explained above, Table 1 of Teitelbaum 1971 shows the molar ratios for two batches of copolymer-1. The molar ratio of alanine, glutamic acid, lysine, and tyrosine for Batch 1 is 6.0: 1.9: 4.7: 1.0 and the molar ratio for Batch 2 is 6.7: 2.1: 4.2: 1.0. (PTX 499; Sept. Tr. (Sampson) 550:18-551:2.) There is a 2% total difference between the molar ratio of Batch 1 and exactly 6:2:5:1 and a 12% total difference between the molar ratio of Batch 2 and exactly 6:2:5:1. (PTX 988 at 5; Sept. Tr. (Sampson) 552:3-21.) Despite these differences in molar ratio, the two batches were reported as being equally effective in suppressing EAE. (Sept. Tr. (Sampson) 549:11-24; PTX 499 at 247 (Table 8).) In fact, the authors themselves concluded that the

two batches of copolymer-1 showed similar biological activity. (PTX 499 at 247; Sept. Tr. (Sampson) 552:12-18.)

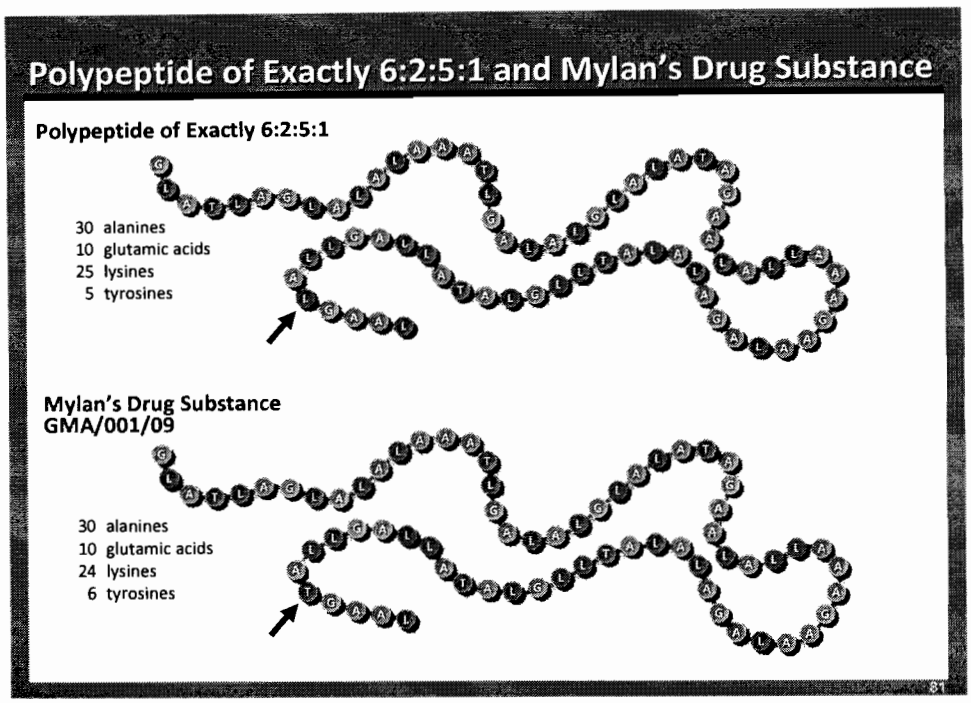
Thus, as Dr. Sampson testified, Teitelbaum 1971 demonstrates that a total amino acid difference of up to 12% from exactly 6:2:5:1 does not materially affect the biological activity of a copolymer-1 sample. Mylan's drug substance, which differs from exactly "6:2:5:1" by only 4.5%, would therefore not be expected to have materially different biological activity from a copolymer-1 sample with a molar ratio of exactly 6:2:5:1. (Sept. Tr. (Sampson) 552:14-553:15.) Indeed, Mylan's testing of its own product demonstrates that it is biologically active in the EAE model. (PTX 318; Sept. Tr. (Owens) 640:23-641:17.)

Accordingly, the molar ratio of Mylan's proposed product is insubstantially different from "approximately "6:2:5:1." (Sept. Tr. (Sampson) 543:14-544:17, 552:14-553:15.) See Boehringer Ingelheim Vetmedica, Inc., 320 F.3d at 1351 (relying on similar biological properties to conclude that claimed and accused elements were insubstantially different and, therefore, equivalent).

Dr. Sampson also explained that the 4.5% total difference between the molar ratio of the amino acids in Mylan's proposed product and exactly 6:2:5:1 translates into a single amino acid difference for an average copolymer-1 chain with 70 amino acids, which would have a molecular weight of about 7,500 daltons.

(Sept. Tr. (Sampson) 548:1-18.) This single amino acid difference is illustrated in Figure 14 below.

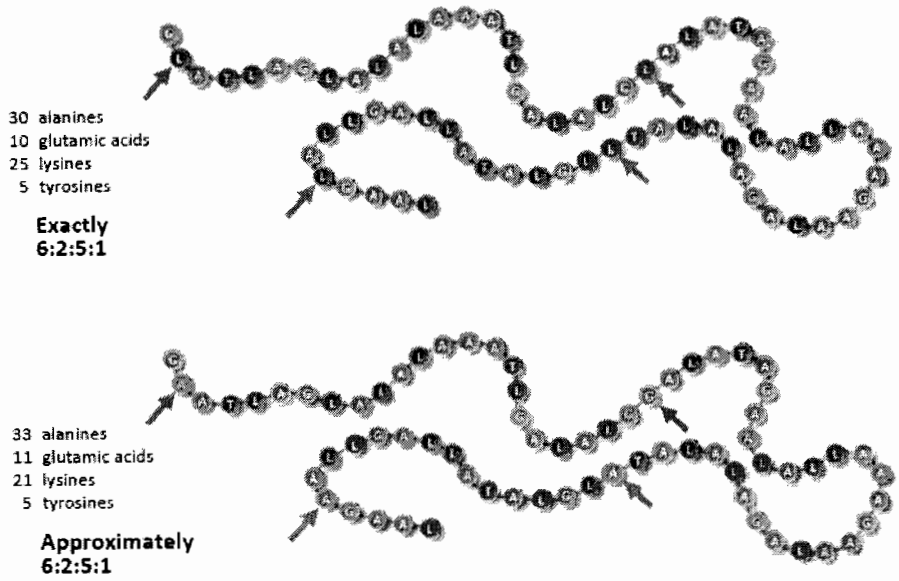
Figure 14



(PTX 987 at 81; PTX 988 at 4.)

By contrast, as can be seen in Figure 15 below, there is a four amino acid difference in that same 70 amino acid chain between Batch 2 of Teitelbaum 1971 and a polypeptide having a molar ratio of exactly "6:2:5:1." (Sept. Tr. (Sampson) 556:12-557:19.)

Figure 15



(PTX 988 at 10.)

The single amino acid difference in Mylan's product cannot be viewed as substantial in light of the four amino acid difference of Teitelbaum Batch 2, which is expressly defined as copolymer-1.

In their proposed findings of fact and conclusions of law, Mylan argues, for the first time, that prosecution history estoppel and the prohibition against recapturing subject matter deliberately left unclaimed bars Teva from expanding the scope of "approximately 6:2:5:1" under the doctrine of equivalents. According to Mylan, during the prosecution of the '098 patent, Teva surrendered any equivalents of copolymer-1 having a molar ratio of "approximately 6:2:5:1."

It is well-settled "that a party's failure to include a legal theory or defense in the pre-trial order results in its subsequent abandonment or waiver." Colli v. Wirth, No. 94 Civ. 3234 (LBS), 1996 WL 442835, at *1 (S.D.N.Y. Aug. 6, 1996) (citations omitted). The reason for this rule is simple: to prevent "trial by ambush." See, e.g., Katt v. City of New York, 151 F. Supp. 2d 313, 347 (S.D.N.Y. 2001). Mylan's prosecution history estoppel argument is even more egregious than "trial by ambush" because it waited until after the trial to raise this defense. See id.

Had Mylan raised this defense earlier, Teva could have attempted to "overcome the presumption that prosecution history estoppel bars a finding of equivalence"—assuming Mylan had been able to establish the defense—by providing "expert testimony and . . . other extrinsic evidence relating to the relevant factual inquiries[,]" including, "for example, the state of the art and the understanding of a hypothetical person of ordinary skill in the art at the time of the amendment." See Glaxo Wellcome, Inc. v. Impax Labs., Inc., 356 F.3d 1348, 1353-54 (Fed. Cir. 2004) (citations and internal quotation marks omitted). Without notice that it needed to provide any evidence to this effect, Teva was clearly prejudiced by Mylan's failure to raise this defense until after the conclusion of the trial. Accordingly, the Court finds that Mylan waived its prosecution

history estoppel argument with regard to infringement under the doctrine of equivalents. See, e.g., Colli, 1996 WL 442835, at *1-2.

For the reasons set forth above, even if the molar ratio of the amino acids in Mylan's product did not fall within the literal scope of "approximately 6:2:5:1," which it does, it would be equivalent to "approximately 6:2:5:1."

iv. Mylan's Product Meets the Molecular Weight Limitations

The molecular weight limitations of the asserted claims can be divided into three categories: 1) average molecular weight limitations; 2) copolymer-1 fraction limitations; and 3) TFA copolymer-1 fraction limitations. At trial, Dr. Grant explained why Mylan's ANDA product meets the molecular weight limitations of each of the asserted claims. (Sept. Tr. (Grant) 265:2-268:3.) Mylan offered no evidence rebutting Dr. Grant's conclusions.

1) Average Molecular Weight Limitations

The Court construed "average molecular weight" to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (CCO at 40 and n.10; Sept. Tr. (Grant) 211:5-15; PTX 986 at 25.) Mylan's method for determining the peak molecular weight values of its product involves using an appropriately calibrated suitable gel

filtration column. (Sept. Tr. (Grant) 250:23-254:22; PTX 318 at MYL0000111-12; PTX 330 at MYL0000765-66.)

Based on Dr. Grant's testimony, which the Court credits, and the peak molecular weight data in Mylan's ANDA, Mylan's proposed product meets the molecular weight limitations of claim 1 of the '808 patent and claim 1 of the '589 patent, which require a copolymer-1 having an average molecular weight of "about 5 to 9 kilodaltons;" claims 1 and 6 of the '847 patent and claims 1, 8, 9, 12, 23, 30, and 31 of the '539 patent, which require a copolymer-1 having an average molecular weight of "about 4 to about 9 kilodaltons;" and claim 10 of the '539 patent, which requires a copolymer-1 with an average molecular weight of "6.25 to 8.4 kilodaltons." (Sept. Tr. (Grant) 259:24-260:22; PTX 986 at 24, 45.)

2) Copolymer-1 Molar Fraction Limitations

Based on Dr. Grant's calculations using Mylan's electronic data, which the Court credits, Mylan's proposed product meets the molecular weight limitations of Claims 1, 2, and 3 of the '430 patent, which require the copolymer-1 to have over 75% of its molar fraction within the molecular weight range of 2 and 20 kDa; claims 8 and 30 of the '539 patent, which require the copolymer-1 to have less than 2.5% of its molar fraction with molecular weights above 40 kDa; claims 9, 10, and 31 of the '539 patent and claim 8 of the '098 patent, which require that the

copolymer-1 have over 75% of its molar fraction between the molecular weights of 2 and 20 kDa and less than 2.5% of its molar fraction with molecular weights greater than 40 kDa; claim 1 of the '476 patent, claim 1 of the '161 patent, and claim 1 of the '098 patent, which require that the copolymer-1 have over 75% of its molar fraction between the molecular weights of 2 and 20 kDa and less than 5% of its molar fraction with molecular weights greater than 40 kDa. (Sept. Tr. (Grant) 262:14-263:21; 1463:16-1465:25; 1466:9-19.)

3) TFA Copolymer-1 Molar Fraction Limitations

Based on Dr. Grant's calculations using Mylan's electronic data, which the Court credits, Mylan's proposed product meets the molecular weight limitations of Claims 1, 2, and 3 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent, which require that the TFA copolymer-1 that is made as a result of treatment of protected copolymer-1 with hydrobromic acid have over 75% of its molar fraction with molecular weights between 2 and 20 kDa. (Sept. Tr. (Grant) 265:2-15.)

v. Mylan's Process Meets the Process Limitations

Of the 22 asserted claims of the patents-in-suit, twelve claims are directed either to a method of manufacturing copolymer-1 or to a copolymer-1 that is made by a particular

process. Mylan has not disputed that the manufacturing process in its ANDA meets these claim limitations.

Based on the information in Mylan's ANDA, the stipulation entered into by Mylan, and Dr. Gokel's testimony, Mylan's process meets the "reacting protected copolymer-1 with hydrobromic acid" limitation found in claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1, 2, and 3 of the '898 patent, claims 1, 2, and 3 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent; the "treating trifluoroacetyl copolymer-1" limitation found in claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1, 2, and 3 of the '898 patent, claims 1, 2, and 3 of the '430 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, and claims 1 and 6 of the '847 patent; the "purifying" limitation found in claim 1 of the '808 patent, claim 1 of the '589 patent, and claims 1 and 6 of the '847 patent; the "selecting a predetermined molecular weight profile" limitation of claims 1, 2, and 3 of the '898 patent; the "for a time and at a temperature predetermined by test reaction" limitations of claims 1, 2, and 3 of the '898 patent, claims 1, 2, and 3 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent; and the "copolymer-1 faction" limitations of claim 1 of the '161 patent and claim 1 of the '476 patent. (Sept. Tr. (In Chambers Stip.) 440-43; Sept. Tr. (Gokel) 349:4-350:18, 368:14-374:9,

439:11-447:19; 447:12-17, 448:16-469:7; 478:10-469:7; PTX 321 at MYL0000251-54, 262, 647, 649; PTX 987 at 45-55, 100-10.)

vi. Mylan Meets the Treatment Limitations

At trial, Dr. Lisak testified regarding Mylan's infringement of the claim limitations related to treatment of multiple sclerosis. His testimony was unrebuttted. Based on his testimony, which the Court credits, Mylan's proposed product meets the "method of treating multiple sclerosis" limitation found in claim 1 of the '476 patent; the "administering to a subject in need thereof" limitation found in claim 1 of the '476 patent; the "pharmaceutically effective amount" limitation found in claim 1 of the '476 patent and claim 1 of the '161 patent; the "treatment of multiple sclerosis" limitation found in claim 1 of the '161 patent; the "suitable for treating multiple sclerosis" limitation found in claim 1 of the '539 patent; the "dose therapeutically effective to treat multiple sclerosis" limitation found in claim 12 of the '539 patent; the "a method for treating a patient suffering from multiple sclerosis" limitation found in claims 23, 30, and 31 of the '539 patent; the "administering to a patient in need thereof" limitation found in claims 23, 30, and 31 of the '539 patent; and the "suitable for treating multiple sclerosis" limitation found in claim 1 of the '098 patent. (Sept. Tr. (Lisak) 137:5-147:19; PTX 734 at MYL0004949; PTX 985 at 20.)

In addition, based on the stipulation entered into by Mylan, Mylan's proposed product meets the limitations of "pharmaceutical composition" and "pharmaceutically acceptable excipient" in claims 12, 23, 30, and 31 of the '539 patent. (PTX 935.)

Finally, the Court finds that Mylan would induce physicians to infringe the '476 and '539 patents if its ANDA were approved. Mylan knew of those patents before filing its ANDA, as it filed a certification with the FDA and sent a notice letter to Teva specifically referencing the patents-in-suit, including the '476 patent and the '539 patent. (PTX 965 (S. Rao Dep.) at 123:25-124:14; JPO ¶¶ 89-90, 94-95.) Mylan's proposed product label would induce doctors to prescribe its ANDA product to treat multiple sclerosis and thereby induce infringement of claim 1 of the '476 patent and claims 23, 30, and 31 of the '539 patent. See AstraZeneca LP, 633 F.3d at 1060 ("The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of [the alleged infringer's] affirmative intent to induce infringement.") (citation omitted).

vii. Mylan Infringes All Asserted Claims

In sum, based on the testimony of Dr. Lisak, Dr. Grant, Dr. Sampson, and Dr. Gokel, the evidence they discussed and referenced during their testimony, and Mylan's stipulations, the

Court finds, by a preponderance of the evidence, that the manufacture and sale of Mylan's proposed glatiramer acetate product would infringe each of the asserted claims both literally and under the doctrine of equivalents.

D. Findings of Fact as to Sandoz

i. Sandoz's ANDA Product and its Active Ingredient

The active ingredient in Sandoz's proposed product is described as glatiramer acetate. (Sept. Tr. (Gokel) 360:16-18.) Sandoz and Momenta acknowledge that glatiramer acetate is also known as copolymer-1. For example, Sandoz's labeling for its proposed product describes its active ingredient as "glatiramer acetate (formerly known as copolymer-1)." (Sept. Tr. (Lisak) 141:13-143:19; PTX 206 at SDZ00000031.) Sandoz internal documents likewise make clear that one of the names for its active ingredient is "copolymer-1." (Sept. Tr. (Grant) 220:13-221:7; PTX 141 at MMT00391607.) In addition, Momenta scientist Mani Iyer, who was in charge of manufacturing and developing Sandoz's glatiramer acetate, specifically testified that Sandoz's product is a "copolymer-1 composition." (PTX 960 (Iyer Dep.) at 25:8-10.)

1) Amino Acid Composition

The glatiramer acetate active ingredient in Sandoz's proposed product is composed of the four amino acids glutamic

acid, alanine, lysine and tyrosine. (Sept. Tr. (Gokel) 414:23-415:9; PTX 219 at SDZ00002024-25; PTX 351 at SDZ00018614.) Sandoz's ANDA provides data on the relative proportions of glutamic acid, alanine, lysine and tyrosine in its proposed product, expressed as molar fractions. (Sept. Tr. (Gokel) 417:19-22, 420:12-17; PTX 219 at SDZ00002025; PTX 913 at 28.) According to Sandoz's ANDA, the lots it produced have the following molar fractions of glutamic acid, alanine, tyrosine and lysine, respectively: drug substance lots 077K7277, 0.147: 0.436: 0.083: 0.334; drug substance lot 087K7253, 0.142: 0.419: 0.083: 0.356; drug product lot CT0743, 0.134: 0.444: 0.083: 0.340; and drug product lot CT0750, 0.126: 0.421: 0.083: 0.370. (Sept. Tr. (Gokel) 416:14-419:6; PTX 219 at SDZ00002025; PTX 987 at 89.)

In its [redacted] Briefing Book, Sandoz provided the molar fractions for an additional drug substance lot—lot 051M7282. (Sept. Tr. (Gokel) 420:3-17.) The molar fractions of glutamic acid, alanine, tyrosine, and lysine for this lot are 0.136: 0.427: 0.093: 0.344. (Sept. Tr. (Gokel) 420:3-17; Sept. Tr. (Sampson) 546:22-547:15; PTX 913 at 28; PTX 987 at 93-95; PTX 988 at 3.)

2) Molecular Weight

Sandoz's proposed product has a specification for peak average molecular weight between 5,000 and 9,000 daltons.

(Sept. Tr. (Grant) 222:6-17.) As set forth in Figure 16 below, the data in Sandoz's ANDA demonstrates that each of its lots falls within the specified 5,000-9,000 daltons range. (Sept. Tr. (Grant) 222:6-17; PTX 349 at SDZ00017949; PTX 351 at SDZ00018608-611; PTX 986 at 26.)

Figure 16

Lot	Peak Average Molecular Weight (Da)
077K7277	8407
087K7253	7275
058K7278	7216
078K7276	7104
128K7276	5932
029K7279	7641
049K7275	6977
049K7276	7366
059K7275	7199
CT0743	8274
CT0750	7417

Source: PTX 351 at SDZ00018608-11; PTX 349 at SDZ00017949

Sandoz determined these peak molecular weight values using SEC with TSK gel G 3,000 and G 2,000 columns. (Sept. Tr. (Grant) 214:19-215:5.) Sandoz calibrated the SEC columns using nine peptide standards that (i) had amino acid compositions consistent with the composition of copolymer-1 and (ii) had the same size-to-molecular weight relationship as copolymer-1. (Sept. Tr. (Grant) 215:6-13.) In addition to having a specified peak molecular weight, Sandoz's product also has particular molecular weight distribution characteristics, some of which are

shown in Figure 17 below. (Sept. Tr. (Grant) 230:13-233:14; PTX 986 at 33.)

Dr. Grant used electronic molecular weight data generated by Sandoz, during its SEC measurements of five Sandoz drug substance lots, to calculate the percentage (on a molar fraction basis) of the copolymer-1 molecules in each lot that have a molecular weight between 2 and 20 kilodaltons and the percentage having molecular weights above 40 kilodaltons. (Sept. Tr. (Grant) 230:13-233:14.) These percentages are listed in Figure 17 below.

Figure 17

	% molar fraction between 2 and 20 kilodaltons (%)	% molar fraction above 40 kilodaltons (%)
077K7277	≥ 91.99	≤ 0.36
087K7253	≥ 85.00	≤ 0.28
049K7275	≥ 90.82	≤ 0.23
049K7276	≥ 87.36	≤ 0.24
059K7275	≥ 88.83	≤ 0.25

Source: PTX 377

Using the electronic molecular weight data for the same five Sandoz drug substance lots, Dr. Grant also calculated the molar fraction percentages of molecules having molecular weights between 2 and 20 kilodaltons in the TFA copolymer-1 intermediate that corresponded to each lot. (Sept. Tr. (Grant) 236:22-239:4;

PTX 986 at 40.) These percentages are listed in Figure 18 below.

Figure 18

Trifluoroacetyl copolymer-1 corresponding to sample	% TFA molar fraction between 2 and 20 kilodaltons (%)
077K7277	≥ 91.45
087K7253	≥ 89.69
049K7275	≥ 92.82
049K7276	≥ 91.34
059K7275	≥ 92.07

Source: PTX 377

ii. Sandoz's Manufacturing Process

Before it entered into the agreement with Momenta, Sandoz worked on developing its own process for making generic Copaxone®. Dr. Anup Ray, a principal scientist at Sandoz and its Rule 30(b)(6) designee on Sandoz's processes for manufacturing copolymer-1, was tasked with this project. (PTX 364 (Topic 18); PTX 966 (Ray Dep.) at 18:13-15, 23:2-24:10, 30:13-16.) The first thing Dr. Ray did after being given his assignment was perform a literature search. (PTX 966 (Ray Dep.) at 32:13-15.) Following the literature search, Dr. Ray's initial strategy was to make generic Copaxone® using the method described in Teva's patent. (PTX 966 (Ray Dep.) at 42:6-15.)

Dr. Ray subsequently began work on developing alternative processes for making generic Copaxone®. (PTX 889; PTX 966 (Ray

Dep.) at 81:11-83:20, 108:5-19.) Sandoz's strategy was to develop a route that "circumvented" Teva's patented method. (PTX 123 at SDZ00014130.) Dr. Ray testified he received instructions from a Sandoz lawyer on these alternative processes. (PTX 966 (Ray Dep.) at 127:8-11.)

Dr. Ray eventually devised an alternative process for making copolymer-1 that he concluded was "very different from known Teva patented process." (PTX 115; PTX 117 at SDZ00011436; PTX 966 (Ray Dep.) at 92:6-11.) Sandoz filed a patent application on this process, and Dr. Ray was a named inventor. (PTX 155.) The parties cite no evidence in the record indicating the fate of this patent application.

Momenta's efforts to design a process for making generic Copaxone® were led by Dr. Iyer, who was then a Principal Scientist at Momenta. (PTX 960 (Iyer Dep.) at 5:20-6:9, 16:20-21, 18:3-19:10, 19:20-20:2.) Like Dr. Ray, the first thing Dr. Iyer did when he got his assignment was review the literature on copolymer-1, including the '808 patent. (Sept. Tr. (Bishop) 1075:19-1076:12; PTX 960 (Iyer Dep.) at 19:23-20:2, 147:9-16.) Dr. Iyer understood that Teva's method for making copolymer-1 was a "Patented Process." (PTX 135; PTX 777; PTX 960 (Iyer Dep.) at 452:12-46:19.)

Momenta's process development strategy was set forth in a December 2005 presentation by Dr. Iyer. (PTX 141.) Phase I of

the project was to replicate the "literature process." (PTX 141 at MMT00391608, 610-14.) The "literature process" was Momenta's internal designation for Teva's patented process.[15] (PTX 960 (Iyer Dep.) at 130:7-9, 130:11-14, 130:17.) Phase II was to modify the process to "stay outside the process claims." (PTX 141 at MMT00391608, 647-51.) Phase III was to make further modifications to "add[] additional distance from a[n] IP standpoint." (PTX 141 at MMT00391608, 652-56.)

Steve Brugger, Vice-President of Strategic Product Development for Momenta, acknowledged in a presentation given to Sandoz that there were "[m]ultiple opportunities for development of alternate process." (PTX 119 at MMT01078913; PTX 957 (Brugger Dep.) at 74:19-75:10.)

Dr. Iyer's team worked on replicating the patented "literature process." (PTX 960 (Iyer Dep.) at 32:7-19, 32:21-22, 32:23-25.) At the same time, Momenta contracted out work on developing a "non-literature process." (PTX 960 (Iyer Dep.) at 32:7-19, 32:21-22, 32:23-25, 33:16-34:8.) Momenta also did its own experimental work on an alternative non-literature process, and eventually filed a patent application on alternative routes for making copolymer-1. (PTX 177; PTX 785; PTX 960 (Iyer Dep.) at 159:24-160:18.) Momenta stopped working on an alternative process in 2007, and decided to go forward with filing its ANDA,

[15] At his deposition, Dr. Iyer testified that the "literature" Momenta was following "included everything." (PTX 960 (Iyer Dep.) at 130:7-17.)

using Teva's patented process. (PTX 960 (Iyer Dep.) at 37:7-10, 41:6-13, 113:16-19, 127:24-128:3, 130:7-17, 138:5-13; PTX 957 (Brugger Dep.) at 78:16-79:23.)

A May 2007 internal Momenta presentation explained Momenta's reasoning for abandoning the development of an alternative, non-infringing process. Momenta decided to file its ANDA using Teva's patented process because it "[e]nable[d] a first-to-file approach" and "[m]itigate[d] risk regarding chemical equivalence." (PTX 172 at MMT01287394.) In other words, as Dr. Iyer explained, Momenta decided to copy Teva's patented process for making copolymer-1 instead of developing its own process because it provided the quickest route to a regulatory filing. (PTX 960 (Iyer Dep.) at 127:18-128:3.) Dr. Iyer further testified that the time of 17 hours and temperature of 26° used in Step 2 of his process—the debenzylation step—was copied out of Teva's patent. (PTX 960 (Iyer Dep.) at 147:17-25, 148:3-7, 148:9-11.)

Broadly speaking, Sandoz's ANDA uses the four-step process described in the patents-in-suit to make its proposed product. In Step 1, as in the patent process, Sandoz combines the N-carboxyanhydrides of alanine, benzyl protected glutamic acid, TFA protected lysine and tyrosine with the initiator diethylamine to form protected copolymer-1, which Sandoz calls

Intermediate-1. (Sept. Tr. (Gokel) 348:13-22, 357:2-359:11; PTX 216 at SDZ00001937-38.)

In Step 2, as in the patent process, Intermediate-1 is reacted with HBr/acetic to form TFA protected copolymer-1, which Sandoz calls Intermediate-2. (Sept. Tr. (Gokel) 359:5-11, 368:4-8; PTX 216 at SDZ00001937-38.) Prior to amending its ANDA on October 27, 2011 (Hagberg Reply Decl. Ex. A, at SDZ00133705-06, SDZ132331-32, SDZ132337-39), Sandoz used the time and temperature of the Step 2 reaction to control the molecular weight of its product and to ensure that it meets the specification of 5,000 to 9,000 daltons. (Sept. Tr. (Gokel) 361:20-363:13; Sept. Tr. (Sampson) 1641:18-1642:8; PTX 213; PTX 214 at SDZ00000186.) Sandoz determined the target time and temperature for Step 2 using "profile runs." (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.)

During these profile runs, samples of Intermediate-1 were taken at varying times during the Step 2 HBr/acetic acid reaction. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.) The samples were then subjected to Steps 3 and 4 of Sandoz's manufacturing process and converted to glatiramer acetate. The average molecular weights of the resulting batches of glatiramer acetate were determined. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.) With this data, Sandoz was able to determine the window of time for the Step 2 reaction

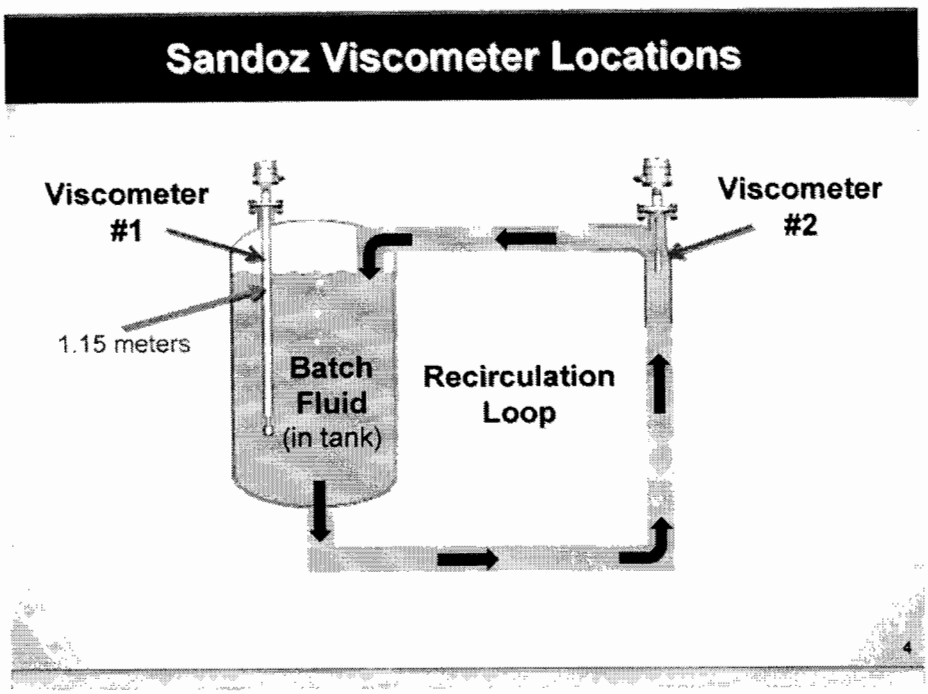
that would allow Sandoz to obtain glatiramer acetate having an average molecular weight between 5,000 and 9,000 daltons. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.)

The reaction conditions of time and temperature determined from the profile runs were applied to Sandoz's production batches. (Sept. Tr. (Gokel) 424:12-425:15; Sept. Tr. (Bishop) 1098:16-1099:6; PTX 214 at SDZ00000186.) Sandoz ran Step 2 for 43-47 hours at a temperature of 20 ± 2°C. (Sept. Tr. (Bishop) 1098:1-1099:6; PTX 353 at SDZ00017631-32.)

In its [redacted] ANDA amendment, Sandoz and Momenta represented that they have ceased using a time and temperature model. Sandoz and Momenta currently employ an in-process viscometry method to determine the endpoint of their HBr/acetic acid Step 2 depolymerization reaction. (Hagberg Reply Decl. Ex. A at SDZ00133705-06, SDZ132331-32, SDZ132337-39.) At trial, Dr. Laird explained that, in this model, a viscometer is inserted into a tank in which the depolymerization reaction takes place, where it "measures the viscosity and also measures the temperature . . . at the same point at which the viscosity is measured." (Sept. Tr. (Laird) 1131:14-23.) A second, back-up viscometer is inserted into a recirculation loop, where it measures both viscosity and temperature at a different location in the reaction tank from the first viscometer." (Sept. Tr.

(Laird) 1131:24-1132:3.) Sandoz's in process method is depicted in Figure 19 below.

Figure 19



(DTX 3580 at 4.)

Viscosity is a property that describes the fluidity of a solution. (Sept. Tr. (Gokel) 427:7-11.) For example, gasoline and water have a low viscosity, whereas honey has a high viscosity. (Sept. Tr. (Gokel) 427:7-11.) The premise of the viscometer model is that the viscosity of an Intermediate-1 sample at a given temperature can be correlated with the average molecular weight of the final glatiramer acetate product. (Sept. Tr. (Gokel) 426:3-427:6; PTX 913 at 36.) The Step 2 HBr/acetic acid reaction is stopped when a viscosity is reached

that provides a final glatiramer acetate product having the targeted average molecular weight of 7,300 daltons. (Sept. Tr. (Gokel) 432:11-23; PTX 914 at MMT01630953.)

Sandoz previously determined the Intermediate-1 viscosity values that would give the glatiramer acetate final product with the targeted average molecular weight of 7,300 daltons using test reactions. In these test reactions, samples of Intermediate-1 were reacted with HBr/acetic acid at varying times and temperatures, and the viscosity values were measured. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 106-114.) The samples of Intermediate-1 were then converted to glatiramer acetate, and the average molecular weights of the glatiramer acetate samples were determined. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 106-114.)

Using this data, Sandoz determined what viscosity value of Intermediate-1 at a given temperature would result in final glatiramer acetate product having an average molecular weight of 7,300 daltons. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 106-14.) Sandoz took the viscosity and temperature information it obtained and created a table of predetermined targeted viscosity values for given reaction temperatures. (Sept. Tr. (Gokel) 436:18-439:6; PTX 928 at MMT01707035.) The table contains temperatures ranging from 20.0°C to 24.0°C, in increments of two tenths of a degree, and their corresponding

targeted viscosity values. (Sept. Tr. (Laird) 1159:19-1160:3; PTX 928 at MMT01707035.) The Step 2 reaction is stopped when the targeted viscosity value is reached for the Step 2 reaction temperature. (Sept. Tr. (Gokel) 430:17-431:24; PTX 914 at MMT01630952-53; PTX 928 at MMT01707035.)

Momenta documents indicate that as time increases, viscosity decreases. (PTX 914 at MMT01630951-53.) Thus, the longer Intermediate-1 reacts with HBr/acetic acid, the lower its viscosity. This enables Sandoz to use viscosity, which changes as a function of time, rather than time itself, to monitor the progress of the reaction and determine when to stop it in order to obtain glatiramer acetate having an average molecular weight of 7,300 daltons. (Sept. Tr. (Gokel) 430:7-16, 434:9-17.)

In Step 3 of the Sandoz and patent processes, Intermediate-2 is treated with piperidine, which removes the TFA protecting groups from the lysines. (Sept. Tr. (Gokel) 359:17-360:9, 368:9-13; PTX 216 at SDZ00001937-38.) Sandoz's ANDA refers to the resulting product as Intermediate-3. In Step 4, the final step of both the Sandoz and patent processes, Intermediate-3 is purified by a step called diafiltration. During this step, acetic acid is used. (Sept. Tr. (Gokel) 360:3-18, 361:3-19; PTX 216 at SDZ00001937-38, 949.) The product of Step 4 is glatiramer acetate, or copolymer-1. (Sept. Tr. (Gokel) 360:3-18; PTX 216 at SDZ00001937-38.)

iii. Sandoz's ANDA Product Label

The proposed label for Sandoz's ANDA product has the identical indication and dosage information as Teva's Copaxone® label. (Sept. Tr. (Lisak) 141:13-145:6; PTX 206 at SDZ00000034, 044; PTX 697.) Sandoz's proposed product label states that the product is "indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis." (Sept. Tr. (Lisak) 141:13-145:6; PTX 206 at SDZ00000034.) If Sandoz's ANDA product is approved by the FDA, its use would comprise a method of treating multiple sclerosis (Sept. Tr. (Lisak) at 145:21-146:1, 146:23-147:1), and Sandoz's proposed label would encourage physicians to use the ANDA product to treat patients with multiple sclerosis. (Sept. Tr. (Lisak) 147:16-19.)

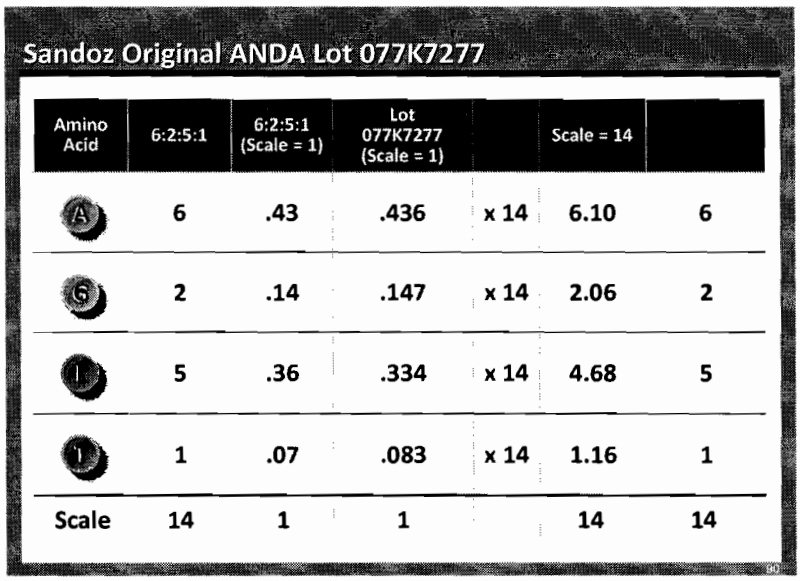
E. Conclusions of Law as to Sandoz's Product

i. Sandoz's Proposed Product Infringes Each of the Asserted Claims because Sandoz's Product is Copolymer-1

Up to the eve of trial, Sandoz did not dispute that its proposed generic product was copolymer-1. Then, in its pretrial submissions, Sandoz argued, for the first time, that its proposed product is not copolymer-1 because it does not have an amino acid molar ratio of approximately 6:2:5:1. Sandoz's argument lacks merit.

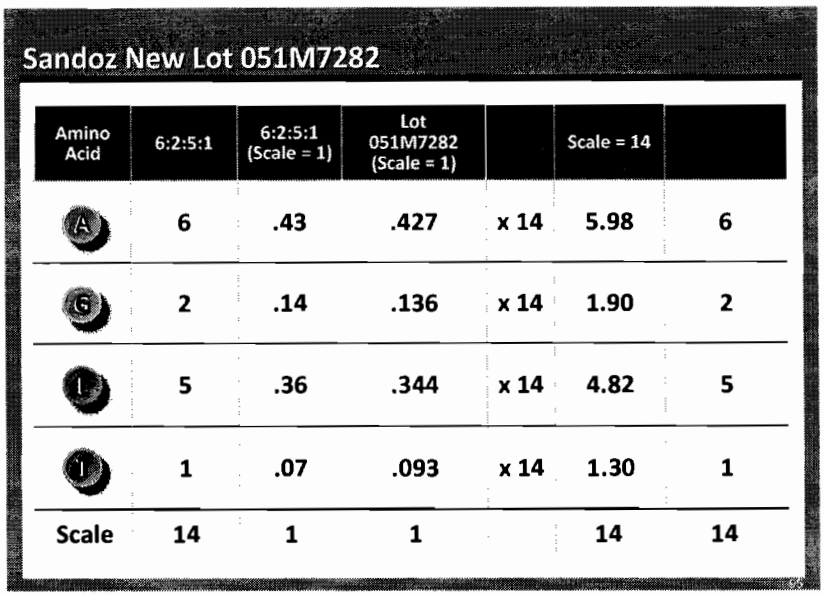
As explained above, Sandoz's ANDA provides molar fraction data for its proposed product. At trial, Dr. Gokel testified that when Sandoz's molar fraction data and "6:2:5:1" are compared on the same scale, it is plain that Sandoz's molar ratio is approximately 6:2:5:1. (Sept. Tr. (Gokel) 417:14-421:16; PTX 987 at 90.) This can be seen in Figure 20 below. Dr. Gokel's testimony, which the Court credits, was unrebutted.

Figure 20



Contrary to what Sandoz argues, the result is no different if the new data from Sandoz's [redacted] Briefing Book is considered. At trial, Dr. Gokel testified that the molar ratio in Sandoz's new lot is approximately 6:2:5:1. (Sept. Tr. (Gokel) 420:3-422:15; PTX 987 at 95.) This can be seen in Figure 21 below. This testimony, which the Court also credits, was also unrebutted.

Figure 21



Sandoz New Lot 051M7282

Amino Acid	6:2:5:1	6:2:5:1 (Scale = 1)	Lot 051M7282 (Scale = 1)		Scale = 14	
A	6	.43	.427	x 14	5.98	6
G	2	.14	.136	x 14	1.90	2
L	5	.36	.344	x 14	4.82	5
T	1	.07	.093	x 14	1.30	1
Scale	14	1	1		14	14

Sandoz's proposed product therefore literally meets the limitation of "approximately 6:2:5:1" and is copolymer-1 within the meaning of the asserted claims. Moreover, even if Sandoz's product did not literally meet the requirement of a molar ratio of "approximately 6:2:5:1," it would meet that requirement under the doctrine of equivalents.

As shown below in Figure 22, the percent total difference in amino acid ratios between Sandoz's product and exactly 6:2:5:1 is 4.4%. (Sept. Tr. (Sampson) 546:21-547:22; PTX 988 at 3.) For the reasons discussed above with respect to Mylan's product, Sandoz's proposed product is equivalent to approximately 6:2:5:1.

Figure 22

	Exactly "6:2:5:1"	Exactly "6:2:5:1" (expressed as %)	Sandoz's Molar Fraction	Expressed as %
A Alanine	.429	42.9%	.427	42.7%
G Glutamic Acid	.143	14.3%	.136	13.6%
L Lysine	.357	35.7%	.344	34.4%
T Tyrosine	.071	7.1%	.093	9.3%
Total	1	100%	1	100%
				4.4% total difference

Molar fraction data taken from PTX 913 at MMT01630061

ii. Sandoz's Product Meets the Molecular Weight Limitations

At trial, Dr. Grant explained why Sandoz's ANDA product meets the molecular weight limitations of each of the asserted claims. (Sept. Tr. (Grant) 265:2-268:3.) Sandoz did not offer any testimony to rebut Dr. Grant's conclusions.

1) Average Molecular Weight Limitations

Sandoz's method for determining the peak molecular weight values of its product involves using an appropriately calibrated suitable gel filtration column. (Sept. Tr. (Grant) 212:4-218:17; PTX 209 at SDZ00002017.) Based on Dr. Grant's testimony, which the Court credits, and the peak molecular weight data in Sandoz's ANDA, Sandoz's proposed product meets the molecular weight limitations of claim 1 of the '808 patent and claim 1 of the '589 patent, which require a copolymer-1

having an average molecular weight of "about 5 to 9 kilodaltons"; claims 1 and 6 of the '847 patent and claims 1, 8, 9, 12, 23, 30, and 31 of the '539 patent, which require a copolymer-1 having an average molecular weight of "about 4 to about 9 kilodaltons"; and claim 10 of the '539 patent, which requires a copolymer-1 with an average molecular weight of "6.25 to 8.4 kilodaltons." (Sept. Tr. (Grant) 223:20-225:2.)

2) Sandoz's Proposed Post-Trial Claim Construction

In its post-trial claim construction briefing, Sandoz asks the Court to modify the claim construction of all claims with a molecular weight limitation to exclude copolymer-1 compositions with a weight average molecular weight of 10 kilodaltons or greater. Sandoz claim construction left two questions unanswered. The first is whether the molecular weight described in the prior art '550 patent was determined by ultracentrifugation. The second is whether the results in the '550 patent referred to weight average molecular weight as opposed to z-average molecular weight. Sandoz contends that the evidence at trial established that the '550 patent was determined by ultracentrifugation and that the results in the '550 patent referred to weight average molecular weight. Based on Teva's statements to the PTO while prosecuting the patents-in-suit, Sandoz argues that the claims exclude copolymer-1

compositions that have weight average molecular weight greater than 10 kilodaltons.

There is no dispute that a person of ordinary skill in the art would look to the 1971 Teitelbaum article for information regarding the '550 patent. At trial, Dr. Scandella testified that, based on the 1971 Teitelbaum article, a person of ordinary skill in the art would understand that the '550 patent's reference to copolymer-1 with a molecular weight of 10 kilodaltons refers to molecular weight determined by ultracentrifugation. (Sept. Tr. (Scandella) at 1288:9-1290:2.) He testified further that the particular type of ultracentrifugation described in the 1971 Teitelbaum article—using sedimentation and diffusion measurements from a Spinco model E ultracentrifuge—would provide weight average molecular weight. (Sept. Tr. (Scandella) at 1290:6-10.) Because Teva allegedly disclaimed copolymer-1 compositions with weight average molecular weights in excess of 10 kilodaltons during the prosecution history of some of the patents-in-suit, Sandoz contends that all of the claims with a molecular weight limitation should exclude copolymer-1 compositions with a weight average molecular weight of 10 kilodaltons or greater. Under this claim construction, Sandoz argues, its proposed product does not infringe the patents-in-suit because its proposed

product has a weight average molecular weight greater than 10 kilodaltons.

As an initial matter, Sandoz has produced batches of copolymer-1 with a weight average molecular weight lower than 10 kilodaltons. (PTX 913-R at 53; PTX 349-R at 55.) To the extent Sandoz argues that the weight average molecular weight of its lots will be different when marketed, Sandoz offers nothing but the conclusory statements of its attorneys. The Court gives no weight to these assertions.

With respect to Dr. Scandella's trial testimony, it is undisputed that his expert reports were silent regarding the type of average molecular weight that could be obtained from a Spinco model E centrifuge. Pursuant to Rule 26(a)(2)(B)(i) of the Federal Rules of Civil Procedure, an expert's report "must contain . . . a complete statement of all opinions the witness will express and the basis and reasons for them." Fed. R. Civ. P. 26(a)(2)(B)(i). Courts have routinely excluded expert testimony in cases such as this. See, e.g., Silivanch v. Celebrity Cruises, Inc., 171 F. Supp. 2d 241, 256-57 (S.D.N.Y. 2001).

Further, the Court has no doubt that Teva was prejudiced by its inability to examine the basis of Dr. Scandella's opinion at his deposition or to elicit more specific testimony from its own experts to counter Dr. Scandella's opinion. Nonetheless, the

Court will not strike Dr. Scandella's testimony because the Court credits Dr. Grant's cross-examination testimony that ultracentrifugation can yield, "among others," number average molecular weight and z-average molecular weight. (Sept. Tr. (Grant) 1483:25-1484:21, 1488:9-11.) Mylan's expert, Dr. Ryu, also opined, during claim construction, that ultracentrifugation could provide z-average molecular weight, in addition to weight average molecular weight. (Dkt. 273 at 43.)

In regard to Dr. Scandella's claim that a person of ordinary skill in the art would understand that the '550 patent's reference to a copolymer-1 with a molecular weight of 10 kilodaltons refers to molecular weight determined by ultracentrifugation based on the 1971 Teitelbaum article (Sept. Tr. (Scandella) 1288:9-1290:2), Dr. Grant and Dr. Zeiger both testified that the reference to 10 kilodaltons in the '550 patent does not refer to copolymer-1. (Sept. Tr. (Grant) 1435:2-15, 1436:5-16; Sept. Tr. (Zeiger) 930:21-932:12.) The Court credits the testimony of Dr. Grant and Dr. Zeiger.

To the extent Sandoz rehashes its argument about Teva's statements to the PTO, in view of Sandoz's failure to offer any new evidence on this point, there is no basis for the Court to revisit its finding that Teva's prosecution history statements did not "'clearly and unambiguously express surrender of' copolymer-1 with a weight average molecular weight greater than

10 kilodaltons." (CCO at 42 (quoting Sorensen v. Int'l Trade Comm'n, 427 F.3d 1375, 1378 (Fed. Cir. 2005).) Lastly, to the extent Sandoz again points the Court to the testimony of Dr. Arnon, Dr. Sela, and Dr. Pinchasi regarding the molecular weights described in the '550 patent, as the Court previously found and as Sandoz itself admits, their testimony was not available to those of ordinary skill in the art in 1994. (CCO at 43.)

For the reasons provided above, the Court rejects Sandoz's proposed post-trial claim construction.[16]

3) Copolymer-1 Molar Fraction Limitations

Based on Dr. Grant's calculations, which the Court credits, Sandoz's proposed product meets the molecular weight limitations of claims 1, 2 and 3 of the '430 patent, which require the copolymer-1 to have over 75% of its molar fraction within the molecular weight range of 2 and 20 kDa; claims 8 and 30 of the '539 patent, which require the copolymer-1 to have less than 2.5% of its molar fraction with molecular weights above 40 kDa; claims 9, 10, and 31 of the '539 patent and claim 8 of the '098 patent, which require that the copolymer-1 have over 75% of its molar fraction between the molecular weights of 2 and 20 kDa and less than 2.5% of its molar fraction with molecular weights

[16] To the extent Sandoz attempts to poke holes in the Court's construction of "average molecular weight" as "peak molecular weight" in its proposed post-trial claim construction, Sandoz does not ask the Court to construe "average molecular weight" differently.

greater than 40 kDa; claim 1 of the '476 patent, claim 1 of the '161 patent, and claim 1 of the '098 patent, which require that the copolymer-1 have over 75% of its molar fraction between the molecular weights of 2 and 20 kDa and less than 5% of its molar fraction with molecular weights greater than 40 kDa. (Sept. Tr. (Grant) 233:23-235:2.)

4) TFA Copolymer-1 Molar Fraction Limitations

Based on Dr. Grant's calculations, which the Court credits, Sandoz's proposed product meets the molecular weight limitations of claims 1, 2, and 3 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent, which require that the TFA copolymer-1 that is made as a result of treatment of protected copolymer-1 with hydrobromic acid have over 75% of its molar fraction with molecular weights between 2 and 20 kDa. (Sept. Tr. (Grant) 239:11-240:8.)

iii. Sandoz's Process Meets the Process Limitations

With the exception of the "predetermined by test reaction" limitation, Sandoz has not disputed that the manufacturing process in its ANDA meets the process limitations of the asserted claims. Based on Dr. Gokel's testimony, which the Court credits, and the information in Sandoz's ANDA, Sandoz's process meets the "reacting protected copolymer-1 with hydrobromic acid" limitation found in claim 1 of the '808

patent, claim 1 of the '589 patent, claims 1 and 2 of the '898 patent, claims 1 and 2 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent; the "treating trifluoroacetyl copolymer-1" limitation found in claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1, 2, and 3 of the '898 patent, claims 1, 2, and 3 of the '430 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, and claims 1 and 6 of the '847 patent; the "purifying" limitation found in claim 1 of the '808 patent, claim 1 of the '589 patent, and claims 1 and 6 of the '847 patent; the "selecting a predetermined molecular weight profile" limitation of claims 1, 2, and 3 of the '898 patent; and the "copolymer-1 fraction" limitations of claim 1 of the '161 patent and claim 1 of the '476 patent. (Sept. Tr. (Gokel) 349:4-350:18, 354:16-363:13, 447:20-469:7.)

iv. Sandoz's Viscometer Process Meets the Test Reaction Limitations

Sandoz's viscometer process comprises a table of temperatures and viscosity values. (Sept. Tr. (Gokel) 430:7-434:22; PTX 914 at MMT01630951-52; PTX 928 at MMT01707035.) These data are based on test reactions, as the Court has construed that term. (Sept. Tr. (Gokel) 436:18-439:10; PTX 923 at MMT01694006, 106-24.) At trial, Dr. Laird agreed that these data were obtained from test reactions. (Sept. Tr. (Laird) 1160:4-8.)

The temperature in the viscometer model is predetermined, as there is a pre-set temperature target of 21°C. The viscometer model also has a column that identifies particular temperatures in tenths of a degree. (Sept. Tr. (Gokel) 432:11-23, 435:14-436:3; PTX 914 at MMT01630954-55; PTX 928 at MMT01707035-36.)

Time is predetermined according to the viscometer model because there is a predetermined relationship between time and viscosity. As Dr. Gokel testified, "Sandoz Momenta determined . . . a relationship between time and viscosity and then used that to determine the end point for Step 2." (Sept Tr. (Gokel) 434:9-17.) "Viscosity reflects the time point at which the reaction should be stopped because" Sandoz "calibrated their systems so that the viscosity correlates." (Sept Tr. (Gokel) 515:8-10; see also 518:14-17 ("My understanding is that the end point for the viscosity measurement corresponds to the time the reaction needs to run at a specified temperature so that the desired molecular weight structure will be obtained.").) While Sandoz may be correct that an operator could not know "with complete certainty" that after a certain time period a targeted viscosity level would be reached, if the operator "has the time correlation, then he or she could know . . . what time that correlates to in terms of the viscosity"; albeit, not with "complete certainty." (Sept Tr. (Gokel) 519:12-18.)

The Court finds that Sandoz's overall process for determining when to stop the HBr/acetic acid reaction in order to obtain a copolymer-1 having an average molecular weight of 7,300 daltons is insubstantially different from the process claimed in the patents-in-suit. See Adams Respiratory Therapeutics, Inc. v. Perrigo Co., 616 F.3d 1283, 1293 (Fed. Cir. 2010) ("The proper inquiry is whether the accused value is insubstantially different from the claimed value."); Boehringer Ingelheim Vetmedica, 320 F.3d at 1351 ("Under the doctrine of equivalents, a claim limitation not literally met may be satisfied by an element of the accused product if the differences between the two are 'insubstantial' to one of ordinary skill in the art.") (citations omitted).

Determining when to stop the reaction in order to obtain a copolymer-1 having an average molecular weight of 7,300 daltons by using test reactions to predetermine a relationship between temperature, viscosity, and time to stop the reaction is insubstantially different from using test reactions to predetermine a pre-set time to stop the reaction. In either case, a copolymer-1 having an average molecular weight of 7,300 daltons is obtained. To the extent that "[a] viscometer is different from a clock" (Sept. Tr. (Gokel) 517:1-4), Sandoz's process simply uses viscosity as a surrogate for time in order to ensure that it achieves the predetermined 7,300 daltons

average molecular weight. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 106-14; see also Sept. Tr. (Laird) 1132:10-16.) Given Sandoz's correlation of time, temperature, viscosity, and average molecular weight, its viscometer method for determining when to stop the Step 2 reaction is only insubstantially different from the claimed method of using time to determine when to stop the reaction. (Sept. Tr. (Gokel) 430:7-16, 434:9-17, 436:4-17.) Sandoz's predetermined viscosity values serve the same purpose, and achieve the same result, as the predetermined time limitation in the claims. (Sept. Tr. (Gokel) 430:17-431:15, 432:10-23, 433:24-434:17.)

Thus, under the doctrine of equivalents, Sandoz's viscometer model meets the "predetermined by test reaction" limitation in claims 1-2 of the '898 patent, claims 1-2 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent. In addition, because Sandoz's process targets a temperature of 21°C and can range only from 20.0°C to 24.0°C, the temperature limitation ("about 20-28°C") of claim 2 of the '898 patent and claim 2 of the '430 patent is met.

v. Sandoz Meets the Treatment Limitations

Based on Dr. Lisak's testimony, which the Court credits, Sandoz's proposed product meets the "method of treating multiple sclerosis" limitation found in claim 1 of the '476 patent; the "administering to a subject in need thereof" limitation found in

claim 1 of the '476 patent; the "pharmaceutically effective amount" limitation found in claim 1 of the '476 patent and claim 1 of the '161 patent; the "treatment of multiple sclerosis" limitation found in claim 1 of the '161 patent; the "suitable for treating multiple sclerosis" limitation found in claim 1 of the '539 patent; the "dose therapeutically effective to treat multiple sclerosis" found in claim 12 of the '539 patent; the "a method for treating a patient suffering from multiple sclerosis" found in claims 23, 30, and 31 of the '539 patent; the "administering to a patient in need thereof" limitation found in claims 23, 30, and 31 of the '539 patent; and the "suitable for treating multiple sclerosis" limitation found in claim 1 of the '098 patent. (Sept. Tr. (Lisak) 137:5-147:19; PTX 985 at 20.)

In addition, based on the stipulation entered into by Sandoz, Sandoz's proposed product meets the limitations of "pharmaceutical composition" and "pharmaceutically acceptable excipient" in claims 12, 23, 30, and 31 of the '539 patent. (PTX 936.)

Finally, Sandoz would induce physicians to infringe the '476 and '539 patents if its ANDA were approved. Sandoz knew of those patents before filing its ANDA, as it filed a certification with the FDA and sent a notice letter to Teva specifically referencing the patents-in-suit, including the '476 and '539 patents. (PTX 254 at SDZ00016843; JPO ¶¶ 89-90, 94-

95.) Sandoz's proposed product label would induce doctors to prescribe its ANDA product for treatment of multiple sclerosis and thereby induce infringement of claim 1 of the '476 patent and claims 23, 30, and 31 of the '539 patent. See AstraZeneca LP, 633 F.3d at 1060 ("The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of [the alleged infringer's] affirmative intent to induce infringement.") (citations omitted).

vi. Sandoz Infringes All of the Asserted Claims

In conclusion, based on the testimony of Dr. Lisak, Dr. Grant, Dr. Sampson, and Dr. Gokel, the documentary evidence they referred to during their testimony, and Sandoz's stipulations, the Court finds, by a preponderance of the evidence, that Sandoz's manufacture and sale of its proposed glatiramer acetate product would infringe each of the asserted claims.

II. INVALIDITY DEFENSES

A. Best Mode

Mylan, but not Sandoz, argues that the patents-in-suit are invalid for violating the best mode requirement of 35 U.S.C. § 112. It argues that inventor Eliezer Konfino failed to disclose: (a) the use of phenol as a bromine scavenger in the claimed synthetic process and (b) copolymer-1 with "low bromotyrosine" amounts. Mylan also argues Teva is judicially

estopped from arguing that making low bromotyrosine copolymer-1 using phenol was a routine detail that would have been obvious to a person of ordinary skill in the art in 1994.

Mylan and Teva agree that if Mylan's best mode defense were successful, it would invalidate the only claim in each of the following patents: the '808 patent, the '589 patent, the '476 patent, and the '161 patent. Mylan contends that if its best mode defense were successful, it would also invalidate all of the claims in the '898 patent and the '430 patent, because all of the claims recite the step of using HBr in the preparation of copolymer-1. Teva disagrees, arguing that if Mylan's best mode defense were successful, it would only apply to claims 1, 2, and 3 of both the '898 patent and the '430 patent. Mylan also contends that if its best mode defense were successful, it would invalidate claims 2, 3, 4, 5, and 8 of the '847 patent, because these claims recite the step of using HBr in the preparation of copolymer-1. Lastly, there is no disagreement that Mylan's best mode defense does not implicate the '539 patent or the '098 patent. Because the Court finds that Mylan has failed to establish its best mode defense by clear and convincing evidence, any disagreement between Teva and Mylan regarding the claims that are implicated by Mylan's best mode defense are irrelevant.

i. General Principles

"Section 112 of the Patent Act provides that the patent specification 'shall set forth the best mode contemplated by the inventor of carrying out his invention." Ajinomoto Co., Inc. v. Int'l Trade Comm'n, 597 F.3d 1267, 1272 (Fed. Cir. 2010) (quoting 35 U.S.C. § 112, ¶ 1). To comply with the best mode requirement, "an inventor must disclose the preferred embodiment of his invention as well as preferences that materially affect the properties of the invention." Id. at 1272-73 (citation omitted). The requirement is limited, however, "to 'the invention defined by the claims.'" Id. at 1273 (citations omitted). As a result, the "threshold step in a best mode inquiry is to define the invention by construing the claims." Id. (citation omitted). Here, that has already been done.

Since the invention has been defined, the Court turns to the two-prong inquiry for determining compliance with the best mode requirement. The Court must first "determine whether, at the time the patent application was filed, the inventor possessed a best mode of practicing the claimed invention." Ajinomoto Co., 597 F.3d at 1273 (citation omitted). This prong is subjective and "focuses on the inventor's own personal preferences as of the application's filing date." Id. (citation omitted). "[I]f the inventor has a subjective preference for one mode over all others," the Court must, second, "determine whether the inventor 'concealed' the preferred mode from the

public." Id. (citation omitted). The second prong "asks whether the inventor's disclosure is adequate to enable one of ordinary skill in the art to practice the best mode of the invention." Id. (citation omitted). "This second inquiry is objective, depending on the scope of the claimed invention and the level of skill in the relevant art." Wellman, Inc. v. Eastman Chem. Co., 642 F.3d 1355, 1360 (Fed. Cir. 2011) (citation omitted).

The Federal Circuit has repeatedly explained that "[t]he best mode requirement does not require the disclosure of 'routine details' that would be apparent to one of ordinary skill in the art practicing the invention." Liquid Dynamics Corp. v. Vaughn Co., Inc., 449 F.3d 1209, 1223 (Fed. Cir. 2006) (citation omitted). "The best mode requirement" also "does not extend to 'production details,' including commercial considerations such as equipment on hand, availability of materials, relationships with suppliers, or customer requirements." Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1331 (Fed. Cir. 2002) (citations omitted).

Mylan bears the burden of establishing a violation of the best mode requirement with clear and convincing evidence. See, e.g., id.

ii. The Use of Phenol to Pre-treat HBr/Acetic Acid

Eliezer Konfino was the only inventor named on the patents-in-suit involved in the development of the claimed synthetic process, which was used to consistently and reproducibly produce a lower molecular weight copolymer-1. (July Tr. (Pinchasi) 66:16-68:25; PTX 1 at 4:29-6:3; DTX 3567 (Konfino Dep. Tr.) at 60:8-63:9, 182:9-19, 184:6-11; DTX 4019 (Pinchasi 12/21/2009 Dep.) at 20:3-21:11.) Konfino, a bench chemist, was involved in development activity, but was not involved in manufacturing copolymer-1 on a commercial scale. (Sept. Tr. (Kent) 761:20-23, 1736:22-25; DTX 3567 (Konfino Dep.) at 25:8-23, 28:18-24; DTX 4019 (Pinchasi 12/21/2009 Dep.) at 18:6-18, 20:3-11.) He retired and ceased all involvement with copolymer-1 development in 1991. (PTX 3567 (Konfino Dep.) at 29:14-19, 34:11-14, 39:2-5, 117:2-15.)

In some experiments, Konfino used a reagent called phenol to pre-treat the HBr/acetic acid he used during the debenzylation step of the synthetic process he was developing. (DTX 3567 (Konfino Dep.) at 113:17-114:21.) During these experiments, he used phenol to reduce or "scavenge" free bromine from the HBr/acetic acid he was using as part of the debenzylation reaction. (DTX 3567 (Konfino Dep.) at 113:17-114:5.) As explained above, free bromine present in HBr/acetic acid can react with tyrosine moieties to form an impurity known as bromotyrosine. (Sept. Tr. (Gokel) 1597:24-1600:23; Sept. Tr.

(Owens) 631:21-632:6; Sept. Tr. (Kent) 771:19-23.) Reducing the presence of free bromine can, as a result, reduce amounts of bromotyrosine in copolymer-1. (Sept. Tr. (Owens) 611:15-25; Sept. Tr. (Kent) 666:16-24.) At the time Mr. Konfino was developing his synthetic process, Teva's specification for bromotyrosine content in copolymer-1 was less than 0.5%. (Sept. Tr. (Kent) 1736:15-17; PTX 52 at TEV1177354-57; DTX 1270 at 211.)

Although he used phenol in some experiments, in many others, Konfino did not use phenol to scavenge free bromine. (Sept. Tr. (Kent) 761:20-762:2, 762:23-765:25, 1737:1-4; PTX 52 at TEV1177220, TEV1177226-27, TEV1177352-33, TEV1177354.) Indeed, in experiments conducted in March 1991—the last month for which his lab notebooks report copolymer-1 experiments before his retirement—Konfino used HBr/acetic acid from the same supplier, once with phenol and once without phenol and in each case obtained copolymer-1 with bromotyrosine amounts that were within Teva's less than 0.5% specification. (Sept. Tr. (Kent) 763:25-765:25; PTX 52 at TEV1177354-57.) Konfino also obtained copolymer-1 and TFA copolymer-1 with a bromotyrosine content of less than 0.5% in a number of other experiments in which he did not use phenol. (Sept. Tr. (Kent) 761:24-762:2, 762:23-765:25, 1737:1-4; PTX 52 at TEV1177220, TEV1177226-27, TEV1177352-33, TEV1177354.) Until he left Teva in 1991, Konfino

continued to make copolymer-1 without the use of phenol. (Sept. Tr. (Kent) 762:3-11.)

Konfino never considered the use of phenol to be part of the synthetic process that he developed. (DTX 3567 (Konfino Dep.) at 113:22-117:15.) At his deposition, he testified:

> Q. So you were using phenol to clean hydrobromic acid?
>
> A. I made a lot of experiments that did not become part of the process, and that's one of them.
>
> * * *
>
> Q. Did you use bromine scavengers in your Copolymer-1 processes?
>
> A. Not in my process.
>
> Q. In your process, did you want to get rid of excess bromine?
>
> A. There was no need to.
>
> Q. Why?
>
> A. We changed solvents or we changed other conditions, so there was no need.
>
> * * *
>
> Q. What do you consider to be your process?
>
> A. The process is written down, is described in the patent.
>
> * * *
>
> Q. What differences, if any, are there between the process described in your patent and the process for making Copolymer-1?
>
> A. I believe there is no difference at all[.]

* * *

Q. I'm asking whether you learned more things about the Copolymer-1 process at Teva between your departure in 1991 and your signing of the patent application in 1994?

A. The 1994 patent described my process.

Q. And that was your process as of 1991?

A. The same.

(PTX 3567 (Konfino Dep.) at 113:23-117:15.)

The documents Mylan cited at trial do not support the conclusion that Konfino considered use of phenol to be part of "his process" or a "best" way to make copolymer-1. Mylan's best mode expert, Dr. Kent, cited and gave a considerable amount of attention to a document Konfino authored, stating that pre-treating HBr/acetic acid "with 1% phenol proved to be the most convenient" way to lower the bromotyrosine level of copolymer-1. (PTX 708-T at TEV000324554.) It does not follow, however, that Konfino viewed the use of phenol to be part of his process merely because he described it as "convenient." This is particularly true in view of his testimony, which the Court credits, that he had other means of controlling free bromine available to him. (Sept. Tr. (Kent) 765:17-23; PTX 3567 (Konfino Dep.) at 113:22-117:15.)

In regard to the description of phenol as "the most convenient" method for lowering the bromotyrosine level of

copolymer-1, Dr. Kent conceded there are any number of reasons Konfino may have described phenol this way. For example, it could have been "the most convenient" because it was "the nearest [bottle] when [Mr. Konfino] put his hand out to the lab bench." (Sept. Tr. (Kent) 771:13-16.) Another possible, reasonable inference is that phenol was convenient simply because it was the least expensive way of pre-treating HBr/acetic acid. The fact that both of these explanations are entirely plausible effectively proves that the mere characterization of phenol as "the most convenient" means of reducing free bromine does not constitute clear and convincing evidence that it was Konfino's best way of making copolymer-1.

Mylan also points to a manufacturing protocol for copolymer-1 as evidence of Konfino's best mode. (DTX 999 at TEV001222365-RC—387-RC.) Konfino's name appears nowhere in the document, however. (Sept. Tr. (Kent) 765:24-766:8; DTX 999 at TEV001222365-RC—387-RC.) As a result, it has no bearing on Konfino's subjective state of mind—the first prong on the best mode inquiry. Moreover, it is undisputed that Konfino was a bench scientist, who was in no way involved in manufacturing copolymer-1 on a commercial scale. (Sept. Tr. (Kent) 1736:22-25; DTX 3567 (Konfino Dep.) at 25:8-23, 28:18-24; DTX 4019 (Pinchasi 12/21/2009 Dep.) at 18:6-18, 20:3-11.)

Mylan also highlights a 1993 report listing several "major improvements" to the manufacturing process of copolymer-1, one of which reads: "HBr/acetic acid is treated with phenol before use, thus preventing side reaction of free residual bromine with a tyrosine moiety." (DTX 1270 at TEV000312175.) Like the previous document, however, this document does not list Konfino as an author and was written in 1993—more than a year after Konfino retired and ceased all involvement in the Copaxone® project. (Sept. Tr. (Kent) 766:18-767:5; DTX 1270.) Thus, this document cannot possibly reflect Mr. Konfino's subjective state of mind.

The Court also finds that use of phenol would have been a routine production detail at the time of the patent application. Phenol was readily available in 1994 and was "widely used in peptide chemistry." (Sept. Tr. (Kent) 771:9-16.) It was well known to persons of ordinary skill in the art at the relevant time that some amount of free bromine could be present in HBr/acetic acid depending on the quality or type of HBr/acetic acid used. (Sept. Tr. (Gokel) 1592:14-1593:4; Sept. Tr. (Kent) 754:7-10.) It was also well known at the time that phenol could be used to reduce the presence of free bromine in HBr/acetic acid. (Sept. Tr. (Gokel) 1591:11-1592:13; Sept. Tr. (Kent) 756:5-8; PTX 961 (Kota Dep.) at 130:18-131:18.) Accordingly, use of phenol to reduce the presence of free bromine in

HBr/acetic acid would have been a routine production detail at the time of the patent application. (Sept. Tr. (Gokel) 1591:11-1592:13; Sept. Tr. (Kent) 756:5-8; PTX 961 (Kota Dep.) at 130:18-131:18.)

iii. The Level of Bromotyrosine Impurity

There is also no evidence Konfino viewed any particular level of bromotyrosine copolymer-1 to be part of his invention. Mylan offered no testimony from Konfino on this question. While Konfino recorded making copolymer-1 with a bromotyrosine content that fell below Teva's specification[17] for bromotyrosine at the time—0.5% (Sept. Trial Tr. (Kent) 1736:15-17; PTX 52 at TEV1177354-357; DTX 1270 at 211)—Mylan presented no evidence that Konfino viewed copolymer-1 with a low bromotyrosine content as part of his best mode. Thus, there is no support, much less clear and convincing evidence, from which the Court can find that Konfino subjectively viewed "low bromotyrosine" levels as a requirement for the copolymer-1 he was making.

In addition, the evidence indicates that reducing amounts of bromotyrosine was a routine production detail. Bromotyrosine is an impurity that may be created during the synthetic process used to make copolymer-1. (Sept. Tr. (Gokel) 1603:13-1604:2;

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[17] (See DTX-1271 at TEV000324714 (June 1990 memorandum authored by Konfino and D. Salner, describing making TFA-copolymer-1 with a bromotyrosine content of less than 0.1%); see also PTX-708-T at TEV000324554 (Konfino August 1991 memorandum, reporting he made copolymer-1 with a bromotyrosine content that fell below "the specifications").)

Sept. Tr. (Owens) 615:8-16, 634:22-635:8; PTX 349 at SDZ00017963.) All of the experts and parties agree that bromotyrosine is an impurity in the context of copolymer-1. (Sept. Tr. (Gokel) 1597:24-1600:23, 1603:13-1604:2, 1606:17-1607:18; Sept. Tr. (Kent) 771:19-772:10; Sept. Tr. (Owens) 632:4-633:12; PTX 963 (B. Rao 6/30/2010 Dep.) at 240:7-9; PTX 320 at MYL0000685-86; PTX 349 at SDZ0017963; PTX 78 at TEV000000196.) In fact, bromotyrosine is one of a long list of impurities that are controlled in copolymer-1. (Sept. Tr. (Gokel) 1597:24-1600:23; PTX 78 at TEV000000196-97; PTX 320 at MYL0000685-86.)

There also is no disagreement that it is standard practice within the pharmaceutical industry to reduce impurities in a product. Mylan's expert, Dr. Kent, and fact witness, Dr. Owens, both agreed that reducing impurities like bromotyrosine is standard practice in the pharmaceutical industry. (Sept. Tr. (Kent) 773:3-14; Sept. Tr. (Owens) 633:7-12.) This is consistent with the testimony of Teva's expert, Dr. Gokel, who explained that it would be a "routine matter for anyone trying to make a product at any scale, laboratory, or manufacturing, to try to reduce impurities as much as possible." (Sept. Tr. (Gokel) 1597:18-23; 1607:19-1608:2.)

Mylan cites to U.S. Patent No. 7,495,072 ("'072 patent"), issued in 2009 to inventor Ben Zion Dolitzky and assigned to

Teva, as evidence that using phenol to reduce bromotyrosine was not routine. (DTX 1925.) The fact that Teva obtained a patent for a process involving the use of phenol to scavenge free bromine in copolymer-1, Mylan argues, judicially estops Teva from arguing that the use of phenol to scavenge free bromine in copolymer-1 was a routine production detail that would have been obvious to a person of ordinary skill in the art with respect to the patents-in-suit. Mylan is wrong.

The '072 patent is directed to a solution for a manufacturing problem that arose many years after Konfino left Teva in 1991. (Sept. Tr. (Gokel) 1595:9-15, 1596:23-1597:14.) Specifically, the '072 patent discusses means of using bromine scavengers, including phenol, to eliminate the presence of bromotyrosine and to remove a red color that had been detected in syringes of aqueous solutions of Copaxone®. (Sept. Tr. (Gokel) 1593:8-1594:2, 1594:18-1595:20; DTX 1925 at 10:5-10, 12:41-13:67.) The patent explicitly states that older methods of Copaxone® production—which are not claimed in the '072 patent—used phenol as a bromine scavenger to produce copolymer-1 with reduced levels of bromotyrosine. (Sept. Tr. (Gokel) 1631:7-1633:17; DTX 1925 12:41-13:67.) Thus, the '072 patent is directed to a "new" and improved process that produces Copaxone® with no detectable amounts of bromotyrosine and no red color. (Sept. Tr. (Gokel) 1631:7-1632:21; DTX 1925 at 12:41-13:67.)

At trial, Mylan's expert, Dr. Kent, admitted that the bromotyrosine specification in the '072 patent (0.2% or none detectible) is lower than the specification in place when Konfino was working at Teva (0.5%), providing further evidence that the '072 patent was directed to a different problem and has no bearing on Konfino's experiments. (Sept. Tr. (Kent) 1735:1-1736:17.) Since the '072 patent is directed to a different problem, namely the elimination of bromotyrosine and the removal of an unwanted color from an aqueous form of Copaxone®, rather than merely reducing bromotyrosine, it does not establish that using phenol to reduce amounts of free bromine was not routine as of 1994.

iv. The Patents' Lack of Disclosure Regarding Phenol Is Not a Best Mode Violation

There is no dispute that the patents-in-suit do not disclose the use of phenol to pretreat HBr/acetic acid used in the debenzylation step of the synthetic process claimed in the patents-in-suit. Defendants have nevertheless failed to prove, by clear and convincing evidence, that this amounts to a best mode violation.

Konfino testified unequivocally that the use of phenol was not part of "his process" at the time he retired from Teva in 1991 and that the process he used is the one described in the patents-in-suit. (PTX 3567 (Konfino Dep.) at 113:22-117:15.)

This unambiguous testimony, which the Court credits, is strong evidence that Konfino did not subjectively consider the use of phenol part of his best mode for making copolymer-1. See Minco, Inc. v. Combustion Eng'g, Inc., 95 F.3d 1109, 1116 (Fed. Cir. 1996) (affirming a finding of no best mode violation where the trial court relied on the inventor's testimony that the undisclosed information was a production decision and that he did not consider it to be a superior method of operation); see also Shearing v. Iolab Corp., 975 F.2d 1541, 1546 (Fed. Cir. 1992) (affirming a jury verdict of no best mode violation where the inventor testified that, although he sometimes used the alleged best mode to align the lens, he had no preference and embraced any method that did so).

The documents relied upon by Mylan at trial reinforce this conclusion. Konfino's lab notebooks indicate he only used phenol in some of his experiments synthesizing copolymer-1, made copolymer-1 without using phenol a number of times, and was still making copolymer-1 without using phenol at the time he left Teva in 1991. The other documents relied upon by Mylan are either irrelevant to Konfino's subjective state of mind or do not support a conclusion that Konfino viewed the use of phenol to be part of a best way of making copolymer-1. Mylan has thus failed to show that Konfino subjectively viewed the use of

phenol to be part of a best mode. See Minco, Inc., 95 F.3d at 1116; see also Shearing, 975 F.2d at 1546.

Unable to establish the requisite first prong, Mylan's best mode defense fails. See Young Dental Mfg. Co. v. Q3 Special Prods., Inc., 112 F.3d 1137, 1144 (Fed. Cir. 1997) (explaining that "one proceeds to the second inquiry" "[i]f the inventor had a best mode of practicing the claimed invention"). Even assuming examination of the second prong were necessary, which it is not, Mylan fails to demonstrate that the disclosure of phenol would have been required in order to satisfy the best mode requirement. Since phenol was both widely used in peptide chemistry at the time of the patent application and was a known scavenger of free bromine, its use was both a "true" and "routine" manufacturing detail that did not need to be disclosed in the patents to comply with the best mode requirement. See, e.g., Young Dental Mfg. Co., 112 F.3d at 1144.

v. The Patents' Lack of Disclosure Regarding a "Low Bromotyrosine" Content of Copolymer-1 Is Not a Best Mode Violation

Mylan's other best mode argument—that the patents should have disclosed a "low bromotyrosine" content for copolymer-1—also fails. Mylan offered no direct evidence from Konfino supportive of this claim. Indeed, Konfino was never questioned about the bromotyrosine content of copolymer-1 during his deposition. (PTX 3567 (Konfino Dep.).) The only evidence

offered at trial from which any inference concerning Konfino's subjective beliefs could be drawn suggests that bromotyrosine was not important to him. In 1991, Mr. Konfino reported that bromotyrosine was "non-toxic" and Dr. Kent acknowledged this fact at trial. (Sept. Tr. (Kent) 668:22-669:10; PTX 708 at TEV000324554.) Mylan has thus failed to satisfy the subjective prong of the best mode defense. See Minco, Inc., 95 F.3d at 1116; Shearing, 975 F.2d at 1546.

Furthermore, producing copolymer-1 with lower bromotyrosine levels also amounts to a "true" and "routine" manufacturing detail that need not be disclosed to comply with the best mode requirement. The evidence demonstrates that bromotyrosine is an impurity in copolymer-1 and it is standard practice in the pharmaceutical industry to reduce the amounts of impurities in a pharmaceutical product like copolymer-1. (Sept. Tr. (Kent) 773:3-14; Sept. Tr. (Owens) 633:7-12; Sept. Tr. (Gokel) 1597:18-23.) In addition, as explained above, reducing bromotyrosine would have been "routine" given that phenol was a widely used reagent at the time and known to be capable of reducing free bromine in HBr/acetic acid. (Sept. Tr. (Gokel) 1591:11-1592:13; PTX 961 (Kota Dep. Tr.) at 130:18-131:18.) Accordingly, reducing amounts of a bromotyrosine impurity would have been both a "true" and "routine" production detail at the time of the patent application and did not need to be disclosed to comply

with the best mode requirement. See, e.g, Young Dental Mfg. Co., 112 F.3d at 1144.

B. Inequitable Conduct

Defendants allege Dr. Pinchasi committed inequitable conduct by: (1) intentionally deceiving the PTO to believe there was a clear relationship between molecular weight and toxicity; (2) not informing the PTO of her alleged reservations about the RBL test; and (3) intentionally deceiving the PTO by describing a relationship between the RBL test and human side effects that had not been observed. For the reasons set forth below, Defendants fail to prove inequitable conduct by clear and convincing evidence.

i. General Principles

"To prevail on the defense of inequitable conduct, the accused infringer must prove that the applicant misrepresented or omitted material information with the specific intent to deceive the PTO." Therasense, Inc. v. Becton, Dickinson & Co., 649 F.3d 1276, 1287 (Fed. Cir. 2011) (en banc) (citation omitted). Defendants "must prove both elements—intent and materiality—by clear and convincing evidence." Id. (citation omitted). If Defendants prove both elements, the Court "must weigh the equities to determine whether the applicant's conduct before the PTO warrants rendering the entire patent unenforceable." Id. (citation omitted).

In Therasense, Inc., the Federal Circuit explained that "[i]ntent and materiality are separate requirements" and that courts "should not use a 'sliding scale,' where a weak showing of intent may be found sufficient based on a strong showing of materiality, and vice versa." Id. at 1290 (citation omitted). With respect to the first requirement—specific intent to deceive the PTO—in cases "'involving nondisclosure of information, clear and convincing evidence must show that the applicant made a deliberate decision to withhold a known material reference.'" Id. (citation omitted). "In other words," the Federal Circuit explained in Therasense, Inc., "the accused infringer must prove by clear and convincing evidence that the applicant knew of the reference, knew that it was material, and made a deliberate decision to withhold it." Id. In view of the fact that "direct evidence of deceptive intent is rare," the Federal Circuit added, "a district court may infer intent from indirect and circumstantial evidence." Id. (citation omitted). "[T]o meet the clear and convincing evidence standard," however, "the specific intent to deceive must be 'the single most reasonable inference able to be drawn from the evidence.'" Id. (citation omitted).

With respect to the second prong—materiality—in Therasense, Inc., the Federal Circuit explained that "the materiality required to establish inequitable conduct is but-for

materiality." Id. at 1291. "[I]n assessing the materiality of a withheld reference, the court must determine whether the PTO would have allowed the claim if it had been aware of the undisclosed reference." Id. In making this determination, courts "should apply the preponderance of the evidence standard and give claims their broadest reasonable construction." Id. at 1291-92 (citation omitted). While but-for materiality must generally be proven "to satisfy the materiality prong of inequitable conduct," the Federal Circuit "recognizes an exception in cases of affirmative egregious misconduct." Id. at 1291-92. "When the patentee has engaged in affirmative acts of egregious misconduct, such as the filing of an unmistakably false affidavit, the misconduct is material." Id. at 1292 (citations omitted). "Because neither mere nondisclosure of prior art references to the PTO nor failure to mention prior art references in an affidavit constitutes affirmative egregious misconduct, claims of inequitable conduct that are based on such omissions require proof of but-for materiality." Id. at 1292-93.

ii. The Decision to File the '037 Application

The '037 patent application, which all of the patents-in-suit claim priority to (JPO ¶ 79), was drafted in one night by Dr. Pinchasi, Dr. Ilan Schwartz, Dr. Ralph Haber, and Neil Nachshen. (DTX 1393 (Nachshen Dep. 10/13/10) at 21:7-11, 22:3-

15; DTX 1389 (Haber Dep. 10/07/10) at 46:1-20; July Tr. (Pinchasi) 116:24-117:11, 203:18-22.) On May 24, 1994, Nachshen, an employee in Teva's Patent Department, asked Dr. Pinchasi whether she was aware of any publications related to copolymer-1 that were due for publication. (DTX 1393 (Nachshen Dep. 10/13/10) at 11:22-12:4, 20:22-21:7.) Dr. Pinchasi informed Nachshen that she believed a paper was going to be published that same day in the Proceedings of the National Academy of Sciences ("PNAS"). (DTX 1393 (Nachshen Dep. 10/13/10) at 20:22-21:7.)

Nachshen confirmed the publication date with PNAS at approximately 4:00 p.m., Israeli time, on May 24, 1994. (DTX 1393 (Nachshen Dep. 10/13/10) at 21:16-23:13.) At that point, Nachshen told others at Teva that "if they wanted to have a patent position, today was the day they needed to file." (DTX 1393 (Nachshen Dep. 10/13/10) at 19:18-20:14, 28:9-14; DTX 1394 (Nachshen Dep. 10/13/10) at 28:3-6.) At his deposition, Nachshen recalled that Dr. Pinchasi approved filing a patent application. (DTX 1393 (Nachshen Dep. 10/13/10) at 20:15-17.) Although Dr. Pinchasi had never been involved in preparing a patent application before that day (July Tr. (Pinchasi) at 122:24-123:4), given that she was the project manager for the copolymer-1 project at Teva at that time, there is nothing remarkable about the fact that she was involved in the decision

to file a patent application on this occasion. (July Tr. (Pinchasi) 11:6-12).

The '037 application was faxed to the United States for filing with the PTO sometime before 4:00 a.m., Israeli time, on May 25, 1994. (DTX 1393 (Nachshen Dep. 10/13/10) at 22:3-13, 41:15-19; 62:11-22.) Nachshen drafted the '037 application with the assistance of Dr. Pinchasi, Dr. Haber, and Dr. Schwartz, in consultation with attorneys from the New York City and Washington, D.C. offices of Kenyon & Kenyon LLP. (DTX 1393 (Nachshen Dep. 10/13/10) at 19:6-13, 20:15-17, 21:7-11, 40:25-41:3, 41:8-12; July Tr. (Pinchasi) 116:9-20, 117:6-11.) Nachshen, who, at the time, had little to no knowledge regarding the subject matter of the patent application, relied upon the others working with him, including Dr. Pinchasi, to provide technical assistance on the subject matter described and claimed in the patent application. (DTX 1393 (Nachshen 10/13/2010 Dep.) at 22:16-23:6, 23:20-24:21, 26:10-23, 26:24-27:19, 28:25-293, 29:7-16, 32:11-32:24, 33:4-6, 34:24-35:19.)

Dr. Pinchasi provided biological data, specifically in vivo and in vitro RBL degranulation toxicity data, for potential use in the application. (July Tr. (Pinchasi) at 117:6-14, 122:4-7.) Although Dr. Pinchasi provided toxicity data for potential use in the application, she testified at trial that she was "not involved" in the selection of any data that actually went into

the '037 application. (July Tr. (Pinchasi) at 146:4-5.) Whether she selected any of the data is largely irrelevant, however, because before the '037 application was filed, Dr. Pinchasi reviewed it and confirmed that it accurately reflected what she knew about the biological toxicity profile of copolymer-1, as measured by the in vivo and in vitro RBL toxicity tests. (July Tr. (Pinchasi) at 129:1-17.)

iii. The Relevant Contents of the '037 Application

The '037 application contains the same Example 2 that appears in the patents-in-suit described above. (Compare PTX 1 at 3:20-4:27 with PTX 10 at TEV003009932-35.) As explained above, Example 2 is entitled "Toxicity Analysis." The '037 application stated, first, in relevant part with respect to the in vivo test, that "[t]hree batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 kDa (less than 2.5% copolymer-1 species over 40kDa) and 22 kDa (more than 5% copolymer-1 species over 40kDa) were subjected to" this test. (PTX 10 at TEV003009932.) Because none of the mice in the 7.3 and 8.4 kDa batches died, these batches "were both designated 'non-toxic,' whereas in the batch with the average molecular weight of 22kDa, 3 out of 5 mice had died . . . and it was consequently designated 'toxic.'" (PTX 10 at TEV003009933.)

Second, with respect to the in vitro RBL test, the '037 application included a page explaining that the RBL test "was

developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system." (PTX 10 at TEV003009934.) In support of this representation, the '037 application cited two publications: "E.L. Barsumian, C. Isersky, M.G. Petrino and R.P. Siraganian, Eur. J. Immunol. 11, 317 (1981)" and "R.P. Siraganian, Trends in Pharmacological Sciences, October 1983, 432." (PTX 10 at TEV003009934.) The '037 application, like the specification of the patents-in-suit, also stated that "[t]he RBL degranulation test is . . . used in order to screen out those batches of [copolymer-1] which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects." (PTX 10 at TEV003009934; PTX 1 at 3:63-67.)

In regard to the RBL test results, the '037 application explains that "[f]our batches of copolymer-1, with average molecular weight between 8,250-14,500 were analyzed for both the % of species with molecular weight over 40 kDa and for degranulation of RBL's." (PTX 10 at TEV003009935.) The results were summarized in the following table:

Average M.W.	% of species with M.W. over 40 kDa	% Serotonin Release
6,250	<2.5	12.4
7,300	<2.5	21.0
13,000	>5	66.9
14,500	>5	67.8

(PTX 10 at TEV003009935.) The '037 application concluded that "when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa." (PTX 10 at TEV003009935.)

Lastly, the '037 application had different claims from the ones that ultimately issued in later applications that resulted in the patents-in-suit. In particular, the '037 application had no claims directed to copolymer-1 with an average molecular weight in any particular range. (July Tr. (Pinchasi) at 131:11-23; PTX 10 at TEV003009937.) The claims in the '037 application were directed to the percent of species above 40 kilodaltons or the percent of species between 2 and 20 kilodaltons. (PTX 10 at TEV003009937.)

iv. The April 1994 Data Table

Defendants contend the patents-in-suit were obtained based on the assertion, stemming from Example 2, that copolymer-1 with an average molecular weight below 10 kDa exhibits unexpectedly less toxicity than copolymer-1 in the prior art, including the prior art range of 10 kDa and higher disclosed in the '550 patent. (See PTX 13 at TEV000304142-43 ('808 patent prosecution history, 2/14/97 Office Action citing the '550 patent and acknowledging that the "polymers of the prior art are disclosed to have a specified minimum molecular weight of 10,000" daltons), TEV000304151 ('808 patent prosecution history, 7/14/97

Amendment acknowledging that "the cited reference ['550 patent] teaches a minimum molecular weight of 10 kilodaltons"); see also PTX 14 at TEV00309204; PTX 17 at TEV000304385; PTX 18 at TEV000310451; PTX 19 at TEV000304498; PTX 21.)

Example 2, however, included only a small fraction of Teva's toxicity data. Defendants argue that by providing the PTO with only a sliver of Teva's toxicity data, Dr. Pinchasi intentionally withheld toxicity data from the PTO that undermined the black and white relationship between molecular weight and toxicity described in the '037 application. In support of this argument, Defendants rely heavily on a toxicity data table that Dr. Pinchasi reviewed about a month before the '037 application was filed ("April 1994 Data Table"). (July Tr. (Pinchasi) 123:5-9, 123:17-124:1, 150:2-9 (acknowledging she handwrote the date, April 11, 1994, on the April 1994 Data Table); DTX 999A at TEV001222355-RC; DTX 3149-T (translated version of DTX 999A (at TEV001222355-RC).) Two copies of the April 1994 Data Table were located in Nachshen's patent prosecution files for the patents-in-suit. (DTX 999A at TEV001222355-RC, TEV001222417-RC.)

The April 1994 Data Table contains information for thirteen copolymer-1 batches. (DTX 999A at TEV001222355-RC.) The information includes the average molecular weight for each batch, as well as in vivo and in vitro RBL toxicity data for

each batch. (DTX 999A at TEV001222355-RC.) The April 1994 Data Table is shown in Figure 23 below:

Figure 23

[illegible]	[illegible]	[illegible] SHLECT B	[illegible] RBL	SAFETY IN VIVO	SKIN IRRITATION
123-094	6250	41.0	12.4	0/5	N.T
123-090	7300	43.3	21	0/5	14±2.5 (14±1.2)
123-095	8400	40.8	25.6	0/5	11.6±1.5(12±1.2)
04792	9250	43.9	31.3	0/5	13.8±1(14±1.2)
04892	9600	44.2	50.5 (?)	0/5	N.T.
04992	9900	43.9	51.5 (?)	0/5	13.8±1.2(14±1.2)
123-096	10,950	44.2	39.8	0/5	N.T.
04592	11,050	45.3	41.3	0/5	16±1.2(16.4±0.8)
04692	11,900	45.8	41.7	0/5	N.T.
04492	12,150	47	47.6	0/5	18±1.8(17.2±1)
196/2	13,000	[illegible]	66.9	0/5	16.2±1(17±1.55)
196/1	14,500	[illegible]	67.8	0/5	15.6±0.8(14.8±1)
186/1	22,000	[illegible]	60.3	3/5	N.T.

(DTX 999A at TEV001222355-RC.)

The three in vivo mouse assays and four in vitro RBL assays disclosed in Example 2 of the '037 application (and the specification of the patents-in-suit) match data from the April 1994 Data Table exactly. (Compare DTX 999A at TEV1222355-RC with PTX 1 at 3:20-4:27; see also DTX 1391 (Hausdorff Dep. 9/14/10) at 177:12-179:1; DTX 1236 (Declaration of Teva 30(b)(6) witness Sharon Hausdorff, stating that the April 1994 Data Table (TEV001222417) "contain[s] data which appear in the patents").) The chart below, which was created by Mylan, shows, in the shaded boxes, the only data from the April 1994 Data Table that was provided to the PTO:

Batch Number	Average Molecular Weight	Peak III Select	% Release RBL	Safety In vivo	Skin Irritation
123-094	6250	41.0	12.4	0/5	N.T.
123-090	7300	43.3	21	0/5	14 ± 2.5 (14±1.2]
123-095	8400	40.8	25.6	0/5	11.6 ± 1.5(12±1.2]
04792	9250	43.9	31.3	0/5	13.8 ± 1(14±1.2]
04892	9600	44.2	50.5 (?)	0/5	N.T.
04992	9900	43.9	51.5 (?)	0/5	13.8 ± 1.2(14±1.2]
123-096	10,950	44.2	39.8	0/5	N.T.
04592	11,050	45.3	41.3	0/5	16 ± 1.2(16.4 ± 0.8)
04692	11,900	45.8	41.7	0/5	N.T.
04492	12,150	47	47.6	0/5	18 ± 1.8(17.2 ± 1)
196/2	13,000	45.7	66.9	0/5	16.2 ± 1(17 ± 1.55)
196/1	14,500	44.66	67.8	0/5	15.6 ± 0.8(14.8±1)
186/1	22,000	47.27	60.3	3/5	N.T.

At trial, Dr. Pinchasi testified that she was not sure whether she personally created the April 1994 Data Table, but that she believes it was one of many summary tables created during the development of copolymer-1 to compare chemical and biological data related to different batches. (July Tr. (Pinchasi) 124:13-125:1.) She also testified that she may have considered the information in the April 1994 Data Table when she was gathering biological data for the '037 application, but that she had no specific recollection of doing so. (July Tr. (Pinchasi) 125:2-7.) Without any evidence to the contrary and in view of Dr. Pinchasi's demeanor and the fact that she was

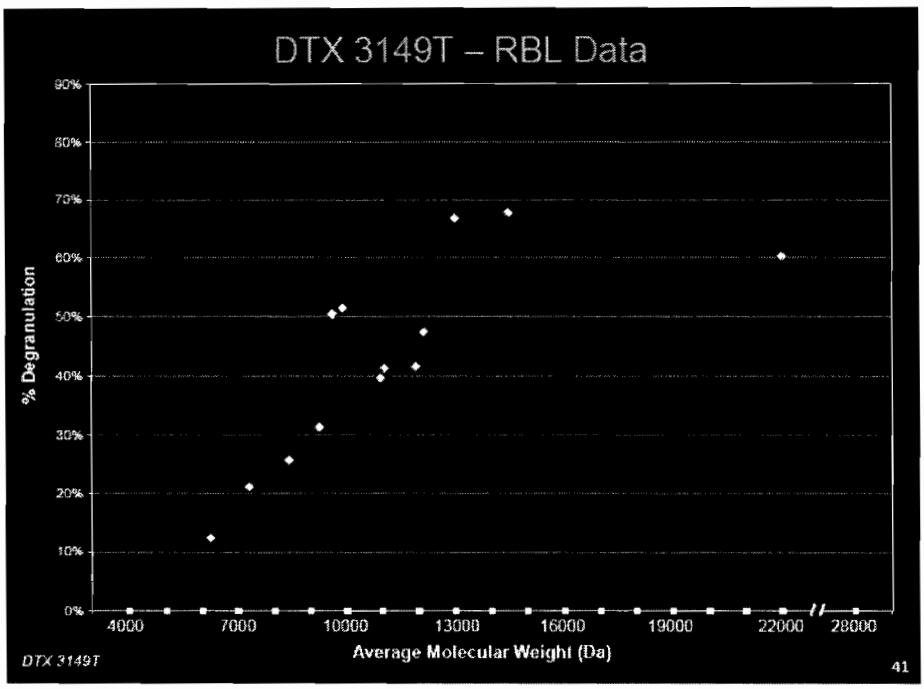
testifying about a patent application that was filed over seventeen years ago, the Court has no basis for not crediting her testimony regarding her recollection of the April 1994 Data Table.

v. The April 1994 Data Table Is Consistent with Example 2

Moreover, contrary to Defendants' argument, the April 1994 Data Table was not inconsistent with the data in Example 2. Example 2 discloses a correlation or trend between molecular weight and toxicity: "when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa." (PTX 1 at 4:25-27; (PTX 10 at TEV003009935; July Tr. (Baird) at 600:3-6 (explaining the converse: "if the percent of high molecular weight species is high, greater than 5 percent, then the percent of release of serotonin, which is indicative of toxicity, is high").)

At trial, Dr. Baird, a recognized expert in the RBL degranulation test, whose testimony the Court credits, took the molecular weight and RBL degranulation data contained in the April 1994 Data Table and plotted them on the graph shown in Figure 24 below. She found that the data in the April 1994 Data Table show the same trend as seen in Example 2—increasing RBL degranulation with increasing molecular weight. (July Tr. (Baird) 603:7-604:5; PTX 887 at 40.)

Figure 24



Dr. Pinchasi also testified that the data in the April 1994 Data Table "very clearly" shows a correlation: "the higher the average molecular weight, the higher percentage of RBL release." (July Tr. (Pinchasi) 125:14-19.) In fact, even Defendants' expert, Dr. Kimber, conceded (with caveats) that the RBL data in the April 1994 Data Table, like all of the other data he has seen in this case, reflect a trend of increasing RBL degranulation with increasing average molecular weight. (July Tr. (Kimber) 446:22-447:15 ("[W]hat I've seen . . . is a correlation, a dot plot, . . . between average molecular weight and degree of activity in the RBL assay, with mean values. [I]f

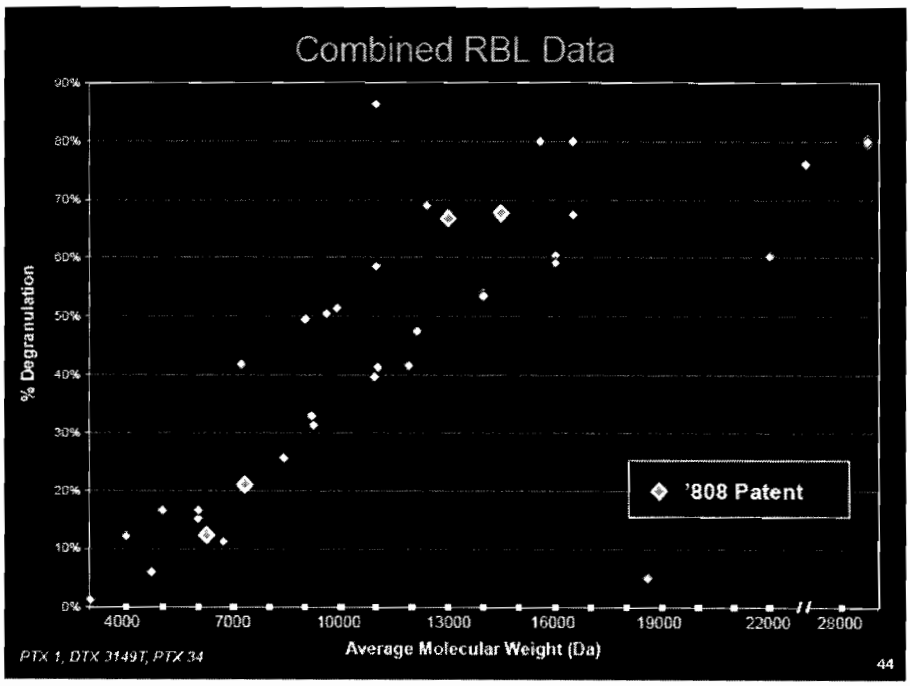
you do that, there certainly appears to be a higher likelihood of high levels of degranulation with higher molecular weight compared with lower molecular weight."), 465:2-3, 466:10-19.)

vi. Example 2 Is Representative of Teva's Toxicity Data as a Whole

The Weizmann and Teva scientists performed hundreds of RBL degranulation tests on batches of copolymer-1 while developing the product. (July Tr. (Arnon) 332:8-334:2; PTX 34T; PTX 36T; PTX 53T; PTX 54.) The April 1994 Data Table contains only a small fraction of those test results. The evidence at trial showed that the data in Example 2 was a fair and accurate representation of the data generated by the Teva and Weizmann scientists as a whole. (July Tr. (Arnon) 332:8-334:2; July Tr. (Pinchasi) 30:14-20, 80:13-81:13; July Tr. (Baird) 601:13-24; PTX 887 at 44.)

To demonstrate this, Dr. Baird took molecular weight and RBL degranulation data for several different batches of copolymer-1 found in Teva's internal files that had been cited by Defendants' experts and added them to the graph she created for the data in the April 1994 Data Table. The results are shown below in Figure 25:

Figure 25



The Court agrees with Dr. Baird that the data, again, showed "a very clear trend" consistent with the trend shown in Example 2. (July Tr. (Baird) 601:13-24, 605:14-18; PTX 887 at 44.)

Teva and Weizmann's in vivo toxicity data is also consistent with Example 2, and Defendants provided no expert testimony to the contrary. Although the only copolymer-1 batch in the April 1994 Data Table that failed the in vivo toxicity test had a molecular weight of 22,000 daltons, Teva and Weizmann had internal data on many batches of copolymer-1 with molecular weights between 10,000 and 22,000 daltons that had failed that test. (July Tr. (Pinchasi) 126:4-8; PTX 34-T.)

Further, Defendants did not provide their expert Dr. Kimber with all of the RBL degranulation and in vivo mouse test data that had been produced by Teva in this case. (July Tr. (Kimber) 426:21-429:16, 438:13-439:1.) Accordingly, Dr. Kimber did not know whether the data in the April 1994 Data Table reflected the universe of toxicity data that had been generated by Weizmann and Teva, and could not provide an opinion on whether Teva's data as a whole was consistent with Example 2. (July Tr. (Kimber) 438:18-439:5.)

vii. The Patent Office Was Aware That Not All High Molecular Weight Copolymer-1 Batches Were Toxic

Contrary to Defendants' argument, Example 2 does not represent that all batches of copolymer-1 above 10 kDa were toxic. First, Example 2 does not explicitly state that all batches above 10 kDa were toxic and that all batches below were not. (PTX 1 at 3:20-4:27; PTX 10 at TEV003009932-35.) Second, to the extent Defendants attempt to read such a statement into Example 2 by emphasizing that Dr. Pinchasi did not disclose that Teva possessed toxicity data for additional batches of copolymer-1, Example 2 explicitly rejects such an interpretation: "when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity is low, and vice versa." (PTX 1 at 4:25-27; PTX 10 at TEV003009935.) As Dr. Baird explained, this statement indicates

a trend in the data, not any hard cut-off. (July Tr. (Baird) 600:7-14.)

Moreover, Dr. Bornstein's 1987 article, cited in the specification of the patents-in-suit (and in the '037 application), explicitly states that some batches of copolymer-1 with a molecular weight between 14,000 and 23,000 daltons showed less than 30% degranulation in the RBL assay—i.e., they were "non-toxic."[18] (PTX 1 at 1:25-28; PTX 11 at TEV000309437; PTX 31 at 408-09.) The file histories indicate that the PTO examiner reviewed and considered the Bornstein article during the prosecution of the patents-in-suit. (PTX 18 (File History of U.S. Patent No. 6,362,161 ("'161 File History")) at TEV000310385-89; PTX 14 (File History of U.S. Patent No. 5,981,589 ("'589 File History")) at TEV000309018-21; PTX 21 (File History of U.S. Patent No. 7,199,098 ("'098 File History")) at TEV000308838-842.)

In view of the specification and the prosecution, the Court finds that the PTO was aware that not all higher molecular weight copolymer-1 batches were toxic.

viii. Dr. Pinchasi's Views on the RBL Degranulation Test

[18] As explained earlier, Weizmann scientists adopted the RBL degranulation test to test toxicity, and designated as "toxic" and discarded batches that released 30% or more serotonin upon exposure to copolymer-1. (July Tr. (Arnon) 327:8-330:18; PTX 31 at 409.)

In a December 1989 memo, Dr. Pinchasi set forth her rationale for adopting a second screening test, the in vivo toxicity test, in addition to the RBL degranulation test. (DTX 3385.) Defendants point to this memo as evidence that Dr. Pinchasi knew the RBL test was unreliable, not reproducible, and could not be used as a toxicity screen.

As an initial matter, Defendants are correct that the December 1989 memo criticized the RBL test. The memo notes "that the RBL system is inconsistent in its reproducibility, and both inter-assay and intra-assay large variations were observed." (DTX 3385 at TEV001222393.) It also notes that "many times we see that a whole experiment is skewed, either upward or downward, without our controls detecting it" and concludes that "we thus feel that this assay can not be properly controlled." (DTX 3385 at TEV001222394.) Although the RBL test was "very convenient for the screening of many batches at a time," because of its shortcomings, "the RBL system is not sufficiently reproducible so as to afford the ultimate analysis for the safety of our batches." (DTX 3385 at TEV001222392.) Because the in vivo test was "dependable" and "found to be almost totally reproducible[,]" (DTX 3385 at TEV001222393), it

was adopted to complement the RBL test. (July Tr. (Pinchasi) at 29:1-19.)[19]

At trial, Dr. Pinchasi testified that the RBL test was "very good" for screening "toxic batches during process development and preparation." (July Tr. (Pinchasi) at 103:10-13.) "[B]ecause of its relatively high variation," Dr. Pinchasi added, Teva decided the RBL test was not "sufficiently reproducible to [serve] as a sole, as a single, an only methodology to be used to decide whether a batch is safe for clinical use or not." (July Tr. (Pinchasi) at 103:13-16.) Accordingly, Dr. Pinchasi explained, Teva concluded it "needed another complementary test." (July Tr. (Pinchasi) at 103:16-17.)

Despite the reservations discussed above, the evidence shows Teva continued to use the RBL test after the December 1989 memo, in conjunction with the in vivo test, until at least December 1992. (PTX 723; PTX 62.) Thus, the Court finds, even though Dr. Pinchasi (and Teva) believed the RBL test had reliability and reproducibility issues, that did not stop them from continuing to use it as a toxicity screen.

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[19] Defendants also emphasize the fact that the memo criticized "upper permitted level of RBL degranulation (40%)" inherited from the Weizmann Institute as "arbitrar[y.]" (DTX 999A at TEV001222392-RC.) They also highlight that the memo suggested adopting a 50% cutoff, which the memo deemed "non-arbitrary and meaningful." (DTX 999A at TEV001222393-RC.)

ix. Professor Arnon Believed the RBL Degranulation Test To Be a Reliable Screening Test for Toxicity

The evidence at trial also established that Dr. Pinchasi did not select the RBL degranulation test. One of the other inventors of the patents-in-suit, Professor Arnon, selected the test after concluding that it was an appropriate assay for screening batches of copolymer-1 for toxicity. Even after Teva took on development of copolymer-1, the RBL testing continued to be performed at the Weizmann Institute. (July Tr. (Pinchasi) 30:7-20; July Tr. (Arnon) 332:8-25; July Tr. (Baird) 608:25-609:10.)

Before adopting the RBL degranulation test, Professor Arnon personally read all of the literature about the test, including articles by Dr. Reuben Siraganian's group at NIH, who were the leading experts on the test. (July Tr. (Arnon) 321:19-25.) One of the literature references Professor Arnon considered was the 1981 Barsumian article referenced above. Dr. Barsumian was a member of the Siraganian group at NIH. The Barsumian article reported that the RBL degranulation test had a reproducibility of approximately 20%. (July Tr. (Arnon) 325:14-326:1; PTX 522 at 320.) Given this data, Dr. Barsumian concluded that the test was "quite reproducible." (July Tr. (Arnon) 321:19-326:13, 337:7-16; PTX 522 at 322.) Based on the literature available at the time and Professor Arnon's experience with biological

assays, she and her colleagues at the Weizmann Institute determined that the RBL degranulation test, with its approximately 20% reproducibility, was "quite reliable." (July Tr. (Arnon) 321:8-326:25, 336:2-337:17; PTX 522; PTX 711; DTX 3114.)

Teva and Weizmann's protocol for performing the RBL degranulation test was contained in a specification drafted by Weizmann scientist Dr. Teitelbaum, not Dr. Pinchasi. Professor Arnon reviewed the RBL specification. (July Tr. (Pinchasi) 89:23-91:4; July Tr. (Arnon) 334:14-23; DTX 3114.) The RBL specification was later signed and approved by Dr. Pinchasi. (July Tr. (Pinchasi) 89:23-91:4; DTX 3114.) According to the RBL specification drafted by Dr. Teitelbaum, the RBL degranulation test was used "to screen out those batches of cop-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects." (DTX 3114 at TEV000881362.) As indicated above, this exact statement was included in the '037 application and the specification of the patents-in-suit. (PTX 10 at TEV003009934; PTX 1 at 3:63-67.) At trial, Professor Arnon testified that, to this day, she believes this is an accurate statement of the appropriate use of the RBL degranulation test. (July Tr. (Arnon) 334:24-335:14.)

The RBL specification shows that the test was validated, meaning that it was proven to be precise and reproducible enough

for the purposes for which it was being used. (July Tr. (Pinchasi) 92:22-93:17; DTX 3114 at TEV000881368.) The precision of the RBL degranulation test (in terms of its relative standard deviation ("RSD")) was reported as ± 19%, and its reproducibility (in terms of RSD) was reported as ± 26%. (July Tr. (Pinchasi) 94:9-15; DTX 3114 at TEV000881368-69.) Professor Arnon testified that this level of precision and reproducibility was both acceptable and within the range of what the Weizmann scientists expected. (July Tr. (Arnon) 336:2-337:6.)

x. The RBL Degranulation Test Described in the Patent Is a Well-Accepted Test in the Scientific Community

At trial, Dr. Baird testified that the RBL degranulation test is a very reliable and reproducible test that is widely used by the scientific community as a model for immediate hypersensitivity that might occur in humans. (July Tr. (Baird) 585:9-21, 595:4-16, 596:25-597:8, 610:6-20, 611:15-22; PTX 522.) In particular, she agreed with the description of the RBL test set out in the patent, and believes it was reasonable for the Weizmann Institute and Teva scientists to use the test for the purpose described in the patents-in-suit (and the '037 application)—"to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects." (July Tr.

(Baird) 593:21-597:8.) As explained above, this language was taken directly from the RBL specification written by the scientists at the Weizmann Institute. (July Tr. (Pinchasi) 286:11-288:16; PTX 1 at 3:63-67; PTX 10 at TEV003009934; DTX 3114 at TEV000811362.)

The Court also takes note of the fact that Defendants themselves have performed RBL degranulation testing and have acknowledged its acceptance in the scientific community. Dr. Rao, Defendant Natco's President of Research and Development, testified that Natco performed RBL degranulation testing, and that the RBL degranulation test is a "well-known toxicity test for hypersensitivity reactions to products" that is "predictive of hypersensitivity in humans." (PTX 883 (Rao Dep.) at 149:22-150:4.) Defendant Momenta developed an RBL test similar to the one used by Teva and described in the patents-in-suit. Momenta found the precision of its test to be ±35%, substantially lower than Teva's. It nevertheless concluded, and then represented to the FDA, that its RBL degranulation test was reproducible. (July Tr. (Kimber) 451:23-460:17; PTX 230 at MMT00927146; PTX 349 at SDZ0018127-34.)

Although Dr. Kimber, Defendants' expert, testified that the RBL degranulation test is not sufficiently reproducible to draw any conclusions about the toxicity of copolymer-1, he has limited experience with the test, and has never performed the

test himself. (July Tr. (Kimber) 426:1-3, 426:8-17.) His testimony was based entirely on the variability for the test described in the RBL specification. Moreover, at trial, he conceded that the reproducibility of Teva's RBL degranulation test was actually better than both the reproducibility reported in the Barsumian paper and the reproducibility found by Momenta. (July Tr. (Kimber) 449:13-451:9; 458:25-460:17.) For these reasons, the Court does not credit Dr. Kimber's testimony regarding the RBL test.

Lastly, the Court notes that the Bornstein article, which was peer-reviewed, explicitly describes use of the RBL degranulation test as a toxicity screen for copolymer-1 batches. The fact that the article was peer-reviewed constitutes additional evidence that the RBL test was generally accepted by the scientific community. (July Tr. (Arnon) 329:3-331:4; PTX 31 at 409.)

xi. The Patent Office Knew About the Reproducibility of the RBL Degranulation Test

Example 2 of the '037 application and the patents-in-suit cites the same two literature references cited in the RBL specification: the Barsumian and Siraganian articles. The Barsumian article specifically reported a reproducibility of ± 20% for the RBL degranulation test. (PTX 1 at 3:50-55; PTX

522.) Thus, the examiner was aware of the reproducibility of the test when making the decision to allow the claims to issue.

In light of these findings of fact, the Court makes the following conclusions of law with respect to Defendants' claim of inequitable conduct.

xii. The April 1994 Data Table and the RBL Degranulation Information Were Not Material

Defendants assert that Dr. Pinchasi's withholding of toxicity data and her concerns about the RBL test from the PTO constitute "affirmative acts of egregious misconduct." In Therasense, Inc., the Federal Circuit was clear, however, that "neither mere nondisclosure of prior art references to the PTO nor failure to mention prior art references . . . constitutes affirmative egregious misconduct." 649 F.3d at 1292-93. Omissions, such as the ones alleged here, "require proof of but-for materiality." Id. at 1293. To prove materiality under the "but-for" standard, Defendants had to prove "the PTO would not have allowed a claim had it been aware" of the April 1994 Data Table or Dr. Pinchasi's views on the RBL degranulation test. See id. at 1291.

Defendants have failed to establish materiality under that standard. First, with respect to the April 1994 Data Table, the Court concludes that the trend reflected in that Table was evidenced by the other information that was before the PTO and

was, therefore, cumulative. For example, as discussed above, Example 2 was representative of (and consistent with) all of Teva's toxicity data, including the April 1994 Data Table (July Tr. (Arnon) 332:8-334:2; July Tr. (Baird) at 600:3-6, 601:12-24, 603:7-604:5, 605:14-18; July Tr. (Pinchasi) 30:14-20, 80:13-81:13, 125:14-19, 126:4-8; July Tr. (Kimber) 446:22-447:15, 465:2-3, 466:10-19; PTX 34-T; PTX 887 at 40, 44; supra Fig. 26; supra Fig. 27.)

As such, the April 1994 Data Table was not material. See Star Scientific, Inc. v. R.J. Reynolds Tobacco Co., 537 F.3d 1357, 1367 (Fed. Cir. 2008) ("It is well-established . . . that information is not material if it is cumulative of other information disclosed to the PTO.") (citations omitted); Honeywell Int'l Inc. v. Universal Avionics Sys. Corp., 488 F.3d 982, 1000 (Fed. Cir. 2007) ("Information cumulative of other information already before the Patent Office is not material.").

Second, with respect to Dr. Pinchasi's views regarding the RBL test, the evidence at trial established that Teva continued to use the RBL test even after the December 1989 memo that was critical of the RBL test. (PTX 723; PTX 62.) Moreover, to the extent Dr. Pinchasi had reservations about the RBL test, the evidence at trial established that Dr. Arnon, whose testimony the Court credits, viewed (and continues to view) the test as reliable and reproducible enough to screen batches of copolymer-

1 for toxicity. (July Tr. (Arnon) at 320:7-321:18, 321:8-326:25, 327:22-331:4, 336:2-337:17.) The evidence also showed that the scientific community, including literature that was explicitly cited in the '037 application and the specification of the patents-in-suit, recognized the test as a reliable and reproducible model for examining immediate hypersensitivity that might occur in humans. (July Tr. (Baird) 585:9-21, 593:21-597:8, 595:4-16, 596:25-597:8, 610:6-20, 611:15-22; July Tr. (Kimber) 451:23-460:17; PTX 31 at 409; PTX 230 at MMT00927146; PTX 349 at SDZ0018127-34; PTX 522; PTX 711; PTX 883 (Rao Dep.) at 149:22-150:4; DTX 3114 at TEV000811362.) In view of these facts, Defendants have failed to show that "the PTO would not have allowed a claim had it been aware" of Dr. Pinchasi's concerns about the RBL degranulation test. See Therasense, Inc., 649 F.3d at 1291.

xiii. Defendants Failed to Establish that Dr. Pinchasi Intended to Deceive the PTO

Even if Defendants had established materiality, which they did not, they failed to establish by clear and convincing evidence that Dr. Pinchasi intended to deceive the PTO. As an initial matter, Defendants proffered no direct evidence that Dr. Pinchasi intended to deceive the PTO. With respect to indirect and circumstantial evidence, under Therasense, Inc., "specific intent to deceive must be 'the single most reasonable inference

able to be drawn from the evidence.'" 649 F.3d at 1290 (citation omitted). Such an inference cannot be drawn here.

First, in regard to the toxicity data, it is irrelevant whether Dr. Pinchasi personally selected the in vivo and in vitro RBL test batches that were included in the '037 application. The crucial facts are that she reviewed the '037 application before it was filed and confirmed that it accurately reflected what she knew about the biological toxicity profile of copolymer-1, as measured by the in vivo and in vitro RBL toxicity test. (July Tr. (Pinchasi) at 129:1-17.) Because the evidence at trial established that there was a clear trend between increasing RBL degranulation and increasing average molecular weight, "specific intent to deceive" is not "'the single most reasonable inference'" to draw "'from the evidence.'" Therasense, Inc., 649 F.3d at 1290 (citation omitted).

Second, in regard to her concerns regarding the RBL degranulation test, while the RBL degranulation test was not able "to afford the ultimate analysis for the safety of [Teva's] batches[,]" (DTX 3385 at TEV001222392), used in conjunction with the in vivo test, the two tests were "complementary from the point of view of how they can predict clinical safety." (July Tr. (Pinchasi) at 29:18-19.) In view of the fact that Teva continued to use the RBL degranulation test after Dr. Pinchasi's

December 1989 memo that was critical of the RBL test (PTX 723; PTX 62), "specific intent to deceive" is not "'the single most reasonable inference'" to draw from the withholding of Dr. Pinchasi's concerns about the RBL degranulation test from the PTO. Therasense, Inc., 649 F.3d at 1290 (citation omitted).

For the reasons provided above, Defendants failed to establish inequitable conduct by clear and convincing evidence.

C. Lack of Enablement

With Sandoz taking the lead, Defendants argue that the patents-in-suit are invalid for lack of enablement. According to Sandoz, in 1994, a person of ordinary skill in the art would not have been able to make copolymer-1 with the claimed molecular weights without undue experimentation because the patents-in-suit do not identify the standards that should be used to calibrate the SEC column.

i. General Principles

Section 112 of the Patent Act provides, in pertinent part, "[t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same." 35 U.S.C. § 112, ¶ 1. "The test of enablement is whether" a person of ordinary skill in the art "could make or use the invention from the disclosures in the patent coupled

with information known in the art without undue experimentation." U.S. v. Telectronics, Inc., 857 F.2d 778, 785 (Fed. Cir. 1988) (citation omitted); see also Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1253 (Fed. Cir. 2004) (explaining that a patent claim is invalid for lack of enablement "only if one skilled in the art, after reading [it], could [not] practice the invention claimed . . . without undue experimentation") (citation omitted).

Determining "what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988) (citation omitted). In Chiron Corp., the Federal Circuit explained that "[t]he fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation must not be unduly extensive." 363 F.3d at 1253 (citations and internal quotation marks omitted). Indeed, "'a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996) (citation omitted).

In In re Wands, the Federal Circuit explained that "[f]actors to be considered in determining whether a disclosure would require undue experimentation" include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

858 F.2d at 737 (citation omitted).

A "person of ordinary skill . . . is presumed to be aware of all the pertinent prior art." Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 962 (Fed. Cir. 1986) (citation omitted). As a result, "'[a] patent need not teach, and preferably omits, what is well known in the art.'" Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1365 (Fed. Cir. 2006) (alteration in original) (citation omitted).

Lack of enablement must be proven by clear and convincing evidence, see Microsoft Corp. v. i4i Ltd. P'ship, 131 S. Ct. 2238, 2242 (2011), as of the filing date of the patent application, see Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co., 228 F.3d 1338, 1345 (Fed. Cir. 2000).

ii. A Person of Ordinary Skill

The testimony of the experts at trial established that the relevant level of skill in the art was high. And although not all of the experts stated as much, the Court finds that, in

1994, a person of ordinary skill in the art would have had experience and skills in SEC. (Sept. Tr. (Grant) 189:22-190:6; PTX 986 at 3 (an "advanced degree or equivalent in a chemical or biological discipline, and significant experience in the synthesis or characterization of polymers, including proteins or synthetic peptides"); Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9 ("a Ph.D. in chemistry, biochemistry or related field with a minimum of three years of experience in chromatography and specifically in size exclusion chromatography of macromolecules"); Sept. Tr. (Zeiger) 809:10-811:15; DTX 4030 at 4 ("extensive experience in the synthesis, fractionation, and characterization of polymers, such as their hydrodynamic and structural properties, as applied to proteins, synthetic peptides and/or polydisperse peptide mixtures, as well as experience in the determination of the molecular weight distribution and average molecular weights of such polymers by methods such as size exclusion chromatography (SEC), and an understanding of how the standards and conditions used in the molecular weight determination affect the results obtained.")

iii. Self-Standards

As explained above, the specification expressly describes use of a calibrated SEC column.[20] (PTX 1 at 3:6-8.) At trial,

[20] Defendants emphasize a July 4, 1996 Teva document that states, "[I]t should be explicitly stated by which analytical method the molecular weight data were obtained." (DTX 31317 at TEV000290820.) As Dr. Grant testified,

Dr. Grant testified that, in 1994, there were two ways a person of ordinary skill in the art could accurately measure the molecular weight of copolymer-1: self-standards and universal calibration.

In 1994, a person of ordinary skill in the art would have known that to accurately correlate the retention time of the molecules coming out of an SEC column with their molecular weights, the column must be calibrated using standards with the same hydrodynamic characteristics as the sample being measured. (Sept. Tr. (Grant) 1412:6-1413:16; Sept. Tr. (Scandella) 1314:15-1316:24; PTX 961 (Kota Dep.) 18:3-14; PTX 962 (B. Rao Dep.) at 75:6-76:10, 78:14-80:5; PTX 973 (Venkataraman Dep.) at 108:20-109:23; PTX 974 (Wallingford Dep.) 146:9-149:7; PTX 317 at MYL0000111; PTX 553 at 72.) Because self-standards are made from the same material as the sample being measured, by definition, they have the same hydrodynamic volume-to-molecular weight characteristics as the sample being measured. (Sept. Tr. (Grant) 1399:23-1400:13.) As a result, the shape of copolymer-1 has no bearing on the use of self-standards.

By 1994, self-standard calibration had been thoroughly described in the scientific literature. For example, Billingham 1977 states that "[t]he most obvious method is to inject into

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however, that is precisely what the patents-in-suit do: "They explicitly state that you should use size exclusion chromatography." (Sept. Tr. (Grant) 325:17-18.)

the columns a series of monodisperse standards of the polymer under test" and that "[d]irect calibration with the polymer under test can be achieved by using narrow distribution fractions of the polymer." (PTX 514 at 210-11; Sept. Tr. (Grant) 1414:8-1415:17.)

Self-standards can be obtained two ways. The first is to use whole batches of the polymer of interest having different molecular weights ("whole polymer" self-standards). The second is to use narrower fractions of the polymer sample of interest ("fractionated" self-standards). (Sept. Tr. (Grant) 1399:23-1400:13.)

The first method, whole polymer self-standards, involves taking whole batches of the polymer of interest, each batch having a different molecular weight, and determining the molecular weights of the batches by independent (non-SEC) methods. (Sept. Tr. (Grant) 1401:9-11, 1418:7-15.) The whole polymer self-standard method was described in the literature well before 1994. (Sept. Tr. (Grant) 1401:9-11; 1418:7-1420:20; PTX 514 at 211; PTX 566 at 37.) Billingham 1977, for example, describes two different methods of calibration using whole polymer standards in a section entitled "Calibration with Whole Polymer." (PTX 514 at 212-13; Sept. Tr. (Grant) 1401:9-11.) Similar methods are also described in Barth 1991, which includes two sections entitled "Calibration Using Polydisperse Standards

of Known Molecular Weight Averages" and "Calibration Using Standards of Known Molecular Weight Distribution." (Sept. Tr. (Grant) 1419:13-1421:3; PTX 566 at 37-44.)

In 1994, a person of ordinary skill in the art could have made whole batches of copolymer-1 to use as self-standards because the patents-in-suit teach how to make copolymer-1 of varying molecular weights. These batches could then be used as molecular weight standards. (PTX 1, col. 4:59-65; Sept. Tr. (Grant) 1401:19-1402:4; DTX 4022 (Varkony Dep.) at 252:4-13, 252:25-253:6, 257:17-22.) At trial, Dr. Sampson explained that by varying the time and temperature of the HBr/acetic acid reaction step in the synthesis of copolymer-1, the molecular weight of the resulting copolymer-1 can be controlled. (Sept. Tr. (Sampson) 1641:6-1642:8; PTX 992 at 6-7.)

With respect to the second method, the fractionated self-standard method involves taking a mixture of the substance of interest and separating it into smaller portions, or fractions, that can be used as calibration standards. (Sept. Tr. (Grant) 187:8-14.) The fractionated self-standard method had been fully described in the literature prior to 1994. (Sept. Tr. (Grant) 1400:16-18.) For instance, Billingham 1977 states that "[d]irect calibration with the polymer under test can be achieved by using narrow distribution fractions of the polymer, prepared either by preparative fractionation or by preparative

scale GPC." (Sept. Tr. (Grant) 1414:12-1418:6; PTX 514 at 211-12.)

Moreover, fractionation of copolymer-1 into smaller portions of varying molecular weight is described in the patents-in-suit. The patent describes fractionation of copolymer-1 by running a sample through an SEC column and collecting the fractions as they exit the column. (PTX 1, col. 2:57-3:2; Sept. Tr. (Grant) 1400:16-1401:8, 1402:5-9; Sept. Tr. (Scandella) 1322:20-1324:7.) Each of the resulting fractions will have a different molecular weight, which can be independently measured so that the fractions can be used as calibration standards. (Sept. Tr. (Grant) 1402:10-24.)

Once self-standards are made—whole or fractionated—a person of ordinary skill in the art would have measured their molecular weights by an independent (non-SEC) method.[21] (Sept. Tr. (Grant) 205:6-10, 1402:10-18.) The methods available for measuring the molecular weights of self-standards in 1994 included multi-angle light scattering, viscometry, ultracentrifugation, and mass spectrometry. (Sept. Tr. (Grant) 1402:19-1403:2; Sept. Tr. (Scandella) 1318:2-8.)

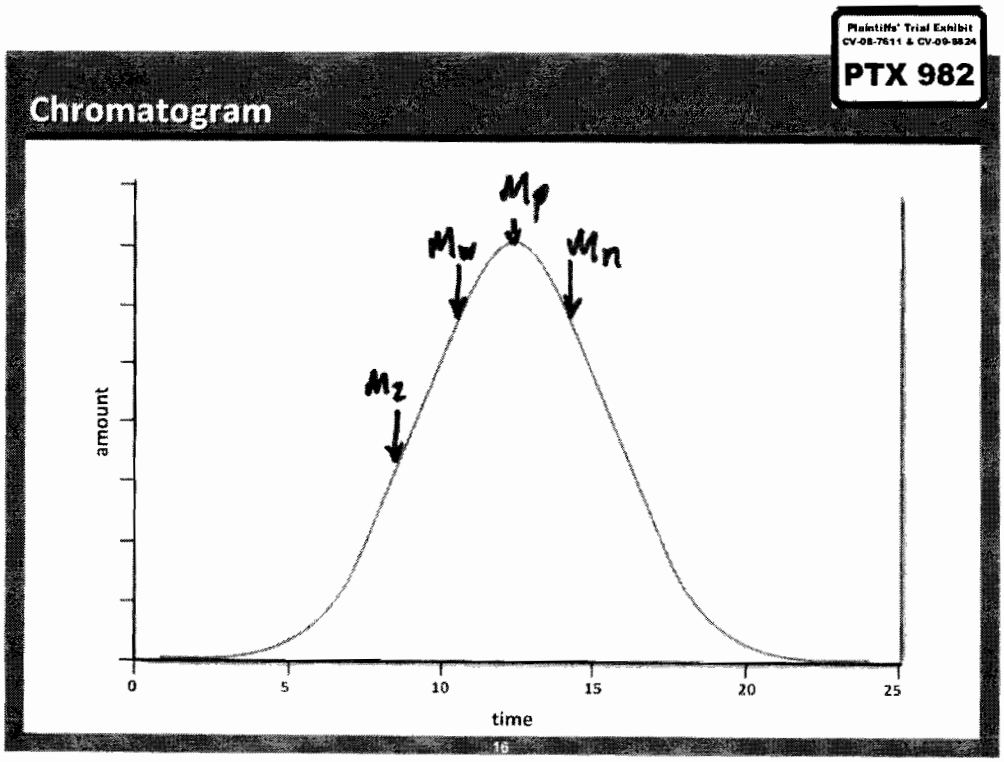
Once the molecular weights of the self-standards had been measured, a person of skill in the art would use them to calibrate the SEC column by running them through the column,

[21] Some of these methods are known as absolute molecular weight methods. (Sept. Tr. (Grant) 1416:14-17.)

recording the times at which they exit the column, and then creating a calibration plot to correlate their molecular weights to their retention times. (Sept. Tr. (Grant) 1402:10-18.)

If self-standards were used for calibration, however, their average molecular weights could vary depending on the absolute method used to determine the molecular weight of the standard. Light scattering, for example, could measure a weight average molecular weight, while osmometry could measure a number average molecular weight. The different average molecular weight values provided by the various techniques would correspond to different retention times along the chromatogram for the sample. (Sept. Tr. (Grant) 1404:7-20; Sept. Tr. (Scandella) 1326:19-1327:16.) If, for instance, the various molecular weights are mapped out on a chromatogram shaped as in PTX-982, the z-average molecular weight (Mz) would come out first (because it is the highest value and larger molecules exit the size exclusion column first), then the weight average molecular weight (Mw), followed by the peak average molecular weight (Mp) at the peak of the chromatogram, and then the number average molecular weight (Mn) after the peak (because it is generally the smallest of the "average" values), as shown below in Figure 26. (PTX 982; Sept. Tr. (Scandella) 1325:2-1326:18; Sept. Tr. (Grant) 1404:23-1405:13.)

Figure 26



At trial, Dr. Scandella testified that the different average molecular weight values measured by the different absolute measurement methods for the standards would result in different calibration curves, which, in turn, would lead to different determined molecular weights for the sample depending on which calibration was used. (Sept. Tr. (Scandella) 1272:3-25; DTX 3581 at 16.) On cross-examination, he admitted, however, that although each different type of measured average molecular weight for a standard would be associated with a different retention time, the demonstrative he used to show the flaw he alleged, depicted all of the different average molecular

weights as being associated with the same retention time. (Sept. Tr. (Scandella) 1326:24-1327:21.)

The Court credits Dr. Grant's explanation regarding why Dr. Scandella's demonstrative was inaccurate. (Sept. Tr. (Grant) 1403:14-1404:20.) Despite the potential difference in the average molecular weight (and hence the corresponding retention time) obtained using different absolute measurement techniques, in 1994, it was well known how to appropriately apply the different measured average molecular weights obtained using different methods to get an appropriate calibration curve that would provide an accurate molecular weight. (Sept. Tr. (Grant) 327:9-16.) The process of obtaining a single accurate calibration curve from the measured molecular weights of self-standards was described extensively in the literature. (Sept. Tr. (Grant) 1403:3-13.) The literature provided numerous examples of procedures that could have been used to resolve calibration curves produced by different absolute molecular weight measurement techniques into a single calibration curve. (Sept. Tr. (Grant) 1408:25-1409:4.)

For fractionated self-standards, for example, Billingham 1977 describes ways to calculate the peak molecular weight of the self-standards such that it can be accurately applied at the peak time. Dr. Grant explained that this means that "since a number average or a weight average is not going to have a time

associated with it that's equal to the peak, you have to do some calculation or adjustment to be able to find what the accurate molecular weight is at the peak." (Sept. Tr. (Grant) 1414:22-1417:3; PTX 514 at 211.) Dr. Grant also explained that a paper from the early 1970s cited by Billingham 1977 describes "several different types of methods that had already been developed by that time to do this adjustment, this calculation of the peak molecular weight from other types of average molecular weights." Dr. Grant explained further that mathematical treatments that could be used to convert number average or weight average molecular weights into peak molecular weights were described in the literature in 1994. (Sept. Tr. (Grant) 1417:4-1418:6; PTX 514 at 211.)

Additionally, Barth 1991 describes a variety of methods for generating calibration curves using polydisperse self-standards. (PTX 566 at 37-41.) Dr. Grant explained that Barth 1991 describes "a process that allows you to determine the accurate molecular weight at the peak for constructing a valid calibration curve" because "Mn and Mw are average molecular weights that can be determined by absolute methods" and "they do not correspond to molecular weights at the same time as the peak." (Sept. Tr. (Grant) 1419:13-1421:3; PTX 566 at 37.)

Dr. Grant further explained that Billingham 1977 and Barth 1991 represent only a very small part of the literature that was

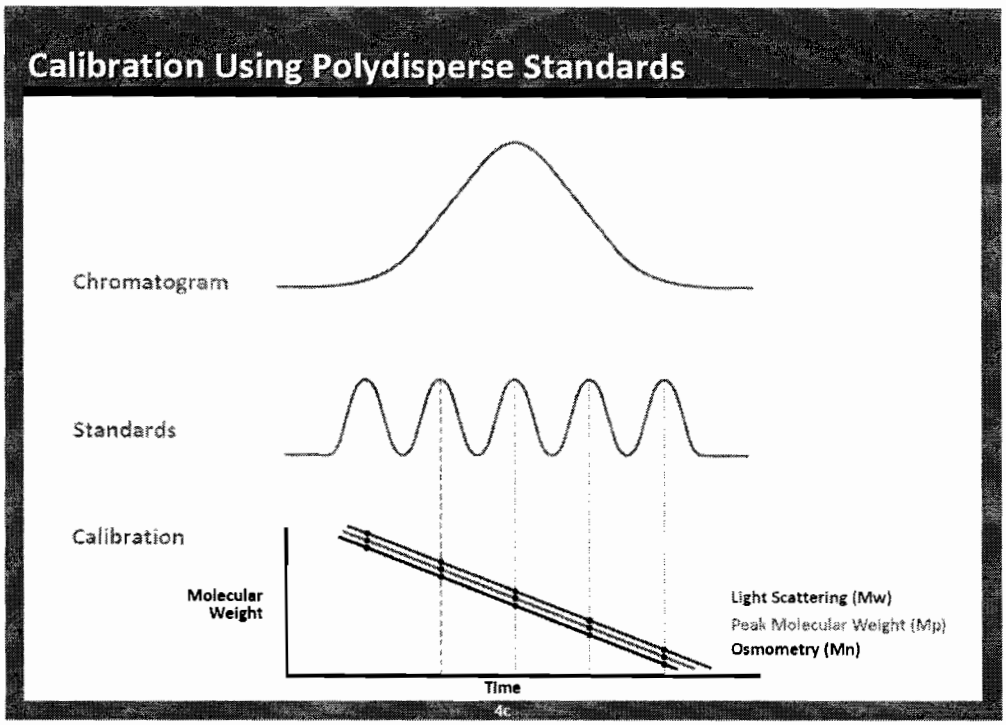
available in 1994 describing the processes for generating valid calibration curves. He emphasized that "there are well described and valid and effective methods to take calibration curves that may be constructed from different types of average molecular weights and resolve them into a single calibration curve, so that . . . in the end you only ha[ve] [a] single valid calibration curve, [which] gives you an accurate molecular weight at the peak of your measuring." (Sept. Tr. (Grant) 1421:4-18.)

At trial, Dr. Grant presented a demonstrative to explain how a person of ordinary skill in the art would apply different average molecular weight results from different techniques to generate a single valid calibration curve. (Sept. Tr. (Grant) 1406:1-1409:11; PTX 990 at 4a-i.) Dr. Grant presented an illustrative chromatogram of five broad self-standards, such as copolymer-1 self-standards, and a calibration curve based on the peak molecular weight times of the self-standards. (Sept. Tr. (Grant) 1406:1-17; PTX 990 at 4a.)

Dr. Grant explained that one would get different calibration curves if the different average molecular weights for the standards obtained through different absolute molecular weight measurement techniques were assigned to the same retention time. This occurs because, as shown in his example, one technique, light scattering, gives a higher average value (a

"weight" average (Mw)) than the peak average value, while a second technique, osmometry, gives a lower average value (a "number" average (Mn)) than the peak average value, but the weight average and number average values are erroneously being applied at the same time (the "peak" time). (Sept. Tr. (Grant) 1406:18-25,1407:7-13; PTX 990 at 4c.)

Figure 27



Dr. Grant explained that an adjustment was described extensively in the pre-1994 literature that addressed this issue. This adjustment would allow the different average molecular weights to be applied at the correct time. Such an adjustment—calculating the molecular weight of the standard at the peak so that it could be accurately applied at the peak time

or appropriately applying the measured average molecular weight of the standard at its appropriate time—would cause the theoretically different calibration curves to be merged into a single accurate calibration curve. (Sept. Tr. (Grant) 1406:25-1407:6; PTX 990 at 4c-i.)

Dr. Grant also demonstrated how a calibration curve based on weight average molecular weight (which is a larger value than the peak molecular weight value and therefore corresponds to a time to the left of the peak) of self-standards could be adjusted. (Sept. Tr. (Grant) 1407:20-1408:8; PTX 990 at 4d.) Similarly, Dr. Grant demonstrated how a calibration curve based on number average molecular weight value (which is smaller than the peak molecular weight value and therefore corresponds to a time to the right of the peak) of self-standards is adjusted. (Sept. Tr. (Grant) 1408:9-24; PTX 990 at 4f.) The adjustment would, in effect, move the weight average molecular weights to earlier times—to the left (because larger molecules come out of the size exclusion column before smaller molecules). This would have the effect of sliding the light scattering calibration curve to the left. (Sept. Tr. (Grant) 1406:18-1407:6.) Similarly, the adjustment would have the effect of moving the osmometry curve to later times—to the right. (Sept. Tr. (Grant) 1407:7-1408:24.) The adjustments are shown in the graphs below:

Figure 28

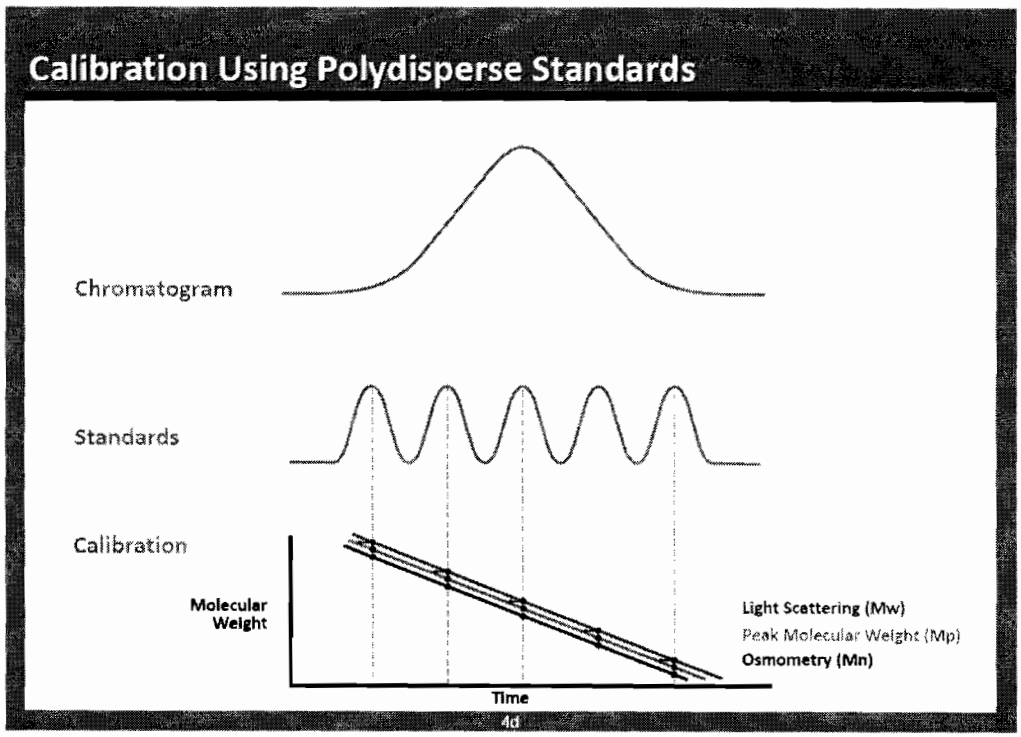
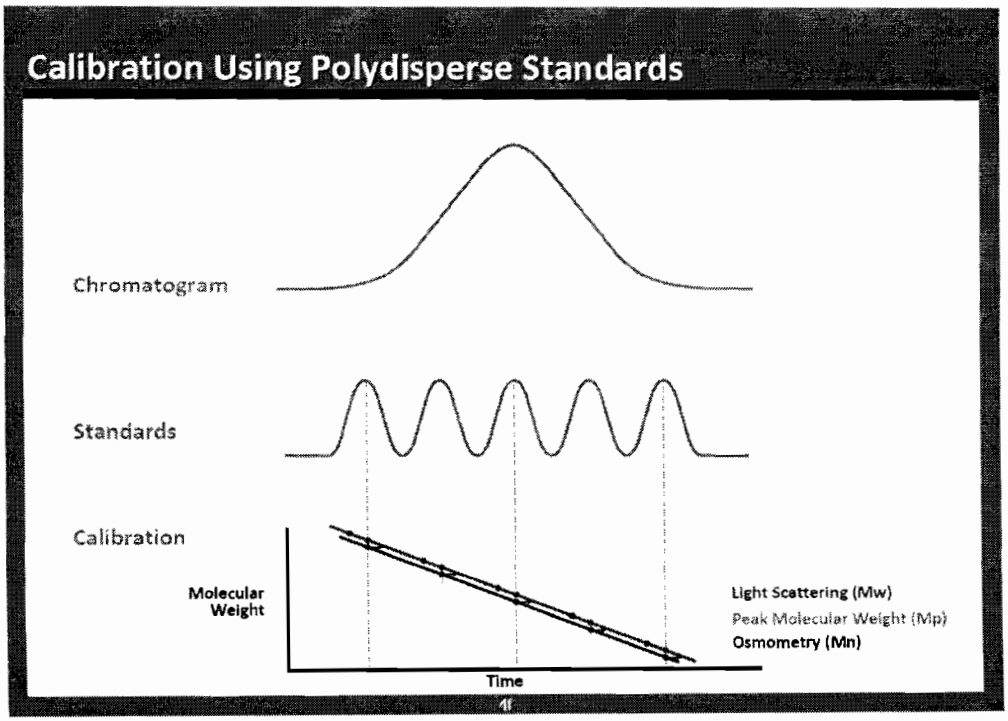


Figure 29



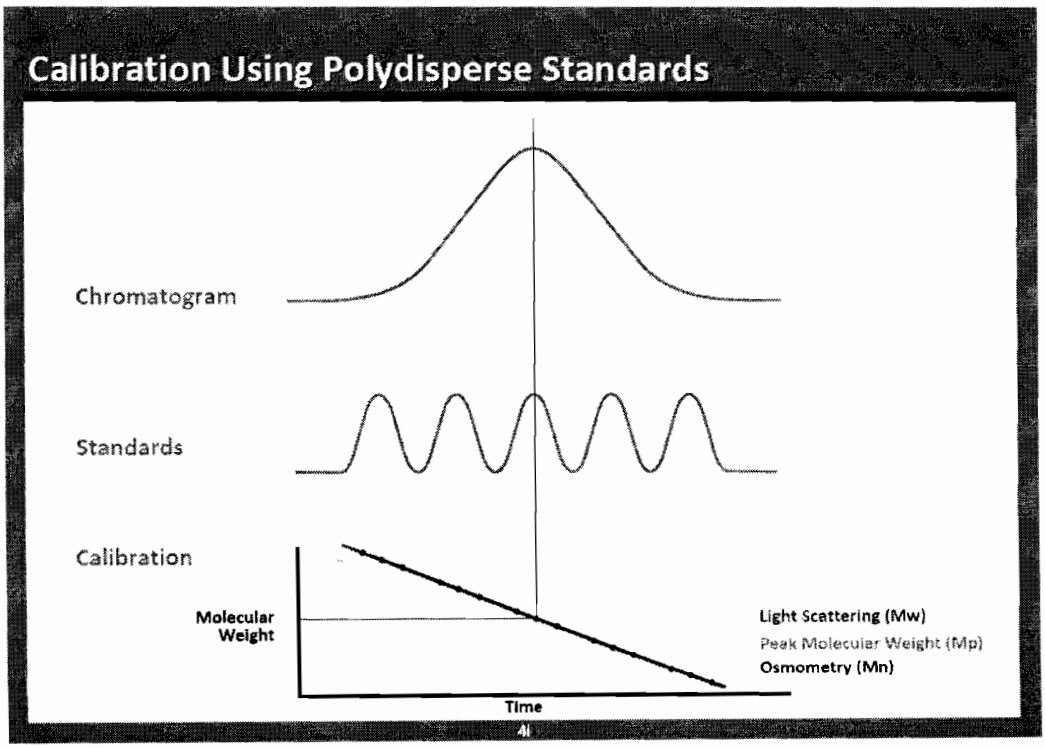
The "end result is that all three calibration curves become one." (Sept. Tr. (Grant) 1408:17-18.)

Dr. Grant further explained how the single calibration curve could be used to obtain an accurate molecular peak molecular weight for a sample:

> At the end of the day, what this means is that you in fact do not have three different calibration curves from which you have to choose which one to use. You in fact have only a single calibration curve that gives you only a single accurate value for the peak of the chromatogram. . . . You locate the time of the peak, come down, find that time on your calibration curve, and you go over and read the molecular weight.

(Sept. Tr. (Grant) 1409:5-16; PTX 990 at 4i.)

Figure 30



Dr. Scandella agreed that techniques for correctly applying the measured average molecular weights of the standards at the correct retention time could have been available in 1994, but testified that he had not "looked at that recently." (Sept. Tr. (Scandella) 1328:7-16.)

iv. Universal Calibration

In 1994, a person of ordinary skill in the art could also have used universal calibration to accurately measure the peak molecular weight and molecular weight distribution (e.g., the percentage of molecules between 2 and 20 kilodaltons or above 40 kilodaltons) of a sample of copolymer-1. (PTX 970 (Svec Dep.) at 320:2-7, 326:14-327:10, 320:22-321:10, 382:8-13, 384:23-385:6, 385:8-19; Sept. Tr. (Grant) 1430:8-1431:23.) According to the theory of universal calibration, the molecular weight values obtained from SEC should not be dependent on the type of standards used for calibration. (PTX 970 (Svec Dep.) at 356:2-8.) Unlike conventional SEC, universal calibration does not require the calibration standards to have the same hydrodynamic volume-to-molecular weight relationship as the sample, because it uses a different physical property—intrinsic viscosity—to allow a correlation of the size of molecules exiting the column to their molecular weight. (Sept. Tr. (Grant) 208:14-20, 1400:6-15.)

Universal calibration has been known since the late 1960s. By 1994, it was well described in the literature. There was extensive literature on universal calibration and a large number of studies that showed that it worked well for a variety of different types of polymers. (PTX 970 (Svec Dep.) at 296:16-22; Sept. Tr. (Grant) 1401:15-18, 1423:11-1430:7; PTX 514 at 213-17; PTX 553 at 73-76.) Furthermore, the ability to measure intrinsic viscosity was routine for persons of skill in the art in 1994. (PTX 970 (Svec Dep.) at 296:23-297:6.)

In 1994, a person of ordinary skill in the art could have used the available scientific literature to set up and carry out universal calibration in order to determine the molecular weight of copolymer-1 without significant experimentation. (Sept. Tr. (Grant) 1431:24-1432:11.) Sandoz's universal calibration expert, Dr. Frantisek Svec, agreed that universal calibration could be used to obtain accurate molecular weight results for a sample, and further that universal calibration could be used to obtain accurate molecular weights for copolymer-1:

> Q. So in your opinion a person of skill in the art could take a copolymer-1 sample and determine an accurate molecular weight?
>
> A. Yes. Take a sample and determine the molecular weight.

(PTX 970 (Svec 05/21/2010 Dep.) at 388:8-12.)

Based on the foregoing, the Court makes the following conclusions of law in connection with Defendants' arguments.

v. Teva's Experimentation with Copolymyer-1

Defendants make two arguments that are not specific to self-standards or universal calibration. The first is based on Teva's experience with copolymer-1. Sandoz claims that from 1987 to 1998, Teva and its consultants (W.R. Grace) used a number of different standards and analytical methods to attempt to measure the molecular weight of copolymer-1, including at least the following standards: globular proteins, polyethylene glycol, denatured proteins, histones, polylysines, self-standards, and synthetic peptide standards; and at least the following analytical methods: SEC, viscometry, ultracentrifugation, osmometry, MALLS, MALDI-TOF mass spectrometry. (See e.g., DTX 1762; DTX 3275; DTX 1269; DTX 1192; DTX 1701; DTX 1764; DTX 3507; DTX 3540.) According to Sandoz, Teva's experimentation from 1987 to 1998 is probative of the complexities of copolymer-1 and the disparate molecular results one would have obtained without knowledge of the standards and analytical methods Teva used.

Even assuming Teva's scientists and consultants were persons of ordinary skill in the art,[22] the fact that Teva

[22] See Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1374 (Fed. Cir. 1999) ("it defies common sense that [the inventor] would waste valuable

experimented with different standards and analytical methods does not constitute clear and convincing evidence of lack of enablement because Defendants never established why Teva experimented with different standards and analytical methods. Without a firm basis for understanding why Teva experimented with different standards and analytical methods, the Court is unable to attach any particular significance to Teva's experimentation or the results described in Teva's and W.R. Grace's memoranda. Indeed, based on the totality of the evidence before the Court, it is entirely plausible that Teva experimented with different methods to deal with regulatory and other scale-up issues, rather than to correct faulty measurements, as Sandoz claims. (See DTX 1770 at TEV000283327.) As a result, the fact that Teva experimented with copolymer-1 from 1987 to 1998 does not, in and of itself, constitute clear and convincing evidence of lack of enablement.

Sandoz's second argument is that, in 1994, it would have been reasonable for a person of ordinary skill in the art to use commercially available protein standards to measure the molecular weight of copolymer-1. Proteins, like copolymer-1, "are polypeptides and . . . there were no other polypeptide molecular weight standards available." (Sept. Tr. (Scandella) 1231:7-13.) In addition, the Superose 12 manufacturer,

resources conducting experiments in other organisms had he not believed that his research associates possessed sufficient skill to perform them").

Pharmacia, recommended globular proteins as the calibration standards for the column. (Sept. Tr. (Scandella) 1231:7-13, 1235:20-1236:17; PTX 752 at TEV000953898.) Using protein standards in 1987, however, Teva found that "[t]he molecular weights of COP-1 batches calculated from the calibration curve of the markers . . . were 4-5 times higher than those obtained by viscosity and ultracentrigue." (DTX 3275 at TEV000304994-95, TEV000304998; Sept. Tr. (Scandella) 1231:16-25.) Because the patents-in-suit failed to disclose this finding, Sandoz argues, if a person of ordinary skill in the art attempted to calibrate the SEC column with commercially available proteins in 1994, that person would not have known that the results were four to five times higher than results obtained from other methods. (Sept. Tr. (Scandella) 1232:20-1233:1.)

The fact is, however, in 1994, a person of ordinary skill in the art would have understood that the polypeptides in copolymer-1 are not globular. (Sept. Tr. (Grant) 1425:12-23; PTX 970 (Svec Dep.) at 395:21-395:24, 396:16-397:8, 397:11-397:17, 397:24-398:15.) As a result, a person of ordinary skill in the art would have understood that globular proteins do not have the same hydrodynamic characteristics as copolymer-1 and thus that they were inappropriate for use in conventional calibration of copolymer-1, as they would provide an inaccurate molecular

weight.[23] (Sept. Tr. (Grant) 272:19-273:25, 1399:8-17; PTX 970 (Svec Dep.) at 394:23-395:3, 398:16-398:25; Sept. Tr. (Scandella) 1290:20-23 ("One would start with globular protein standards, test them, find out that they didn't give accurate molecular weights, go on to survey other commercially available standards . . . .").)

vi. Self-Standards

Defendants make numerous arguments regarding why self-standards would not have been sufficient to enable the patents-in-suit. None of these arguments, however, constitute clear and convincing evidence of lack of enablement.

As an initial matter, Sandoz does not challenge that a person of ordinary skill in the art could have made copolymer-1 self-standards in 1994 using whole polymer or fractionated self-standards. In fact, Sandoz scarcely challenges any of the literary references Dr. Grant discussed at trial. Instead, it complains that the literature does not teach self-calibration for material as complex or complicated as copolymer-1.[24] Sandoz offers no evidence, however, beyond the conclusory testimony of

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[23] Dr. Scandella testified that proteins could be appropriate SEC calibration standards if the results were reported "relative to globular protein standards." (Sept. Tr. (Scandella) 1235:7-13.) Because the patents-in-suit did not make such a notation, however, a person of ordinary skill in the art would not have found that such standards were appropriate given that that person would have known that protein standards would give inaccurate results.

[24] While the literature did not specifically disclose how to measure the molecular weight of copolymer-1, it did describe how to make and use self-standards for samples that were, like copolymer-1, polydisperse. (Sept. Tr. (Grant) 1414:22-1418:18, 1419:22-1421:3, 1422:15-1423:10; PTX 514; PTX 553.)

its experts,[25] which the Court does not credit, that the "complexity" of copolymer-1 presented any particular difficulties with respect to being able to calculate its peak molecular weight or molar fractions using SEC.

Defendants next argue that even if self-standards were used for calibration, one would have obtained a wide range of molecular weight results for copolymer-1 self-standards depending on the analytical method chosen. They argue further that it is not only the type of molecular weight average (Mz vs. Mw vs. Mn) that would vary depending on the method, but also that the molecular weight values themselves would vary across methods, even for the same type of average. While Defendants cite to several seemingly problematic tables and/or batches, Defendants fail to establish that these results were anything more than outliers, which Teva and its consultants knew were wrong.

Sandoz points first to a November 1995 table in a Teva document that lists 15 copolymer-1 markers and their average molecular weights obtained by ultracentrifugation, viscometry, and MALLS. (DTX 3509 at TEV001116167.) The table shows that depending on the method that was used, the molecular weight for

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[25] (See Sept. Tr. (Wall) 1812:17-22 (copolymer-1 "is an incredibly complicated molecule" that "confounds the ability of even very sophisticated investigators to arrive at a molecular weight"); see also Sept. Tr. (Scandella) 1206:9-11 ("The task of creating standards that match a sample as complicated as cop-1 is quite difficult and [may] take years.").)

a given standard varied by up to 2,100 daltons (marker 02095 [5,800-7,900 daltons]) in the lower end of the molecular weight range and up to 3,000 daltons in the upper end of the range (marker BD-402 [22,200-25,200 daltons]). (DTX 3509 at TEV001116167.)

In an effort to buttress the variability shown in Teva's November 1995 table, Sandoz cites an August 1995 document that appears to list the Mw and Mn MALLS results for the same 15 markers (DTX 1699 at TEV000950015), and another document that appears to list additional Mw and Mn results from other molecular weight analyses on the same markers (DTX 1642 at TEV001013041, TEV001013087). Comparing results from separate tables across documents, Sandoz claims, without any expert support or other testimony regarding the validity of the results, that there was a variation of nearly 5,000 daltons for the Mn values (5,200-10,100 daltons) (compare DTX 1699 at TEV000950015 with DTX 1642 at TEV001013041) and a variation of 9,000 daltons for the Mw values (5,800-14,800 daltons) (compare DTX 1699 at TEV000950015 with DTX 1642 at TEV001013041) depending on the analytical method that was used. Sandoz goes on to claim, again without any expert support or other testimony regarding the validity of the results, that the Mw value of marker BD-402 varied from 22,200 to 48,900 daltons depending on

the selected method. (Compare DTX 1699 at TEV000950015 with DTX 1642 at TEV001013041.)

Without any expert testimony that the results in the Tables in DTX 1699 and 1642 can be compared in any meaningful way—much less with the results in Teva's November 1995 table—the Court cannot find that the tables in DTX 1699 or DTX 1642 constitute clear and convincing evidence of variability across different analytical methods. The Court notes that it precluded Sandoz's expert, Dr. Wall, from testifying about DTX 1699 and DTX 1642 on the last day of trial because he had failed to provide any notice prior to that time, pursuant to Rule 26 of the Federal Rules of Civil Procedure, that he intended to offer opinions regarding the results in these documents and it came as a surprise to Teva. (Sept. Tr. 1793:5-11.) The Court expressly admonished defense counsel not to make legal arguments about these (or any other technical) documents without expert testimony. (Sept. Tr. 1795:9-19.)

Sandoz's next argument in support of variability involves a single batch of copolymer-1. Depending on the analytical method that was used, according to Sandoz, batch 13 yielded different molecular weights for the same sample. (See DTX 3581 at 12; see also Sept. Tr. (Scandella) 1259:13-1260:15.)

The first document Sandoz cites is a May 4, 1988 report from W.R. Grace, which reports the molecular weights of

copolymer-1 obtained using an SEC column calibrated with protein standards. (DTX 1762 at TEV003017835.) At trial, Dr. Grant testified that the report itself suggests that the authors "knew full well" that protein standards were not appropriate for copolymer-1. (Sept. Tr. (Grant) 324:15-325:5; DTX 1762 at TEV003017833.) Indeed, the report explicitly states, "Calibration curves based on globular proteins yield COP-1 molecular weights 4-6 times higher than molecular weights calculated by ultracentrifugation or viscosity measurements." (DTX 1762 at TEV003017833.) Moreover, by May 4, 1988, the date of this report, Teva was already using copolymer-1 self-standards and had developed a molecular weight method based on those standards. (Sept. Tr. (Grant) 322:4-13, 1450:13-18, 1451:23-1452:3, 1462:18-23, 1569:7-11; Sept. Tr. (Scandella) 1307:22-1308:2; Sept. Tr. (Wall) 1828:21-1829:5; DTX 3275 at TEV000304999-5000.)

The second document Sandoz relies on is a September 9, 1988 report from W.R. Grace, which discusses the use of polyethylene glycol ("PEG") standards. (DTX 1269.) Sandoz contends that this document demonstrates that different standards yield different results for a copolymer-1 sample. At trial, however, Dr. Grant testified that W.R. Grace's task, as explained in the report, was to look at other analytical techniques and use them for the purpose of determining whether or not a batch of

copolymer-1 was active or toxic. (Sept. Tr. (Grant) 1455:24-1456:11.) While the report discusses PEG standards, it states that they were used for a relative molecular weight estimation ("vs. polyethylene glycol standards"). (DTX 1269 at TEV001090148.) Dr. Grant testified that one skilled in the art would not have believed that using PEG standards (without universal calibration) would give an accurate molecular weight for copolymer-1 because the person of skill would have known that the size-to-molecular-weight ratio of PEG is not the same as copolymer-1. (Sept. Tr. (Grant) 1457:20-24.)[26] The Court credits Dr. Grant's testimony.

Sandoz characterizes the W.R. Grace report as showing molecular weights of fractions of copolymer-1 batch 13 as ranging from 800 to 11,000 daltons using the PEG standards. But, as Dr. Scandella acknowledged, these values are for the copolymer-1 fractions, not the average molecular weight of the batch. (Sept. Tr. (Scandella) 1248:22-25.) Dr. Grant testified that the data have nothing to do with the peak molecular weight of a batch of copolymer-1. (Sept. Tr. (Grant) 1458:1-14.)

Sandoz also relies on the September 9, 1988 W.R. Grace report for its conclusion that vapor phase osmometry would yield

[26] On the other hand, Dr. Grant testified, PEG standards, which were commercially available in 1994, could have been used as universal calibration standards for copolymer-1. (Sept. Tr. (Grant) 1426:4-15, 1504:2-4; Sept. Tr. (Scandella) 1248:12-18.)

erroneous molecular weight values for copolymer-1. The portion of the document Sandoz cites, however, has nothing to do with SEC; it relates to an entirely different technology. As Dr. Grant testified, determining Mn using osmometry is completely different from determining Mp using SEC. (Sept. Tr. (Grant) 1570:8-12.) In addition, Dr. Grant pointed out that there are different types of osmometry, some of which would be appropriate in the context of this case and others that would not. Dr. Grant testified that vapor phase osmometry would not have been an appropriate method to measure the molecular weight of a copolymer-1 standard (Sept. Tr. (Grant) 1506:21-1507:9), but that membrane osmometry would have been more appropriate for copolymer-1 (Sept. Tr. (Grant) 1569:21-1570:7). Dr. Scandella, who testified that vapor phase osmometry was considered an appropriate method, failed to mention the existence of different kinds of osmometry, and conceded that he had not looked at the literature on the appropriateness of vapor phase osmometry. (Sept. Tr. (Scandella) 1318:14-1319:1.) Significantly, W.R. Grace itself acknowledged in the report that it did not believe vapor phase osmometry gave an accurate molecular weight of copolymer-1. (Sept. Tr. (Grant) 1459:5-11, 1460:8-13; DTX 1269 at TEV001090158.)

Because the scientists in the documents Sandoz relies on regarding batch 13 understood that the values they were

reporting were erroneous, Sandoz's argument regarding batch 13 fails.

Lastly, for all of Defendants' arguments regarding the different techniques that Teva used and the allegedly inconsistent results that Teva obtained, Defendants did not cite a single instance where Teva—or anyone for that matter—failed to accurately calculate the peak molecular weight or the molar fraction of copolymer-1.

vii. Universal Calibration

Defendants make several arguments regarding why universal calibration would not have enabled the patents-in-suit. Their first argument is that universal calibration was not identified in the patents-in-suit. This argument fails because a patent need not provide details that would be known and available to those of skill in the art. Singh v. Brake, 317 F.3d 1334, 1345 (Fed. Cir. 2003); see also Ajinomoto Co., 228 F.3d at 1345; United States v. Telectronics, Inc., 857 F.2d 778, 785 (Fed. Cir. 1988); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986). By 1994, universal calibration was well described in the literature and known to a person of ordinary skill in the art. (PTX 970 (Svec Dep.) at 296:16-297:6; Sept. Tr. (Grant) 1401:15-18, 1423:11-1430:7; 1431:24-1432:11; PTX 514 at 213-17; PTX 553 at 73-76.) At his

deposition, Dr. Svec, Sandoz's expert with experience in universal calibration, testified that universal calibration could be used to accurately determine the molecular weight of copolymer-1. (PTX 970 (Svec 05/21/2010 Dep.) at 388:8-12, 320:2-321:10, 326:14-327:10, 382:8-13, 384:23-385:6, 385:8-19.) Thus, there was no reason the patents needed to identify or mention universal calibration.

Defendants' second argument is that there is no evidence that Teva or its consultants ever used universal calibration despite the fact that they were aware of it. In support of this argument, Sandoz cites a May 23, 1988 memo from W.R. Grace. (DTX 3538 at TEV000360384.) The very fact, however, that Teva and its contractors were aware of universal calibration in 1988 merely proves that universal calibration was known and available long before 1994. In addition, Defendants offered no evidence regarding why Teva, although apparently aware of universal calibration, did not use it to measure the molecular weight of copolymer-1. Without any evidence on this issue, the Court is unable to draw any conclusions regarding why Teva did not use universal calibration.

Relying on Dr. Scandella's testimony, Defendants' third argument is that universal calibration was not a common technique in biotechnology in 1994 and 1995. (See Sept. Tr. (Scandella) 1284:13-18.) But neither Defendants nor Dr.

Scandella ever demonstrated a connection between copolymer-1 and biotechnology, or any other relevance of Dr. Scandella's testimony on this point with respect to the issues in this case. In addition, neither Defendants nor Dr. Scandella address the literature Dr. Grant described, which explained universal calibration and made it clear that universal calibration was a well-known technique in 1994. (Sept. Tr. (Grant) 1401:12-18; 1423:11-1430:7; PTX 514 at 213-17; PTX 553 at 73-76.) Moreover, neither Defendants nor Dr. Scandella addressed the fact that by 1994 universal calibration had been known and used for nearly three decades. For these reasons, Dr. Scandella's opinion does not support the position that universal calibration was not a well-known technique in 1994 for determining the molecular weight of copolymer-1.[27]

Defendants' final argument, based entirely on attorney argument, is that characteristics of copolymer-1 would impede a person of ordinary skill in the art from using universal calibration to accurately determine the molecular weight of copolymer-1. Quoting Dr. Scandella, who referenced "ion exchange interactions," Sandoz argues that factors other than size can influence retention time. (Sept. Tr. (Scandella) 1200:1-4.) But Dr. Scandella's testimony had no connection to

[27] As of 1994, Dr. Scandella had never used universal calibration. When asked why, he replied, "I never found a need for it." (Sept. Tr. (Scandella) 1285:1-4.)

universal calibration. Defendants presented no evidence at trial that any interactions occur between copolymer-1 and the column matrix or that there would have been any concerns about any such interactions on the part of a person of ordinary skill in the art in 1994. Defendants also failed to provide any evidence that "ion exchange interactions" were relevant to universal calibration.

Without any supporting explanation from an expert, Defendants quote one sentence from a 1989 article by Marc le Maire that states, "[o]ur data indicate that the concept of universal calibration requires several qualifications and can be used only as an approximation in most cases." (See DTX3353 at 51.) Dr. Scandella read this sentence into the record, but offered no expert opinion that it is relevant, in any way, to this case. (See Sept. Tr. (Scandella) 1287:14-1288:1.) In fact, neither Dr. Scandella nor any other expert in this case testified that universal calibration was not known and readily available, that it would not have worked, or that it would have taken undue experimentation to use the technique on copolymer-1 in 1994.

Pointing to Grant's testimony on direct examination, Sandoz also suggests that universal calibration applies only to flexibly coiled molecules (i.e., random coils). (Sept. Tr. (Grant) 1425:7-23).) However, neither Dr. Grant nor the

textbook about which he was questioned, states that universal calibration is limited to random coils. (See Sept. Tr. (Grant) 1425:1-6; see also PTX 514 at 213.) Defendants also introduced no evidence to this effect at trial. More importantly, both Dr. Grant and Defendants' expert, Dr. Svec, agreed that polypeptides in copolymer-1 are random coils, and both of them explained in detail why a person of ordinary skill in the art would have understood that to be the case in 1994. (See Sept. Tr. (Grant) 1425:12-23, 1427:1-9; see also PTX 970 (Svec 05/21/2010 Dep.) at 395:21-24, 396:16-397:8, 397:11-17, 397:24-398:15.)

Defendants contend that a Teva document indicates that copolymer-1 has a secondary structure and is not a random coil. (See DTX 1113 at TEV00312034.) Although that is what the document appears to state, the Court credits Dr. Grant's testimony that the document does not contain enough information for him to evaluate it. (Sept. Tr. (Grant) 1535:18-1536:11.) The Court also gives more weight to Dr. Grant's and Dr. Svec's opinion that polypeptides in copolymer-1 are random coils. (See Sept. Tr. (Grant) 1425:12-23, 1427:1-9; see also PTX 970 (Svec 05/21/2010 Dep.) at 395:21-24, 396:16-397:8, 397:11-17, 397:24-398:15.)

Defendants also point to another sentence in the le Maire article, which they did not even bother to have an expert read

into the record at trial, to argue that even if the structure of copolymer-1 were a random coil, the use of universal calibration would still be problematic. The sentence reads that the "ambiguity in defining the molecular radius of macromolecules such as random coils and long rods . . . represents an obstacle to universal calibration of gel columns." (DTX 3353 at 55.) The sentence does not say that universal calibration would not work with copolymer-1 or that using universal calibration would require undue experimentation. And, as explained above, Defendants provided no expert testimony to this effect at trial. Defendants essentially make this argument on attorney argument alone. As Teva points out, in another section of the le Maire paper, the authors indicate that universal calibration will work with random coils. The section states that "rather good agreement between the viscosity and gel chromatography data was obtained for dextran and proteins denatured with GuHCl [guanidine hydrochloride]. . . . For proteins denatured in 6 M GuHCl the peptide chain has been described as a random coil." (DTX 3353 at 55.) Without any expert testimony to resolve these seemingly inconsistent statements in the le Maire article, the Court cannot accept Defendants' argument.

viii. In re Wands Factors

Turning to In re Wands, with respect to the first factor—"the quantity of experimentation necessary"—the Court finds

that Defendants failed to provide clear and convincing evidence that the amount "of experimentation necessary" to accurately determine the average molecular weight or molecular weight distribution of a sample of copolymer-1, in 1994, was undue. The patents-in-suit specifically direct a person of ordinary skill in the art to use SEC. (PTX 1 at 3:6-8.) Although the patents-in-suit did not disclose the SEC calibration standards that Teva used, the evidence at trial established that, in 1994, the scientific literature on SEC, generally, and on both self-standards and universal calibration was extensive and would have been known to a person of ordinary skill in the art.[28] (See PTX 514 at 210-17; see also Sept. Tr. (Grant) 1400:16-19, 1401:9-11, 1401:15-18, 1408:25-1409:4, 1410:10-1413:23, 1414:8-1421:18, 1423:11-1430:7; PTX 566 at 37-44; PTX 970 (Svec Dep.) at 296:16-297:6; PTX 553 at 73-76.) Because "'[a] patent need not teach . . . what is well known in the art,'" the fact that the patents-in-suit did not disclose the SEC calibration standards that Teva used does not constitute clear and convincing evidence that accurately determining the average molecular weight or molecular weight distribution of a sample of copolymer-1 in 1994 would

[28] The extensive body of scientific literature, in 1994, regarding SEC generally and on both self-standards and universal calibration establishes that "the state of the prior art"—the fifth In re Wands factor—was well developed. See In re Wands, 858 F.2d at 737 (citation omitted). The "state of the prior art," accordingly, supports a finding of enablement.

have required undue experimentation. See, e.g., Falko-Gunter Falkner, 448 F.3d at 1365 (citation omitted).

The Court rejects Dr. Scandella's testimony that experimentation may have taken "several years." (Sept. Tr. (Scandella) 1227:21-1228:11; 1291:18-25.) As an initial matter, Dr. Scandella failed to address the extensive literature that existed in 1994 regarding SEC, self-standards, and universal calibration. (See PTX 514 at 210-17; see also Sept. Tr. (Grant) 1400:16-19, 1401:9-11, 1401:15-18, 1408:25-1409:4, 1410:10-1413:23, 1414:8-1421:18, 1423:11-1430:7; PTX 566 at 37-44; PTX 970 (Svec Dep.) at 296:16-297:6; PTX 553 at 73-76.) In addition, Dr. Scandella assumed, but never established, that Teva experimented with different standards and analytical methods because it could not accurately determine the molecular weight of copolymer-1. As explained above, Defendants never established why Teva experimented with different standards and analytical methods.

To the extent some experimentation was necessary to accurately determine the average molecular weight or molecular weight distribution of a sample of copolymer-1 in 1994, a fact Teva does not deny and the precise amount of which was not established at trial,[29] the law is well-settled that where the

[29] At his deposition, Varkony testified that he could not "say exactly if it" took "several weeks or more" for Teva to figure out how to calibrate SEC to determine the molecular weight of copolymer-1. (DTX 4022 at 110:10-18.)

level of skill in the art is high, as was the case here,[30] (Sept. Tr. (Grant) 189:22-190:6; PTX 986 at 3); Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9; Sept. Tr. (Zeiger) 809:10-811:15; DTX 4030 at 4), "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered 'undue.'" See Falko-Gunter Falkner, 448 F.3d at 1365 (internal quotation marks omitted); see also Chiron Corp., 363 F.3d at 1253 ("[t]he fact that some experimentation is necessary does not preclude enablement") (citations and internal quotation marks omitted). In view of the patents-in-suit reference to "a calibrated gel filtration column (Superose 12)," (PTX 1 at 3:7-8), and the extensive literature in 1994 regarding SEC, self-standards, and universal calibration, "'a considerable amount of experimentation is permissible'" here. See PPG Indus., Inc., 75 F.3d at 1564 (citation omitted).

ix. The Patents-in-Suit Provided Sufficient Direction or Guidance

The patents-in-suit specifically direct a person of ordinary skill in the art to use SEC. (PTX 1 at 3:6-8.) In addition to this explicit directive, the evidence at trial established that, in 1994, there was extensive scientific literature on SEC, self-standards, and universal calibration,

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[30] "[T]he relative skill of those in the art" is the sixth In re Wands factor. 858 F.2d at 737 (citation omitted).

which would have been known to a person of ordinary skill in the art. (See PTX 514 at 210-17; see also Sept. Tr. (Grant) 1400:16-18, 1401:9-11, 1401:15-18, 1414:8-1418:6, 1419:13-1421:3, 1421:4-18, 1423:11-1430:7; PTX 566 at 37-44; PTX 970 (Svec Dep.) at 296:16-297:6; PTX 553 at 73-76.) In view of this extensive body of scientific literature, the Court finds that the patent specification's instruction to use SEC would have been sufficient guidance for a person of ordinary skill in the art to accurately determine the average molecular weight and molecular weight distribution of a sample of copolymer-1 in 1994.

Example 1 of the patent explicitly discloses the use of SEC to determine the average molecular weight of copolymer-1 samples. (PTX 1 at 2:51-3:18.) The example discloses that the molecular distribution of the copolymer-1 samples was determined using a calibrated size exclusion chromatography column. (PTX 1 at 3:9-18.) The fact that the patents-in-suit include a working example supports a finding of enablement. See, e.g., In re Wands, 858 F.2d at 740 (finding no undue experimentation, where disclosure presents working examples).

Defendants argue that copolymer-1 is complex. This argument fails, however, because, in 1994, high molecular weight copolymer-1 was known in the prior art. In addition, the concept of molecular weight and the measurement of molecular

weight using SEC were well known in 1994.[31] There was also a significant quantity of scientific literature describing SEC and its use for determining the molecular weight of polydisperse polymers such as copolymer-1. Under these circumstances, there is nothing about the nature of the claimed invention that supports a finding that the claims are not enabled.

Defendants argue that the "chemical arts" are unpredictable, and that no prior art provides any guidance on making the claimed invention because the claimed molecular weight ranges are relative to the SEC standards chosen by the patentees. A significant body of scientific literature, however, described molecular weight determination using SEC in 1994. In addition, Defendants presented no evidence of unpredictability relating to measuring the peak molecular weight of copolymer-1. Quoting a case that states that the "chemical arts" are unpredictable does not establish that the use of SEC with respect to copolymer-1 was unpredictable. As described above, there is no evidence that a person of skill in the art would have needed to know the specific SEC standards used by the patentees in order to make and use copolymer-1 within the scope of the claims without undue experimentation. See Koito Mfg. Co.

[31] The fact that high molecular weight copolymer-1 was known in the prior art, coupled with the fact that there was an extensive body of scientific literature, in 1994, regarding SEC generally and on both self-standards and universal calibration, demonstrates that "the state of the prior art" was well developed. See In re Wands, 858 F.2d at 737 (citation omitted).

Ltd. v. Turn-Key-Tech, LLC, 381 F.3d 1142, 1156 (Fed. Cir. 2004); see also Telectronics, 857 F.2d at 785; Hybritech, 802 F.2d at 1384.

To the extent Defendants argue that the specification must enable one of ordinary skill in the art to make Copaxone®, the Court rejects this argument. Copaxone® is a pharmaceutical product with an average molecular weight between 5,000 and 9,000 daltons. The patents-in-suit enable a person of ordinary skill in the art to make copolymer-1 with an average molecular weight within that range. Copaxone®, however, the commercial product, has many additional characteristics besides molecular weight. Contrary to Defendants' argument, there is simply no requirement that the patents enable a person of ordinary skill in the art to match all of the characteristics of Copaxone®.[32]

D. INDEFINITENESS

i. General Principles

Since patents are "presumed to be valid, the evidentiary burden to" prove indefiniteness "is one of clear and convincing evidence." See Young v. Lumenis, Inc., 492 F.3d 1336, 1345 (Fed. Cir. 2007) (citation omitted). To satisfy Section 112's "definiteness requirement, the boundaries of the claim, as

[32] To the extent the Court has not explicitly addressed the seventh and eighth In re Wands factors above, the Court finds that Defendants failed to present any persuasive evidence that "the predictability or unpredictability of the art" or "the breadth of the claims" supports a finding of lack of enablement. 858 F.2d at 737 (citation omitted).

construed by the court, must be discernible to a skilled artisan based on the language of the claim, the specification, and the prosecution history, as well as her knowledge of the relevant field of art." Power-One, Inc. v. Artesyn Techs., Inc., 599 F.3d 1343, 1350 (Fed. Cir. 2010) (citation omitted). A claim is indefinite when it "is 'not amenable to construction or [is] insolubly ambiguous.'" Id. (citation omitted). "[A] claim is not indefinite merely because it poses a difficult issue of claim construction." Id. (citation omitted). "'[I]f the meaning of the claim is discernible, even though the task may be formidable and the conclusions may be one over which reasonable persons will disagree, . . . the claim [is] sufficiently clear to avoid invalidity on indefiniteness grounds.'" Id. (citation omitted). In addition, "the fact that some experimentation may be necessary to determine the scope of the claims does not render the claims indefinite." Exxon Research & Eng'g Co. v. United States, 265 F.3d 1371, 1379 (Fed. Cir. 2001) (citation omitted).

ii. None of the Asserted Claims Are Indefinite

Defendants argue that the Court's construction of the molecular weight terms as being measured using an "appropriately calibrated suitable gel filtration column" results in an insoluble ambiguity because there were different ways to "appropriately" calibrate an SEC column, and because the

different calibrations would not yield the same molecular weight values. Accordingly, Defendants argue, all of the claims that contain the limitation "copolymer-1 having a molecular weight" or "average molecular weight" or that are a "molar fraction" or "species" claims are indefinite.

The Court finds, as an initial matter, that "appropriate" standards are those that yield "accurate" molecular weight measurements. (See Sept. Tr. (Grant) 1505:17-22.) A measurement is "accurate" if it reflects the actual molecular weight of the sample. (See Sept. Tr. (Grant) 218:12-14; see also PTX 970 (Svec 5/21/2010 Dep.) at 321:5-10.) As the Court found and explained above, in 1994, there were at least two ways to accurately measure the molecular weight of copolymer-1 using SEC—namely, self-standards and universal calibration. (See Sept. Tr. (Grant) 1399:18-1400:13; PTX 990 at 2.) SEC is the only method mentioned in the patents-in-suit, and the only method that can generate a peak molecular weight and a molecular weight distribution (Sept. Tr. (Scandella) 1205:20-1206:1)—and all of the experts agreed that SEC can give an accurate molecular weight for copolymer-1. (See Sept. Tr. (Grant) 217:23-218:14, 1399:18-1400:13, 1421:19-1422:8, 1430:8-1431:23, 1462:18-23; PTX 970 (Svec 5/21/2010 Dep.) at 320:2-321:10; Sept. Tr. (Scandella) 1312:2-14; PTX 209 at SDZ00002017-18; PTX 349 at SDZ00017948-49.)

Defendants failed to present clear and convincing evidence that a person of ordinary skill in the art using SEC with appropriate calibration could not achieve consistent and reproducible molecular weight values. To the extent Defendants point to outlier measurements of copolymer-1 in Teva's internal documents, as the Court found and explained above, those batches were recognized as erroneous in the contemporaneous documents. In addition, with respect to batches that used protein standards, those standards were inappropriate because they do not provide accurate molecular weights.

In the final analysis, the evidence presented at trial shows that a person of skill in the art in 1994 would have known how to appropriately calibrate an SEC column to obtain accurate molecular weight values for copolymer-1. Accordingly, the Court finds that none of the asserted claims are indefinite.

E. OBVIOUSNESS

Defendants argue that the patents-in-suit would have been obvious to a person of ordinary skill in the art as of May 24, 1994, the filing date of the '037 application. Defendants claim that copolymer-1 falling within the claimed average molecular weight range, or having the claimed molecular weight distribution, would have been obvious based on the teaching in the prior art. They also argue that certain process limitations

to make copolymer-1 within the desired molecular weight—such as the use of HBr in acetic acid—were obvious.

i. General Principles

Obviousness is a question of law based on underlying factual questions. Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1300 (Fed. Cir. 2007). "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.

To determine whether a claim is obvious, the Court must consider "(1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) evidence of secondary factors, also known as objective indicia of non-obviousness." Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd., 533 F.3d 1353, 1356 (Fed. Cir. 2008). The first three factors "comprise the so-called prima facie case" of obviousness. Mitsubishi Chem. Corp. v. Barr Labs., Inc., 718 F. Supp. 2d 382, 425 (S.D.N.Y. 2010), aff'd, 435 Fed. Appx. 927 (Fed. Cir. 2011).

With respect to the contents of the prior art, the question is "whether the teachings of the prior art, taken as a whole,

would have made obvious the claimed invention." In re Gorman, 933 F.2d 982, 986 (Fed. Cir. 1991). The well-established rule is that an invention is obvious in light of the prior art if "a person of ordinary skill in the art would have had motivation to combine the prior art references and would have had a reasonable expectation of success in doing so." Wyers v. Master Lock Co., 616 F.3d 1231, 1238 (Fed. Cir. 2010) (en banc) (citations omitted). Where the invention has elements that were described in the prior art, "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007).

Where prior art would lead a person of skill away from the invention, the art is said to "teach away" from the invention. DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1327 (Fed. Cir. 2009). The patent holder can rebut a prima facie case of obviousness by showing that the prior art taught away from the invention. Whether the prior art taught away from the invention is a question of fact. Spectralytics, Inc. v. Cordis Corp., 649 F.3d 1336, 1343 (Fed. Cir. 2011).

A patent holder can also rebut a prima facie case of obviousness with evidence of secondary considerations of non-obviousness. Transocean Offshore Deepwater Drilling, Inc. v.

Maersk Contractors USA, Inc., 617 F.3d 1296, 1304-05 (Fed. Cir. 2010). Such evidence includes the extent of commercial success of the patented invention, unexpected properties of the invention, whether the invention satisfies a long-felt need, whether others have failed to find a solution to a problem addressed by the patent, and any copying of the invention by others. See Transocean Offshore Deepwater Drilling, Inc., 617 F.3d at 1304-05; Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1380 (Fed. Cir. 2006).

The party asserting invalidity on the ground of obviousness must prove by clear and convincing evidence 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." 35 U.S.C. § 103; Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007). In evaluating whether the patent challenger has carried its burden, courts are wary of arguments based on improper hindsight. See In re NTP, Inc., 654 F.3d 1279, 1298-99 (Fed. Cir. 2011).

ii. The Scope and Content of the Prior Art

In this context, "prior art" includes art that is analogous to the claimed invention. In re Bigio, 381 F.3d 1320, 1325 (Fed. Cir. 2004). The Court finds the following facts in connection with the scope and content of the prior art.

1) The '550 Patent

The patents-in-suit refer to the '550 patent as a source of the procedure for making copolymer-1. (PTX-1 at 2:15-17) ("[c]opolymer-1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in U.S. Pat. No. 3,849,550"); id. at 2:54-56 ("[t]wo batches of copolymer-1 were prepared according to the methods known in the art, for example, U.S. Pat. No. 3,849,550").)

The '550 patent, which issued to Yeda on November 19, 1974, describes compositions of several copolymers, including copolymer-1. The '550 patent states that the disclosed copolymers generally have a molecular weight "in excess of 10,000, and preferably above about 18,000" daltons. (Sept. Tr. (Grant) 1435:4-1437:19; Sept. Tr. (Zeiger) 839:18-840:18; PTX 26, col. 1:57-68.)

The only specific disclosure of copolymer-1 in the specification of the '550 patent appears in column 2, lines 19-30 of the patent specification. (Sept. Tr. (Grant) 1435:4-1437:19; Sept. Tr. (Zeiger) 933:14-934:18; PTX 26, col. 2:19-30.) There, the '550 patent describes a preferred copolymer, which is copolymer-1, having "a molecular weight of about 20,000 to 25,000" daltons. (Sept. Tr. (Grant) 1436:17-1437:9; Sept. Tr. (Zeiger) 933:21-934:4; PTX 26, col. 2:19-30.)

The '550 patent does not state how the average molecular weights reported in the patent were determined or the

methodology used to generate the measurement. (Sept. Tr. (Grant) 1434:13-16, 1438:2-7; Sept. Tr. (Zeiger) 939:6-19, 956:10-957:13, 958:23-959:3.) The '550 patent contains no disclosure, teaching, or data regarding the molecular weight distribution or molar fractions of any copolymer. (Sept. Tr. (Grant) 1434:13-16, 1438:16-19; 1439:7-24, 1441:1-25; Sept. Tr. (Zeiger) 956:10-18, 957:2-6; PTX 26; PTX 320 at MYL0000616.)

The examiners of each of the patents-in-suit considered the '550 patent extensively during prosecution of the patents-in-suit. (See, e.g., PTX 14 at TEV000309018; PTX 15 at TEV000309103; PTX 17 at TEV000304221; PTX 18 at TEV000310385; PTX 19 at TEV000304453; PTX 20 at TEV000304582; PTX 21 at TEV000308838.) Ultimately, there were no obviousness rejections based on the '550 patent. (PTX 13 at TEV000304151-152; PTX 13-21.)[33]

2) EP '620 Patent Application

European Patent Application No. 0383620 ("the EP '620 Application"), filed by Repligen Corporation on February 16, 1990 and published on August 22, 1990, discloses a biological

[33] During the prosecution of the '808 patent, the examiner rejected then-pending claims 17-20 as prima facie obvious in view of the '550 patent. (See PTX 13 at TEV000304138-144.) The applicants were able to overcome the obviousness rejection over the '550 patent by arguing that the '550 patent did not raise a prima facie case of obviousness by pointing out to the examiner that the '550 patent did not teach or suggest the claimed invention. (PTX 13 at TEV000304151-152.) The applicants did not rely on secondary considerations or unexpected results to overcome the obviousness rejection based on the '550 patent. (See PTX 13 at TEV000304151-152, 162-167.)

process for making genes encoding polypeptides involving the use of recombinant DNA technology. (Sept. Tr. (Grant) 1445:4-22, 1446:23-1447:14; Sept. Tr. (Zeiger) 972:15-20; DTX 1970, p. 11, ll. 32-34.) The process described in the EP '620 Application does not involve the chemical synthesis of N-carboxyanhydrides. (Sept. Tr. (Grant) 1445:4-22, 1446:23-1447:14; Sept. Tr. (Zeiger) 972:15-20; DTX 1970, p. 2, ll. 50-55.)

The EP '620 Application contains no disclosure or teaching regarding a molecular weight distribution or molar fractions of copolymer-1. (Sept. Tr. (Grant) at 1448:17-19; see generally DTX 1970.) The EP '620 Application does not disclose any copolymers having an "average molecular weight" of 5,000 daltons. (Sept. Trial (Grant) 1447:15-1448:10; Sept. Trial (Zeiger) 977:17-20.) Further, the EP '620 Application does not disclose measuring the average molecular weight of any copolymer using size exclusion chromatography, i.e., using an appropriately calibrated suitable gel filtration column. (Sept. Trial (Grant) 1448:11-13; Sept. Trial (Zeiger) 976:15-23.)

3) The Teitelbaum 1971 Article and 1974 Abstract

As described above, Professor Ruth Arnon and her colleagues at the Weizmann Institute discovered copolymer-1 in the 1960s, and first published their research on copolymer-1 in the 1971 Teitelbaum article. Because copolymer-1 was modeled after

myelin basic protein, Professor Arnon and her colleagues aimed for an average molecular weight of about 23,000 daltons. July Tr. (Arnon) 309:21-311:8. The 1971 Teitelbaum article described copolymer-1 as having an average molecular weight of 23,000 daltons. (July Tr. (Arnon) 311:24-312:22; PTX 499 at 242.)

In September 1974, Professor Arnon and her colleagues at the Weizmann Institute published an abstract reporting that copolymer-1 had been found to suppress EAE, a biological model for multiple sclerosis. (PTX 509 at 1172.) The abstract stated that copolymer-1 has a molecular weight of 23,000 daltons. (PTX 509 at 1172.) The abstract further reported that copolymer-1 compositions with molecular weights lower than 17,000 daltons or higher than 50,000 daltons "proved ineffective for the treatment of EAE." (July Tr. (Arnon) 312:23-313:18; Sept. Tr. (Grant) 1442:8-1444:9; PTX 509 at 1172-1173.)

At trial, Dr. Arnon explained that this statement would have deterred a person of ordinary skill in the art from lowering the molecular weight of copolymer-1, (July Tr. (Arnon) 312:23-313:18, 316:25-317:11, 333:7-22), and Dr. Grant concurred with this reading from the perspective of a person of ordinary skill in the art. (Sept. Tr. (Grant) 1442:8-1444:9.) The Court credits that testimony.

4) Prior Art Regarding the Use of HBr/acetic Acid To Achieve Desired Molecular Weight

As discussed, the patentees discovered and described in the patents-in-suit that the process of using HBr in acetic acid during the debenzylation stage would cleave the polypeptides during polymerization and could therefore be used to control the molecular weight of the resulting copolymer-1. (Sept. Tr. (Sampson) 1641:8-23.) The patentees also discovered that a copolymer-1 composition with a predetermined molecular weight profile could be synthesized by varying the time and temperature of the debenzylation reaction using the HBr in acetic acid. (Sept. Tr. (Sampson) 1641:18-1642:8; PTX 1, col. 4:48-col. 6:3.)

Dr. Sampson's testimony at trial, which this Court credits over Dr. Zeiger's testimony to the contrary, was that a person of skill in the art would not have been motivated to use HBr in acetic acid to cleave the peptide bonds in copolymer-1 polypeptides to control the molecular weight of a copolymer-1 sample because the prior art as a whole taught that peptide bonds would not be cleaved during exposure to HBr/acetic acid. (Sept. Tr. (Sampson) 1642:9-1643:6, 1646:22-1647:10, 1689:22-1690:11.) As Dr. Sampson explained, HBr/acetic acid was a standard deprotecting agent used during the synthesis of polypeptides. In those cases, cleavage of the polypeptide chain would need to be minimized or avoided altogether. One of ordinary skill attempting to make polypeptides would not have been motivated to use a reagent that would break polypeptides.

(Sept. Tr. (Sampson) 1642:9-1643:6, 1646:22-1647:10, 1655:13-1656:4; PTX 488.)

The two prior art references that mention the use of HBr/acetic acid during the synthesis of copolymer-1, the '550 patent and the 1971 Teitelbaum article, describe using HBr/acetic acid only for the purpose of debenzylation. (Sept. Trial Tr. (Sampson) 1651:20-1652:11, 1653:4-1655:12; PTX 26, col. 2:53-64; PTX 499 at 243.) Neither of these references mention peptide bond cleavage during the debenzylation step, nor do they mention the use of HBr in acetic acid to control the molecular weight of the resulting copolymer-1 product. (Sept. Trial Tr. (Sampson) 1651:20-1652:11, 1653:4-1655:12; PTX 26; PTX 499.)

Dr. Sampson testified that a person of ordinary skill in the art would have understood that the Weizmann scientists controlled molecular weight by adjusting the ratio of initiator to N-carboxyanhydrides of the respective amino acids during polymerization. (Sept. Trial Tr. (Sampson) 1652:12-1656:4; PTX 499; DTX 1783.)

Meanwhile, a well regarded and widely circulated 1963 paper by Nobel laureate Bruce Merrified stated that peptide bond cleavage would not occur upon exposure to Hbr/acetic acid. J. Am. Chem. Soc., 85: 2149-54 (1963) ("Merrifield 1963"); (PTX 488.) Dr. Merrified had specifically investigated whether

peptide cleavage took place after treatment with HBr/acetic acid in conditions similar to those described in the patents-in-suit (18 hours at 25 celcius) and he found no cleavage. (Sept. Trial Tr. (Sampson) 1644:20-1647:10; PTX 488 at 2151, 2153.)

Similarly, Yaron and Berger, "Multi-Chain Polyamino Acids Containing Glutamic Acid, Aspartic Acid and Proline," Biochimica et Biophysica Acta, 107: 307-332 (1965) ("Yaron & Berger 1965") (DTX 1934), reported that no cleavage of peptide bonds was detected when HBr/acetic acid was used for debenzylation carried out at 2 degrees for 3 days. (Sept. Trial Tr. (Sampson) 1650:7-1651:9; Sept. Trial Tr. (Zeiger) 851:9-853:3; 1685:13-22; PTX 1934.) The authors reported that under those conditions, they were able to obtain 100 percent deprotection of benzyl groups and avoid peptide bond cleavage. (Sept. Trial Tr. (Sampson) 1650:7-1651:9; 1685:13-22; Sept. Trial Tr. (Zeiger) 851:9-853:20; PTX 1934.)

Additionally, Yaron and Berger, "Multichain Polyamino Acids of Well Defined Degrees of Polymerization," Bulletin of the Research Counsel of Israel: Section A, Chemistry, 7A(2):96-97 (1958) ("Yaron & Berger 1958") (DTX 3233), investigated whether peptide bond cleavage occurred when HBr in acetic acid was used to deprotect benzyl groups during the synthesis of copolymers. The authors concluded that "no degradation in the side chains occurred during debenzylation with HBr in glacial acetic acid at

2 degrees for three days." (Sept. Trial Tr. (Sampson) 1650:7-1651:9; Sept. Trial Tr. (Laird) 1146:9-1147:6.) As Dr. Sampson explained, this meant that no peptide bonds had been cleaved even after three days of exposure to HBr/acetic acid.

According to both Dr. Sampson and Sandoz's own expert Dr. Laird, the time and temperature of 2 degrees for three days reported in Yaron and Berger 1958 would be equivalent, through the application of a well-known chemical rule of thumb, to about 22-25 degrees for about 17-18 hours, conditions similar to those reported in the patents-in-suit. (Sept. Trial Tr. (Laird) 1146:9-1147:6; Sept. Trial Tr. (Sampson) 1650:7-1651:9, 1685:13-1686:18; PTX 1934 at 318; PTX 3233 at 97.) Since no cleavage was observed in the conditions used in Yaron and Berger 1958, one of ordinary skill in the art in 1994 would similarly expect that use of HBr in acetic acid for 17 hours at 25°C, as described in Example 4 of the patents-in-suit, would likewise result in no cleavage of peptide bonds. (Sept. Trial Tr. (Sampson) 1685:13-1686:18; DTX 1934 at 318.)

Two of the other prior art references relied on by the Defendants—the Katchalski and Sela reference and the Hayashi reference—discuss the use of HBr for debenzylation purposes in compounds other than copolymer-1, but they contain no independent or original observations concerning peptide bond cleavage. These references simply report discussion of

suspected bond cleavage from earlier literature (Sept. Trial Tr. (Sampson) 1647:11-1648:10), and neither mentions the use of HBr/acetic acid to control molecular weight. (See Sept. Trial (Sampson) 1647:25-1648:10, 1653:10-1655:8; Sept. Trial (Zeiger) 820:17-821:4; DTX 1781; DTX 1783.) Moreover, Hayashi 1985 does not even discuss the use of HBr in acetic acid. (Sept. Trial (Laird) 1150:16-1151:12; DTX 1781 at 464.)

The remaining prior art references relied on by the Defendants discuss possible peptide bond cleavage based upon an observed change in the molecular weight of a peptide after the use of HBr. These references—which include two papers published by Idelson and Blout in 1956 and 1958, and a reference by Appelquist and Doty published in 1962—contain no direct observation or testing to determine whether, in fact, peptide bond cleavage had occurred and whether HBr was responsible for such cleavage. (Sept. Trial Tr. (Sampson) 1648:11-1650:6; DTX 1934 at 317-318 n.21, 331 n.21; DTX 1855; DTX 1784.) At most, the Nylund and Miller 1965 reference states that "the degree of polymerization was always lowered during debenzylation [treatment with HBr in acetic acid]" and concludes that this result is due to "peptide bond cleavage by HBr . . ., thus broadening the molecular weight distribution." (DTX 1784 at 3541.)

iii. Secondary Considerations of Non-obviousness

Multiple sclerosis was first recognized as a distinct disease in the 1860s. (Sept. Tr. (Lisak) 88:8-89:18.) By the early 1990's, there was still no effective treatment that could slow the progress of the disease. (Sept. Tr. (Lisak) 102:2-9, 131:14-136:19; PTX 523; PTX 538; PTX 565; PTX 591.) In 1994, the only disease-modifying treatment available for multiple sclerosis was Betaseron®, an interferon treatment that is ineffective in about 40% of multiple sclerosis patients and that causes significant side effects, including liver and bone marrow problems, depression, and a flu-like syndrome. (Sept. Tr. (Lisak) 125:25-126:3, 103:3-104:2, 104:11-105:18.)[34]

Copaxone®—Teva's copolymer-1 treatment for RRMS—was introduced in 1997. It works differently from interferon treatments and is able to effectively treat many of the patients for whom that treatment is ineffective. (Sept. Tr. (Lisak) 103:3-104:2, 118:9-119:7; 127:15-130:25; PTX 667, PTX 671; see also PTX 963 (B. Rao 9/30/2010 Dep.) at 226:23-228:13 (testifying that Copaxone® has "a better side-effect profile"

[34] Defendants argue that, as of 1986, copolymer-1 had been approved for treatment of patients with RRMS and adduced testimony at trial that in 1994, the need for an effective treatment for RRMS patients was therefore met by the copolymer-1 administered during the Bornstein clinical trial and approved by the FDA for administration to humans. (Sept. Tr. 1362:14-1368:19 (Green).) Because copolymer-1 was not brought to market until 1997, however, the Court finds that, regardless of the reason, there remained a need for effective multiple sclerosis treatments in 1994.

and "a better therapeutic efficacy profile" as compared to the interferon treatments).)

Dr. Grant testified that, based on the data he had seen from Copaxone® certificates, analysis, and calculations, Copaxone® meets the average molecular weight, copolymer-1 molar fraction, and TFA-copolymer-1 limitations of the asserted claims. (PTX 105, PTX 349 at SDZ00017948-949; PTX 392 ; PTX 990 at "Copolymer-1 Molar Fraction Limitations-Copaxone" and "TFA Copolymer-1 Molar Fraction Values-Copaxone"; Sept. Tr. (Grant) 1468:5-1477:15.) Dr. Lisak's testimony at trial also demonstrates that Copaxone® meets the limitations related to treatment of multiple sclerosis. (Sept. Tr. (Lisak) 137:4-147:22; Sept. Tr. (Gokel) 1589; PTX 206; PTX 697; PTX 734.) Dr. Gokel further explained that Teva uses the same process steps that are in the patents-in-suit to make Copaxone®. (Sept. Tr. (Gokel) 1584:9-1590:20.)

Additionally, the testimony at trial was that annual sales of Copaxone® have grown nearly 100-fold from $25 million in 1997 to approximately $2.25 billion in 2010. (Sept. Tr. (Congleton) 49:8-12, 59:18-20.) Sales of Copaxone® in the United States have steadily grown and overtaken sales of its interferon competitors during this time and it has become the treatment of choice for RRMS by nearly a factor of two. (Sept. Tr. (Congleton) 50:12-51:2.) Since its introduction, total sales

for Copaxone® have exceeded $10 billion, despite constant pressure from competitors. (Sept. Tr. (Congleton) 59:21-23, 66:6-7.) Approximately 100,000 patients are currently using Copaxone® to treat their multiple sclerosis. (Sept. Tr. (Congleton) 51:19-22.)

Dr. Lisak, Plaintiff's expert in multiple sclerosis and its treatment, (Sept. Tr. (Lisak) 87:24-88:6), explained that his Copaxone® prescriptions have increased over time because of its clinical advantages over the competing treatments. (Sept. Tr. (Lisak) 119:8-120:9.)

Dr. Lisak's testimony at trial also discussed several failed attempts to develop multiple scelorsis treatments, including Isoprinisone and prednisone; immunosuppressant treatments such as Roquinimex, Gusperimus, Sulfasalazine, and Cladribine (a chemotherapy drug); cytokine modulators Lenercept, Infliximab, and TGF-β2; antigen-derived therapies like oral bovine myelin and Tiplimotide; and monoclonal antibodies, including Muromonab-CD3, Priliximab, and Antova. (PTX 523; Sept. Tr. (Lisak) 132:18-24, 132:25-133:4; PTX 627; Sept. Tr. (Lisak) 133:5-7; PTX 591; Sept. Tr. (Lisak) 133:7-12; PTX 617; Sept. Tr. (Lisak) 133:23-134:6; PTX 623; Sept. Tr. (Lisak) 134:7-10; PTX 60; Sept. Tr. (Lisak) 134:11-14; PTX 6165; Sept. Tr. (Lisak) 134:15-21; PTX 644; Sept. Tr. (Lisak) 134:22-25; PTX

62; Sept. Tr. (Lisak) 135:3-8; PTX 565; Sept. Tr. (Lisak) 135:3-8; PTX 644; Sept. Tr. (Lisak) 135:9-13; PTX 99.)

iv. The Prior Art Does Not Teach Copolymer-1 Compositions with the Claimed Average Molecular Weight Characteristics

Defendants contend that the '550 Patent and the EP '620 Application were prior art suggesting that the claimed copolymer-1 compositions would have been obvious to a person of ordinary skill in the art.

The evidence does not support a conclusion that a person of ordinary skill would read the '550 patent to disclose copolymer-1 of 10,000 daltons and above. While there is no dispute that the '550 patent, in column 1, uses the number 10,000 daltons, (Sept. Tr. (Grant) 1435:4-1437:19; Sept. Tr. (Zeiger) 930:4-931:23), there is insufficient evidence that a person of ordinary skill in the art would understand that molecular weight to apply particularly to copolymer-1 rather than to any of the other copolymers disclosed in the '550 patent.

As Dr. Grant explained, the '550 patent does not disclose copolymer-1 of 10,000 daltons. Rather, in Column 1, lines 57-68, the '550 patent generally discloses that copolymers can be in excess of 10,000 daltons and preferably above 18,000 daltons. (Sept. Tr. (Grant) 1435:2-1436:16; PTX 26, col. 1:57-68.) The patent then explicitly discloses an example of copolymer-1 between 20,000 and 25,000 daltons and claims copolymer-1 between

15,000 and 25,000 daltons. (Sept. Tr. (Grant) 1436:17-1437:19; PTX 26, col. 2:19-30, col. 3:24 - col. 4:23; Sept. Tr. (Zeiger) 930:4-931:23.) Dr. Grant explained that a person of ordinary skill in the art, reviewing this patent as a whole, would conclude that it disclosed copolymer-1 specifically only in the molecular weight range of 15,000 to 25,000 daltons. (Sept. Tr. (Grant) 1437:10-19.)

Defendants rely on Dr. Zeiger's testimony at trial. However, the testimony to which Defendants point actually supports Dr. Grant's reading of the '550 patent. Dr. Zeiger agreed that the reference in the '550 patent to "copolymers . . . in excess of 10,000 daltons" was not a specific reference to copolymer-1. (Sept. Tr. (Zeiger) 932:9-12.) Dr. Zeiger further testified that the preferred molecular weight of the copolymers discussed in column 1 of the '550 patent was "above 18,000 daltons," (Sept. Tr. (Zeiger) 840:16-18), but that the '550 patent taught that due to manufacturing variability, results might be as low as 10,000 daltons. (Sept. Tr. (Zeiger) 841:13-24.) Dr. Zeiger also explained that a person of ordinary skill would "shoot[] for" a molecular weight of 18,000 daltons, but might get a batch as low as "in excess of 10,000 daltons":

> Q. How does that person of ordinary skill in the art approach the disclosures of the process in the '550 patent to produce to the preferred range, what are the factors - what does he look at?

> A. Well, the polymerization, as I mentioned, is going to give some batch-to-batch variability in terms of molecular weight. The fact that the preferred range is above 18,000 would indicate that that's what the patentees are shooting for, but nonetheless they fully acknowledge that they may get something as low as in excess of 10,000.

(Sept. Tr. (Zeiger) 843:9-18.) Dr. Zeiger thus agreed that the '550 patent teaches a person of ordinary skill in the art to target, or "shoot for" higher molecular weights. Lastly, Dr. Zeiger testified only generally about all of the "copolymers" disclosed in the '550 patent; he offered no testimony that the '550 patent as a whole would be interpreted to disclose copolymer-1 of 10,000 daltons. His testimony is therefore insufficient to prove, by clear and convincing evidence, that a person of ordinary skill would interpret the '550 patent to disclose copolymer-1 of 10,000 daltons.

Like the '550 patent, the EP '620 Application does not disclose copolymer-1 compositions with an average molecular weight of about 5,000 to about 9,000 daltons. The EP '620 Application is not even directed to copolymer-1 compositions, as the term "copolymer-1" has been interpreted by the Court. (Sept. Tr. (Grant) 1445:4--1447:-14; Sept. Tr. (Zeiger) 972:15-20; DTX 1970, p. 2, ll. 50-55, p. 11, 1.32-1.34.) Instead, the EP '620 Application is directed to discrete polypeptides made through recombinant DNA technology and identifes a preferred

molecular weight for these individual polypeptides of 15,000 to 23,000 daltons. (Sept. Tr. (Grant) 1448:20-1449:19; Sept. Tr. (Zeiger) 972:15-20, 977:8-978:3; DTX 1970, p. 5, ll. 28-33.)

The Court therefore concludes that, based on the teachings of the '550 patent and the EP '620 Application, a person of ordinary skill in the art would have no reason to select or to make a copolymer-1 composition in the specific average molecular weight range of about 5 to 9 kilodaltons, or within the ranges of "about 4 to about 9 kilodaltons," or 6.25-8.4 kilodaltons.

This is consistent with Teitelbaum 1974, which expressly teaches away from copolymer-1 with an average molecular weight below 17,000 daltons, identifying such a composition as "ineffective" for the treatment of EAE."[35] (July Tr. (Arnon) 312:23-313:18; Sept. Tr. (Grant) 1442:8-1444:9; PTX 509 at 1172-1173.)

v. There Is No "Overlap" in Average Molecular Weight Ranges or Molar Fraction Limitations

The Court rejects Defendants' argument that they have established prima facie obviousness by demonstrating "overlapping" molecular weight ranges between the claimed

[35] Defendants refer to Bornstein 1987 as a piece of art that post-dates Teitelbaum 1974 and establishes that compositions as low as 14,000 daltons were clinically safe and effective. (PTX-31 at 408.) Notwithstanding that teaching, in view of the prior art as a whole, the Court finds that it does not suggest any reason that a person of ordinary skill would change, adjust or lower the average molecular weight of copolymer-1 to the claimed ranges.

copolymer-1 compositions and the copolymer-1 compositions of the prior art.

Defendants' overlap theory is that the '550 patent disclosed copolymer-1 compositions with an average molecular weight of 10,000 daltons or above, which would have the same copolymer-1 polypeptides in almost the same amount as a composition of 5,000 to 9,000 daltons; therefore, a person of ordinary skill would have believed that a copolymer-1 composition with an average molecular weight of about 5,000 to 9,000 daltons would have the same properties as a copolymer-1 composition of 10,000 daltons or above.

In the first instance, as stated above, the Court does not find that the '550 Patent taught a copolymer-1 composition having an "average molecular weight" of 10,000 daltons. Therefore, the average molecular weight ranges disclosed in the relevant prior art—the '550 Patent—do not overlap with any of the claimed ranges.

Even if the '550 patent taught a copolymer-1 composition with an average molecular weight of 10,000 daltons, which it does not, that composition does not overlap with a peak average molecular weight range of 5-9 kilodaltons, about 4-9 kilodaltons or 6.25-8.4 kilodaltons.

In order for an overlap claim to succeed, the prior art must disclose a range that overlaps a claimed range. Lazare

Kaplan Int'l, Inc. v. Photoscribe Techs., Inc., 628 F.3d 1359, 1380-81 (Fed. Cir. 2010) ("[A] prior art reference that discloses a range that encompasses or overlaps a claimed range generally is sufficient to establish a prima facie case of invalidity.") (emphases added). So here, where the claims are directed to an average molecular weight, Defendants must establish that the prior art discloses an average molecular weight that overlaps with the claimed range. See In re Huai-Hung Kao, 639 F.3d 1057, 1066-67 (Fed. Cir. 2011) (requiring that "the claimed range of dissolution rates actually overlaps with the dissolution rate disclosed in [prior art reference]"); In re Kumar, 418 F.3d 1361, 1364 (Fed. Cir. 2005) (analyzing overlap issues for claim directed to average particle size by analyzing the average particle size of the prior art).

Dr. Zeiger admitted during cross examination that there is no overlap between the claimed average molecular weights (i.e., peak molecular weights) and the average molecular weight disclosed in the '550 patent (even with his interpretation of the '550 patent as disclosing copolymer-1 with an average molecular weight of 10,000 daltons). (Sept. Tr. (Zeiger) 938:11-15; 941:8-16.)

Accordingly, with respect to all of the claims directed to average molecular weights, Defendants have not shown an overlap.

Nor is there evidence of any overlap between the prior art and the claimed molar fraction ranges. Those claim limitations require, for example, that more than 75% of the molar fraction of copolymer-1 molecules have a molecular weight between 2,000 and 20,000 daltons or that less than 5% of the molar fraction of copolymer-1 molecules have a molecular weight above 40,000 daltons. (PTX 4, col. 5: 21-col. 6:8; PTX 9, col. 5:41-50.) To establish an overlap on that claim element, then, Defendants must identify a prior art disclosure of a molar fraction of copolymer-1 that overlaps or encompasses the claimed molar fraction ranges, i.e., a prior art reference disclosing percentages of copolymer-1 polypeptide species between 2,000 and 20,000 daltons in a range that overlaps with the range of "more than 75%."

Defendants have not presented reliable evidence to establish such overlap. Defendants only asked Dr. Zeiger to state whether he would expect a person of ordinary skill in the art to believe that there was a "high" percentage of species between 2,000 and 20,000 daltons for a batch of copolymer-1 with an average molecular weight between 10,000 and 15,000 daltons. (See, e.g., (Sept. Tr. 987:8-12 (Zeiger).) That testimony does not establish what percentage of copolymer-1 molecules, on a molar fraction basis, have molecular weights between 2,000 to 20,000 daltons.

To compensate for its lack of evidence of overlap, Mylan attempts to rely on the law of inherency. In this regard, Mylan claims that it is inherent in the compositions' properties that copolymer-1 batches having similar average molecular weights would have had substantial overlap in their molecular weight profiles. It argues that such "inherent properties" are, as a matter of law, considered part of the prior art and therefore within the general knowledge of a person of ordinary skill in the art.

The Court rejects this argument as it is unsupported by the evidence. For one, Mylan has not presented any evidence that the molecular weight distribution of every batch of copolymer-1 made pursuant to the prior art would have the purported overlap, or even that copolymer-1 would have an "inherent" molecular weight distribution.

Moreover, no molar fraction data can be derived from the '550 patent. To determine what percentage of species falls within a particular range requires knowing the overall distribution of all the species in the sample. (See Sept. Tr. (Grant) 228:12-230:7.) But, as Dr. Zeiger admitted, there is no disclosure in the '550 patent of (i) the molar fractions of any type of molecule, (ii) a molecular weight distribution for any copolymer, or (iii) data from which one could calculate the molar fractions for a copolymer-1 sample. (Sept. Tr. (Zeiger)

956:10-957:13.) Accordingly, the '550 patent cannot disclose an overlapping range for any molar fraction claim limitation.

At most, Mylan presented evidence of a limited number of examples in which the molecular weight distribution of samples of copolymer-1 made pursuant to the disclosure of the '550 patent yields a large percentage of species between 2,000 and 20,000 daltons. (Sept. Tr. 879:1-16 (Zeiger); DTX-1704-R at TEV003004347; Sept. Tr. 905:17-21 (Zeiger); DTX-1704-R at TEV003004349.) Such examples (even if correctly characterized) do not establish that every batch of copolymer-1 made pursuant to the processes disclosed in the '550 patent would have greater than 75% of its copolymer-1 molecules, on a molar fraction basis, having molecular weights between 2,000 and 20,000 daltons.

To establish inherency, Mylan must prove that an attribute is necessarily present each time the prior art is practiced. See Trintec Indus., Inc. v. Top-U.S.A. Corp., 295 F.3d 1292, 1295 (Fed. Cir. 2002) ("Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art."). Against this standard, citing a few examples where overlap might occur is legally insufficient to establish that the claimed molar fractions inherently overlap with the molar fractions of the prior art. See also Glaxo Inc. v. Novopharm Ltd., 52 F.3d

1043, 1047-48 (Fed. Cir. 1995) (holding no inherent disclosure of claimed crystalline polymorph by prior art patent where practicing disclosed prior art method could produce claimed polymorph or alternative unclaimed polymorph); W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 1554 (Fed. Cir. 1983) ("Anticipation of inventions set forth in product claims cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references.").

vi. The Defendants Have Not Demonstrated Evidence of Any Reason or Motive to Alter the Molecular Weight of Copolymer-1

Even if Defendants had established an overlapping range, in order to establish a prima facie case based on such theory in the context of this case, Defendants would additionally need to demonstrate a reason for a person of ordinary skill in the art to change the molecular weight of copolymer-1 to the claimed ranges. KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 418 (2007) (confirming that it remains "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does, [as] most, if not all, instances rely upon building blocks long since unconvered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known"); Genetics Inst., LLC v. Novartis

Vaccines & Diagnostics, Inc., 655 F.3d 1291, 1304 (Fed. Cir. 2011).

Here, as in Genetics Inst., LLC, in the field of the patents-in-suit, it cannot be said that a person of ordinary skill in the art would arrive at the invention by the standard course of optimizing variables within a claimed range. Id. at *1305-06 (noting that despite some overlap, "the nontrivial differences in the proteins at issue compel the requirement of identifying a reason for the chemical modification"). Rather, in the field at issue, there is a broad range disclosed in the prior art and, accordingly, there must be a reason identified as to why a person of ordinary skill would select a lower average molecular weight or the claimed molar fractions.

Mylan's cited testimony supports no such conclusion. Mylan relies upon Dr. Zeiger, who testified:

> Q. . . . And what would the person of ordinary skill have expected in 1994 concerning the chemical and biological properties of two batches of copolymer-1 that had substantial overlap in their molecular weight profiles?
>
> A. I would have expected him to perhaps anticipate with an overwhelming or an extremely large percent of sizes in common, that there would be similar biological properties. This is clearly not a one-on-one absolute kind of level, but I would have expected him to anticipate this.

(Sept. Tr. (Zeiger) 873:2-10).) This testimony, unsupported by any citation to a publication or prior art, cannot carry the Defendants' burden on this issue.

There is no other testimony that there would necessarily be an "overwhelming" or "extremely large" overlap of species, or even an explanation of what that means.

Mylan also relies on Dr. Rice's testimony that it was known that changing molecular weight can influence toxicity. However, Dr. Rice admitted during cross-examination that a person of ordinary skill would not have an expectation whether toxicity would increase or decrease by varying molecular weight, only that it could change. (Sept. Tr. (Rice) 1047:14-1048:6.)

The Court therefore concludes that the testimony at trial does not provide clear and convincing proof that a person of ordinary skill would have been motivated to create copolymer-1 in the claimed ranges.

vii. The Claimed Ranges Do Not "Abut" the Prior Art

Defendants also argue that, even if the molecular weight ranges of the prior art do not overlap with the claimed ranges, they are sufficiently close or "abutting" such that the Court should find prima facie obviousness on this basis alone.

Even if the '550 Patent discloses a peak average molecular weight of 10 kilodaltons—and the Court has found that it does not—the "average molecular weight" ranges of the claims and the

'550 patent do not "abut" a range of "about 5 to 9 kilodaltons," "about 4 to about 9 kilodaltons" or "6.25-8.4 kilodaltons." With respect to the peak average molecular weight ranges, in order to abut, prior art and claimed ranges must literally touch. See e.g., In re Woodruff, 919 F.2d 1575, 1576, 1578 (Fed. Cir. 1990) (disclosed range of "about 5%" abutted claimed range of "more than 5%").

A court will only find prima facie obviousness in this context if the ranges are so close that a person of ordinary skill in the art would expect that the properties of such different compounds would be the same. See Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 783 (Fed. Cir. 1985) (finding ranges to be close because a person of ordinary skill would expect similar properties).

Here, Defendants have presented no evidence that a person of ordinary skill would expect the properties of compounds with different molecular weights to be the same. Mylan's analysis of what a person of ordinary skill in the art would expect is grounded on an analysis of documents that Mylan admits are not prior art. (Sept. Tr. (Zeiger) 941:17-944:1, 945:6-12.) The Court finds that Dr. Zeiger's testimony, recounted above, concerning the overlap of species within a copolymer-1 mixture, are irrelevant to the question of whether a person of ordinary skill would consider the molecular weight disclosure of the '550

patent close to, or abutting, the claimed ranges and does not establish that a person of skill would expect similar biological properties between the claimed weight ranges and those in the prior art. And Dr. Zeiger's unsupported speculation that a person of skill might "perhaps anticipate" similar biological properties is insufficient to carry Defendants' clear and convincing burden of proof. See Star Scientific, Inc., 655 F.3d at 1376 (a prior art reference's "speculative and tentative disclosure of what 'might' or 'may' [happen] does not sufficiently direct or instruct one of skill in th[e] art").

With respect to the molar fraction limitations, as stated, the Court finds that there is no explicit or inherent molar fraction in the prior art. Accordingly, it is impossible to establish any relationship, whether overlapping, abutting or otherwise, of the claimed molar fraction attribute and the prior art.

Nor can the EP '620 Application support an "abutting" range theory because, again, it discloses neither copolymer-1 nor an average molecular weight for copolymer-1. (Sept. Tr. (Grant) 1444:13-1448:16; Sept Tr. (Zeiger) 884:23-885:4, 972:15-20, 975:9-23, 976:15-23; DTX 1970, p.2, l. 50.)

viii. The Prior Art "Taught Away" from Molecular Weights in the Claimed Ranges

Even if Defendants had established a prima facie case of obviousness based on a theory of overlapping or abutting ranges, which the Court does not find, Plaintiff has rebutted such case by showing that the prior art taught away from the invention. See Iron Grip Barbell Co. v. USA Sports Inc., 392 F.3d 1317, 1322 (Fed. Cir. 2004).

Teitelbaum 1974 explicitly taught away from copolymer-1 with an average molecular weight below 17,000 daltons, calling them ineffective for treatment of EAE. (July Tr. (Arnon) 312:23-313:18; Sept. Tr. (Grant) 1442:8-1444:9; PTX 509 at 1172-1173.) And, as described, the '550 Patent and the EP '620 Application expressed preferences for higher molecular weights.

Defendants point to the Bornstein studies and Bornstein 1987 which, they claim, taught that having an average molecular weight as low as 14,000 daltons was safe and effective. (PTX-31 at 408, 413-414.) However, Defendants do not offer any explanation of why, notwithstanding the Bornstein research, a person of ordinary skill in the art would believe that copolymer-1 of 5-9 kilodaltons would be active in light of the clear teaching away in Teitelbaum 1974 and the preferences for higher weight copolymer expressed in the '550 Patent and the EP '620 Application.

ix. The Claimed Weight Characteristics of the Patents-in-Suit Are Not Obvious

Because a person of ordinary skill in the art would not have found obvious a copolymer-1 having the claimed average molecular weight or molar fraction limitations, Defendants have failed to prove by clear and convincing evidence that the following claims are invalid for obviousness: claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1 and 6 of the '847 patent, claims 1-3 of the '430 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, claims 1 and 8 of the '098 patent, and claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent.[36]

Claims 1-3 of the '898 patent are not addressed to a specific numerical limitation on the molecular weight of copolymer 1, but rather require a "predetermined molecular weight profile." However, because Defendants have not presented evidence of any reason or motive for a person of ordinary skill in the art to adjust the weight of copolymer-1 to the predetermined molecular weight in those claims, they have not

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[36] The Court rejects Defendants' argument of judicial estoppel, which they raised post trial. The Defendants essentially argue that Teva admitted during the prosecution of the asserted patents that the '550 Patent teaches copolymer-1 of 10 kilodaltons, and so Teva is now estopped from arguing that a molecular weight of 10 kilodaltons is not in the prior art.

"Judicial estoppel applies when a party takes a later position that is inconsistent with a former position in the same dispute, on which the party had been successful and had prevailed based on the former position." Honeywell Int'l, Inc. v. Hamilton Sundstrand Corp., 523 F.3d 1304, 1315 (Fed. Cir. 2008) (citation omitted). "Judicial estoppel is an equitable doctrine invoked by a court at its discretion." Cacace v. Meyer Mktg. (Macau Commer. Offshore) Co., 812 F. Supp. 2d 547, 564 n.17 (S.D.N.Y. 2011) (citation omitted). The Court finds that Defendants have failed to satisfy multiple prongs of the judicial estoppel doctrine, and therefore will not, in its discretion, invoke that doctrine.

demonstrated by clear and convincing evidence that they are prima facie obvious either. See KSR Int'l Co., 550 U.S. at 418-19.[37]

x. The Claimed Process for Making Copolymer-1 in HBr/Acetic Acid Is Not Obvious

Even if Defendants had proven by clear and convincing evidence that a person of ordinary skill in the art would have tried to make a copolymer-1 with the claimed average molecular weights or molecular weight molar fractions, there is nothing to suggest that such person would have attempted to use HBr in acetic acid to achieve that molecular weight or molar fraction.

The only two references that Drs. Zeiger and Laird introduced regarding the use of HBr in acetic acid for synthesizing copolymer-1 were the '550 patent and the Teitelbaum 1971 article. But neither of these references mention peptide cleavage during the debenzylation step, nor do they mention the use of HBr in acetic acid to control the molecular weight of the resulting copolymer-1 product. (Sept. Tr. (Sampson) 1651:20-

[37] The Court also rejects Defendants' attempt to establish a prima facie case of obviousness based on "structural similarity" in chemical structures and properties between the prior art and the claimed compounds. To establish obviousness of a chemical compound, the Federal Circuit now requires that a defendant identify a "lead compound," that is, a compound with which a person of ordinary skill would start the analysis. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343-45 (Fed. Cir. 2000); Takeda Chem. Indus., Ltd., 492 F.3d at 1357-60. Here, Defendants have failed to identify any such compound; therefore, their argument fails.

1652:11, 1653:4-1655:12; PTX 26, col. 2 ll.53-64; PTX 499 at 243.)

Dr. Zeiger, Mylan's expert, testified that the person of ordinary skill in the art would find references suggesting possible cleavage of peptide bonds following the use of HBr in acetic acid by following a "trail" of six references: (i) the '550 patent; (ii) Teitelbaum 1971; (iii) Ben-Ishai and Berger; (iv) Yaron and Berger; (v) Idelson and Blout; and (vi) Nylund and Miller. (Sept. Tr. (Zeiger) 817:19-818:17, 826:25-827:22, 945:14-952:15, 951:23-952:15.) However, this trail includes no prior art publication explaining that the amount of cleavage of a peptide bond could be controlled such that a "predetermined molecular weight profile" could be achieved by using HBr/acetic acid.

There was no evidence to show that a person of skill in the art would have been motivated to try to control peptide cleavage by changing the time and temperature of the reaction. The opinions of Defendants' experts are based on hindsight. Dr. Laird and Dr. Zeiger cite to references reporting that the use of HBr in acetic acid for debenzylation could potentially result in some peptide cleavage. (Sept. Tr. (Laird) 1139:10-1142:9; (Sept. Tr. (Zeiger) 859:22-860:5.).) But neither Dr. Laird nor Dr. Zeiger offered any explanation why the person of ordinary skill in the art would seek to use the debenzylation reaction,

or HBr in acetic acid, to cleave the peptides during the process for making copolymer-1 in view of the prior art. (Sept. Tr. (Laird) 1155:4-23; Sept. Tr. (Zeiger) 817:19-818:17, 945:14-952:15.)

Rather, the evidence shows that a person of skill in the art would not have been motivated to use HBr in acetic acid to cleave the peptide bonds in copolymer-1 polypeptides in order to control the molecular weight of a copolymer-1 sample. As previously noted, Dr. Sampson testified that HBr in acetic acid was used as a step in the synthesis of polypeptides, where the cleavage of the polypeptide chain would be viewed negatively, as something that would need to be minimized or avoided altogether. (Sept. Tr. (Sampson) 1642:9-1643:6, 1646:22-1647:10, 1655:13-1656:17, 1683:16-19; PTX 488.) That testimony is consistent with the prior art relied on by Defendants, which shows that the alleged cleavage disclosed was, at best, an undesirable side reaction, not something that would be viewed as a tool to be used to decrease the molecular weight of copolymer-1. (Sept. Tr. (Sampson) 1642:9-20, 1655:13-1656:4; Sept. Tr. (Laird) 1139:22-1140:8; 1154:2-1155:12.)

Moreover, as explained in detail by Dr. Sampson, Merrifield's 1963 paper carefully considered and studied whether HBr/acetic acid, under conditions similar to those disclosed in the patents-in-suit, would cleave peptide bonds. Merrifield

concluded that it would not. (Sept. Tr. (Sampson) 1644:20-1647:10; PTX 488 at 2151, 2153.) Dr. Zeiger's testimony that the person of ordinary skill in the art would ignore the Merrifield 1963 article because it did not directly address whether HBr in acetic acid could cleave a specific type of peptide - a gamma-benzyl glutamic acid containing peptide - is not credible. That testimony is directly refuted by the testimony of Dr. Laird that the person of ordinary skill in the art would not focus on benzyl containing peptide bonds because all peptide bonds are closely similar. (Sept. Tr. (Laird) 1151:18-25.) Moreover, Dr. Zeiger's focus on gamma-benzyl glutamic acid containing peptides is based on hindsight. Dr. Zeiger did not provide any reason why a person of ordinary skill in the art would conclude that gamma-benzyl glutamic acid bonds is the site of cleavage in protected copolymer-1 polypeptides treated with HBr in acetic acid, nor did Dr. Zeiger identify any reason that a person of skill in the art would have focused on the gamma-benzyl glutamic acid bond other than the fact that it is found in copolymer-1.

In view of the prior art as a whole, the Court concludes that Defendants have failed to establish that there would have been any motivation to adjust the molecular weight of copolymer-1, or that it would have been obvious to do so through the use of the HBr/acetic acid step. Therefore, the Court concludes that

Defendants have failed to prove that the use of Hydrobromic (HBr) acid in acetic acid to cleave peptide bonds in order to control molecular weight would have been obvious to a person of ordinary skill in the art in May 1994. While it was known in the art that HBr in acetic acid could be used for debenzylation, a reaction to remove the benzyl protecting group from an amino acid, such as glutamic acid, there was no prior art disclosure that this reagent could also depolymerize polypeptides to control the average molecular weight.

Certain asserted claims of the patents-in-suit include specific time and temperature limitations. Those include claims 2 and 3 of the '898 patent and claims 2 and 3 of the '430 patent. Defendants have also failed to prove that the person of ordinary skill in the art would have been motivated to select or would have selected any particular time and temperature for the HBr/acetic acid step or that a person of ordinary skill in the art would have had any expectation that selecting a particular time and temperature for performing the HBr in acetic acid deprotection reaction would affect the resulting average molecular weight or molar fractions of the copolymer-1 product. (Sept. Tr. (Sampson) 1644:20-1647:10; 1685:13-1686:18; PTX 488 at 2151, 2153; DTX 1934 at 318.)[38] Thus, Defendants have also

[38] The Court does not believe that Defendants have proven by clear and convincing evidence that it would have been obvious to a person of ordinary skill in the art in May 1994 to select the recited time and temperature

failed to establish that the person of ordinary skill in the art would have selected a time of 10-50 hours and a temperature of 20-28°C or a time of about 17 hours and a temperature of about 26°C for the reaction of protected copolymer-1 with HBr in acetic acid, as recited in claims 2 and 3 of the '898 patent and claims 2 and 3 of the '430 patent. Defendants have therefore failed to demonstrate the obviousness of these claims by clear and convincing evidence.

Claims 1-3 of the '898 patent, which require obtaining a "predetermined molecular weight profile" through the use of HBr in acetic acid would similarly not have been obvious. Defendants have not established by clear and convincing evidence that a person of ordinary skill would have been motivated to set a predetermined molecular weight profile for copolymer-1 or that it would have been obvious that such a molecular weight profile could be controllably achieved through treatment of protected copolymer-1 with HBr in acetic acid.

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conditions to arrive at a particular average molecular weight or molar fraction of copolymer-1 during a process of routine optimization or experimentation of two common chemical reaction variables. Defendants' arguments in this regard are based on hindsight and are rejected. As set forth in detail above, a person of ordinary skill in the art would have had no reason to vary the molecular weight profile of copolymer-1. Moreover, the prior art achieved the higher disclosed molecular weight without using the HBr/acetic acid step to control or adjust the molecular weight. (Sept. Tr. (Sampson) 1642:9-1643:6, 1646:22-1647:10, 1652:12-1656:17, 1689:22-1690:11.) Defendants thus identified no reason a person of ordinary skill in the art would affirmatively use HBr/acetic acid to control or adjust the molecular weight of copolymer-1.

xi. Secondary Considerations of Non-obviousness

There are also secondary considerations that support the Court's conclusion that the asserted claims are not obvious. Secondary considerations "may often be the most probative and cogent evidence [of non-obviousness] in the record." Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed. Cir. 1983).

1) Commercial Success

The commercial success of an embodiment of the claimed invention is strong evidence of its non-obviousness. See Graham v. John Deere Co., 383 U.S. 1, 17 (1966); Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957 (Fed. Cir. 1997) (evidence of commercial success may be "highly probative of the issue of nonobviousness"). To establish commercial success, a patentee must show significant sales in the relevant market and a nexus to the claimed invention (that the success was due to the patented invention). Rolls-Royce, PLC v. United Tech. Corp., 603 F.3d 1325, 1340 (Fed. Cir. 2010).

"[I]f the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus." Brown & Williamson Tobacco Corp. v. Phillip Morris, Inc., 229 F.3d 1120, 1130 (Fed. Cir. 2000). A successful product is "coextensive" with the

claimed invention when it is commensurate in scope with the patented invention, as opposed to only a "component of a commercially successful" product. Mitsubishi Chem. Corp., 718 F. Supp. 2d at 436, 437 (finding a pharmaceutical formulation "coextensive" with the asserted claims where it was an "inextricable and essential part of what doctors are prescribing" and "not a part that can be separated out from the remainder of the product").

As described above, sales of Copaxone® in the United States have steadily grown and overtaken sales of its competitors such that it is now the treatment of choice by nearly a factor of two. Since its introduction, total sales for Copaxone® have exceeded $10 billion, despite constant pressure from competitors.

There is a nexus between Copaxone® and the claimed invention—Copaxone® is coextensive with the asserted claims, as the claimed invention is "an inextricable and essential part of what doctors are prescribing" when they prescribe the product. See id. at 437.

Defendants have failed to present any evidence that Copaxone®'s success was related in any way to extraneous factors such as marketing or advertising, or due to features known in the prior art. In the absence of such evidence, Defendants have failed to rebut the presumed nexus. Ecolochem, Inc. v. S. Cal.

Edison Co., 227 F.3d 1361, 1378 (Fed. Cir. 2000); Brown & Williamson Tobacco Corp., 229 F.3d at 1130 ("The presumed nexus cannot be rebutted with mere argument; evidence must be put forth."); Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 1393 (Fed. Cir. 1988) ("[I]t is thus the task of the challenger to adduce evidence to show that the commercial success was due to extraneous factors . . . . [A]rgument and conjecture are insufficient." (internal quotation marks and citation omitted)).

Therefore, the Court concludes that Copaxone® is a commercial success, which finding supports its conclusion that the asserted claims were not obvious.

2) Long-felt, Unmet Need

"Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness." In re Dow Chem. Co., 837 F.2d 469, 472 (Fed. Cir. 1998) (citation omitted). "The existence of an enduring, unmet need is strong evidence that the invention is novel, not obvious, and not anticipated. If people are clamoring for a solution, and the best minds do not find it for years, that is practical evidence—the kind that can't be bought from a hired expert, the kind that does not depend on fallible memories or doubtful inferences—of the state of knowledge." In re Manhurkar Double Lumen Hemodialysis Catheter Patent Litig., 831 F. Supp. 1354,

1378 (N.D. Ill. 1993), aff'd, 71 F.3d 1573 (Fed. Cir. 1995). Where there is a long-standing need in the medical community for a safe and effective treatment for a particular disease, an invention that fulfills that need is often deemed non-obvious. See Eli Lilly & Co. v. Zenith Goldline Pharmas., Inc., 471 F.3d 1369, 1380 (Fed. Cir. 2006) ("The record shows a long-felt need for a safer, less toxic, and more effective clozapine-like drug."); Pfizer, Inc. v. Ranbaxy Labs. Ltd., 405 F. Supp. 2d 495, 518 (D. Del. 2005) (finding that, despite other products available on the market, "Lipitor® satisfied a long-felt need in the medical community to provide patients with more effective statins to help them achieve their LDL goals"), rev'd on other grounds, 457 F.3d 1284 (Fed. Cir. 2006).

The facts show that by 1994, there remained a long, unmet need for an effective, safe, and tolerable disease-modifying treatment for RRMS. (Sept. Tr. (Lisak) 125:25-127:14.) The introduction of Copaxone® thus fulfilled long-felt, unmet needs for: (a) an additional effective, safe, and tolerable treatment for RRMS; (b) a treatment for RRMS with a unique mechanism of action that worked differently than interferons; and (c) a treatment that had a milder side effect profile than the interferons. (Sept. Tr. (Lisak) 125:25-128:25.) Copaxone®'s fulfillment of each of these long-felt needs are secondary considerations that further support a finding of non-obviousness

concerning the asserted claims of the patents-in-suit. See Eli Lilly & Co, 471 F.3d at 1380 (Fed. Cir. 2006); Pfizer, Inc., 405 F. Supp. 2d at 518.

3) Failure of Others

The repeated failure of others to solve a problem addressed by an invention is further confirmation of the invention's non-obviousness. See Graham, 383 U.S. at 17 (noting that the "failure of others" is a secondary consideration of non-obviousness). In the pharmaceutical industry, the failure of others to develop a safe and effective drug often supports the non-obviousness of a drug that finally achieves success. See, e.g., Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 21 F. Supp. 2d 366, 374 (S.D.N.Y. 1998), aff'd, 231 F.3d 1339 (Fed. Cir. 2000) (stating that the evidence showing that "the pharmaceutical industry at large was attempting to improve upon existing [anti-ulcer drugs] with only a small number of producers coming close to success" supports a finding of non-obviousness); Eli Lilly & Co. v. Zenith Goldline Pharm., 364 F. Supp. 2d 820, 832 (S.D. Ind. 2005), aff'd, 471 F. 3d 1369 (Fed. Cir. 2006).

Evidence was presented at trial of drugs that showed initial promise for the treatment of multiple sclerosis, but that failed because of lack of efficacy or significant side effects. (Sept. Tr. (Lisak) 131:14-136:19; PTX 99; PTX 523; PTX

538; PTX 591; PTX 605; PTX 616; PTX 617; PTX 623; PTX 626; PTX 627; PTX 644.) The patents-in-suit are directed to the problem of developing an effective, safe, and tolerable treatment for multiple sclerosis. Each of the failed attempted therapies were similarly aimed at finding an effective, safe, and tolerable treatment for multiple sclerosis. Copaxone®'s success in light of these failed attempts provides further confirmation of the non-obviousness of the asserted claims. See Yamanouchi Pharm. Co., 21 F. Supp. 2d at 374; Eli Lilly & Co., 364 F. Supp. at 832; see also Uniroyal, Inc., 837 F.2d at 1054 (recognizing the "well established principle that the failure of others to provide a feasible solution to a long standing problem is probative of nonobviousness") (citation omitted).

4) Unexpected Results

Unexpected superior properties or advantages of an invention also indicate non-obviousness. Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 993 (Fed. Cir. 2009). As the Federal Circuit has explained, "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." In re Mayne, 104 F.3d 1339, 1343 (Fed. Cir. 1997) (citation omitted). Unexpected results may be shown with proof that (1) there is a difference between the results obtained and the closest prior art, and (2) the differences would not have been expected by one skilled in the

art at the time of the invention. Procter & Gamble Co., 566 F.3d at 997-98.

The unexpected reduced toxicity of a drug as tested on animal models supports a finding of non-obviousness. See, e.g., Procter & Gamble Co. v. Teva Pharms. USA, Inc., 536 F. Supp. 2d 476, 487-88, 495-96 (D. Del. 2008) (unexpected reduced toxicity demonstrated using a "short term toxicity screen" with rats), aff'd, 566 F.3d 989 (Fed. Cir. 2009); Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 417 F. Supp. 2d 341, 357-58, 385-86 (S.D.N.Y. 2006) (unexpected lower toxicity demonstrated in mice and rat testing, as well as an in vitro chick lens assay).

The record establishes that low molecular weight copolymer-1 was unexpectedly superior to the prior art copolymer-1. The in vivo and in vitro toxicity data generated by the Weizmann scientists and Teva showed that the claimed lower molecular weight copolymer-1 had unexpectedly lower toxicity than higher molecular weight copolymer-1 batches. (See, e.g., July Tr. (Arnon) 333:18-334:2; July Tr. (Pinchasi) 32:1-6, 33:6-35:5, 46:21-47:8, 48:4-49:11, 55:7-58:21, 59:1-70:11; PTX 54; PTX 53; PTX 40.) Dr. Baird considered these and other data, and explained that they established a trend of decreasing toxicity with decreasing molecular weight. (July Tr. (Baird) 603:20-605:18, 607:10-608:15; PTX 34T; PTX54; PTX 887 at 44.) Dr. Pinchasi also described the existence of this trend and stated

that the relationship between molecular weight and toxicity was "very unexpected" since nothing in the literature pointed the development team in that direction. (July Tr. (Pinchasi) 32:1-6.) Defendants' toxicology expert, Dr. Susan Rice, agreed that one of skill in the art would have no expectation with respect to how lowering the molecular weight of copolymer-1 would impact toxicity. (Sept. Tr. (Rice) 1046:25-1047:7.)[39]

The Court accepts this testimony as evidence of unexpected results. See, e.g., Merck Sharp & Dohme Pharms., SRL v. Teva Pharms. USA, Inc., No. 07-1596, 2009 WL 3153316, at *17, *52 (D.N.J. Aug. 19, 2009) (scientists involved in the development of montelukast found the compound to be surprisingly effective); W.R. Grace & Co.-Conn. v. InterCat, Inc., 7 F. Supp. 2d 425, 463-64 (D. Del. 1997), aff'd, 155 F.3d 572 (Fed. Cir. 1998) (activity of a composition "was a complete surprise" to inventors and others involved in the development). The lower toxicity of the low molecular weight copolymer-1 is thus an unexpected result that provides further support for a finding of non-obviousness regarding the asserted claims. See Procter & Gamble Co., 536 F. Supp. 2d at 487-88; Takeda Chem. Indus., Ltd., 417 F. Supp. 2d at 357-58, 385-86.

[39] The court discounts Dr. Rice's testimony that the entirety of toxicity data does not evidence unexpected results, as Dr. Rice failed to consider all the data, and instead based her opinion solely on what was presented in the patent specification and in the April 1994 Data Table. (See Sept. Tr. (Rice) 1042:12-1043:1.)

5) Copying

Even though Defendants are ANDA filers, their deliberate copying of the inventions provides additional evidence of non-obviousness. DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1328-29 (Fed. Cir. 2009); Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1285-86 (Fed. Cir. 2000). "The fact that copying is likely to be present in many Hatch-Waxman Act cases does not allow the court to ignore the copying as evidence of nonobviousness" and, in fact, in the field of new drug design, "the very need for copying results from and emphasizes the unpredictability of medicinal chemistry." Eli Lilly & Co. v. Zenith Goldline Pharms., No. IP 99-38, 2001 WL 1397304, at *14 (S.D. Ind. Oct. 29, 2001); see also Sanofi-Aventis Deutschland GmbH v. Glenmark Pharms., Inc., No. 07-cv-5855, 2011 WL 383861, at *9 (D.N.J. Feb. 3, 2011) ("Copying, as secondary considerations evincing non-obviousness, is [an] important part of demonstrating non-obviousness even in a pharmaceutical patent case against an ANDA filer because an ANDA filer is not required to copy.") (emphasis in original).

Both Sandoz and Mylan attempted to develop alternative processes to manufacture copolymer-1 without infringing claims of the patents-in-suit, but both ultimately settled on following the claimed methods. (PTX 966 (Ray Dep.) at 78:8-84:10, 112:3-119:5; PTX 963 (B. Rao 9/30/2010 Dep.) at 39:25-44:2.)

This evidence of copying further supports a finding that the claims of the patents-in-suit are not obvious.

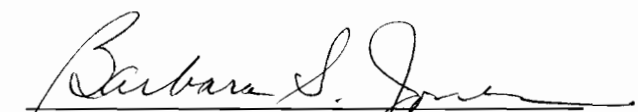
The Court has considered all of the Defendants' remaining arguments and has found them to be without merit.

CONCLUSION

For the reasons provided above, the Court finds that both Mylan's and Sandoz's ANDA infringe all of the asserted claims, and that none of the asserted claims are invalid or unenforceable.

Teva is ordered to submit a proposed judgment incorporating the rulings contained in this Opinion and Order to the Court on or before July 2, 2012.

SO ORDERED:



BARBARA S. JONES
UNITED STATES DISTRICT JUDGE

Dated: New York, New York
June 22, 2012