UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IMMUNEX CORP., *et al.*, v. SANDOZ INC., *et al.*	Civil Action No.: 16-1118 (CCC) **OPINION**

CECCHI, District Judge.

This patent case was brought by Plaintiffs Immunex Corporation ("Immunex"), Amgen Manufacturing, Limited ("Amgen"), and Hoffman-La Roche, Inc. ("Roche") (collectively, "Plaintiffs") against Defendants Sandoz Inc., Sandoz International GmbH and Sandoz GmbH (collectively, "Defendants"). Specifically, this action relates to the validity of claims 11-12 and 35-36 of U.S. Patent No. 8,063,182, which covers the fusion protein etanercept, the active ingredient in Immunex's product Enbrel® (Joint Trial Exhibit ("JTX")-1[1] ("the '182 Patent")), and claims 3, 8, and 10 of U.S. Patent No. 8,163,522, which covers Enbrel®'s method of manufacture (JTX-2 ("the '522 Patent")) (collectively, the asserted claims of the "Patents-in-Suit"). *See* ECF No. 18 ¶ 9. Enbrel® is a brand name biologic drug primarily used to treat rheumatoid arthritis. Id. ¶¶ 43, 45; ECF No. 688 at 11 ¶ 38.

The Court held a two-week bench trial in this matter that began on September 11, 2018 and concluded on September 25, 2018. ECF Nos. 621-622, 627, 629-635. The parties submitted post-trial briefing and proposed findings of fact and conclusions of law through early November 2018. ECF Nos. 648 (*corrected at* 651-2 ("PFOF")), 647 (*corrected at* 649-2 *and subsequently corrected at* 650-1 ("DFOF")), 645 (*corrected at* 651-1 ("Pls. Br.")), 646 (*corrected at* 649-1 *and*

[1] JTX refers to the joint trial exhibits submitted by the parties. These exhibits have been mutually agreed to as admissible.

subsequently corrected at 650-2 ("Defs. Br.")). On November 6, 2018, the parties submitted response briefs. ECF Nos. 653 ("Pls. Reply Br."), 652 ("Defs. Reply Br."). Closing arguments were held on November 19, 2018. ECF No. 656.

Enbrel® is the first U.S. Food and Drug Administration ("FDA") approved fusion protein, approved in November 1998. PFOF ¶¶ 8, 10; DFOF ¶ 12. In August 2016, the FDA approved Defendants' biosimilar version of Enbrel®, called Erelzi™. PFOF ¶ 11; ECF No. 688 at 11 ¶¶ 41-43. Defendants do not contest infringement of the '182 Patent or the '522 Patent. ECF No. 619; PFOF ¶ 16. Therefore, the issue left for this Court to decide is whether the Patents-in-Suit are invalid based on the following legal principles: (1) lack of written description and enablement; (2) obviousness; and (3) obviousness-type double patenting.

This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a). The findings of fact are based on the Court's observations and credibility determinations of the witnesses who testified, and a thorough review of all the evidence admitted at trial. While the Court has reviewed all of the evidence presented, given the length of the trial record, the Court includes references only to the evidence most pertinent to its analysis. For the reasons set forth below, the Court finds that the Patents-in-Suit are not invalid.

I. BACKGROUND

A. Parties

Plaintiff Roche was the first to file the patent applications that eventually issued as the Patents-in-Suit. PFOF ¶ 51. Thereafter, Plaintiffs Amgen and Immunex obtained certain rights from Roche pertaining to the Patents-in-Suit, pursuant to an agreement called the Accord and Satisfaction, which included the right to take over the prosecution of the relevant patent applications and the right to commence an infringement action. JTX-12. Plaintiff Roche is a New Jersey corporation with its principal place of business in New Jersey. ECF No. 18 ¶ 3. Plaintiff

Immunex is a Washington corporation with its principal place of business in California and is a wholly owned subsidiary of non-party Amgen Inc. Id. ¶ 1. Plaintiff Amgen is a corporation of the Territory of Bermuda with its principal place of business in Puerto Rico and is also a wholly owned subsidiary of non-party Amgen Inc. Id. ¶ 2.

Defendant Sandoz Inc. is a Colorado corporation with its principal place of business in New Jersey. Id. ¶ 4. Defendant Sandoz International GmbH is a German corporation with its principal place of business in Germany. Defendant Sandoz GmbH is an Austrian corporation with its principal place of business in Austria and is a subsidiary of Sandoz International GmbH. Id. ¶¶ 6-7. Sandoz Inc. is the United States agent for Defendants Sandoz International GmbH and Sandoz GmbH. Id. ¶ 4. All parties are in the business of developing, manufacturing, marketing, and selling biopharmaceutical products. Id.

B. Background of the Invention

The active ingredient in the biopharmaceutical drug at issue in this case is a fusion protein known as etanercept that is made by combining the extracellular region of a 75 kilodalton Human Tumor Necrosis Factor Receptor with a portion of an IgG1 immunoglobulin. This section will first provide the scientific background of the claimed invention, by explaining each component and its purpose. Next, the Court will provide the relevant research and patent history for the Patents-in-Suit.

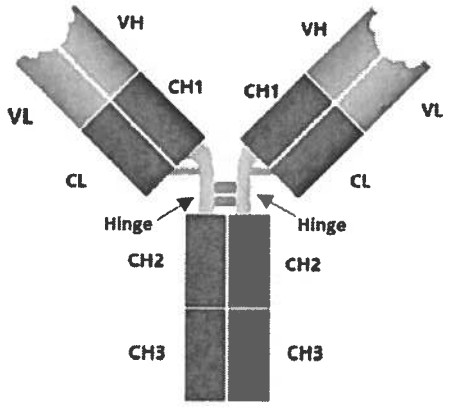
1. Scientific Background

Rheumatoid arthritis is an inflammatory auto-immune disease, i.e. a disease which occurs when "an overactive immune system attacks an individual's own body," and causes bone erosion, narrowing of joint space, and irreversible joint damage. PFOF ¶¶ 32-33. One way to treat rheumatoid arthritis is to "dampen the immune system" and to "inhibit inflammatory reactions." Id. ¶¶ 47-48. The immune system is made up of various cells and antibodies that protect the body

from foreign invaders. Id. ¶ 23. Antibodies have two primary functions: to bind foreign substances known as antigens, and to recruit other immune system components to attack antigens. Id. There are many classes and subclasses of the antibody immunoglobulin or "Ig", of which IgG is one such class. Id. ¶¶ 99, 158. There are four subclasses of human IgG: IgG1, IgG2, IgG3, and IgG4. Id.

IgG is a protein, and proteins are made up of "amino acid residues connected in a strand called a 'polypeptide,' which folds into a three-dimensional shape that imparts certain structural and functional characteristics." Id. ¶ 20. Scientists can identify protein sequences based on the order of amino acids in the protein, with the beginning portion of the sequence referred to as the "N-terminus" and the end portion referred to as the "C-terminus." Id. ¶¶ 21-22.

Structurally, an IgG protein, pictured below, consists of two heavy chains and two light chains, and each chain contains variable and constant regions. Id. ¶ 24. The constant region is the portion that interacts with other components of the immune system to elicit a response. Id. The heavy chain constant region includes the CH1, the hinge, CH2, and CH3 domains while the light chain constant region consists of the CL domain. Id. The variable region of each chain, labeled here as VH and VL, is what binds to the antigen. Id.

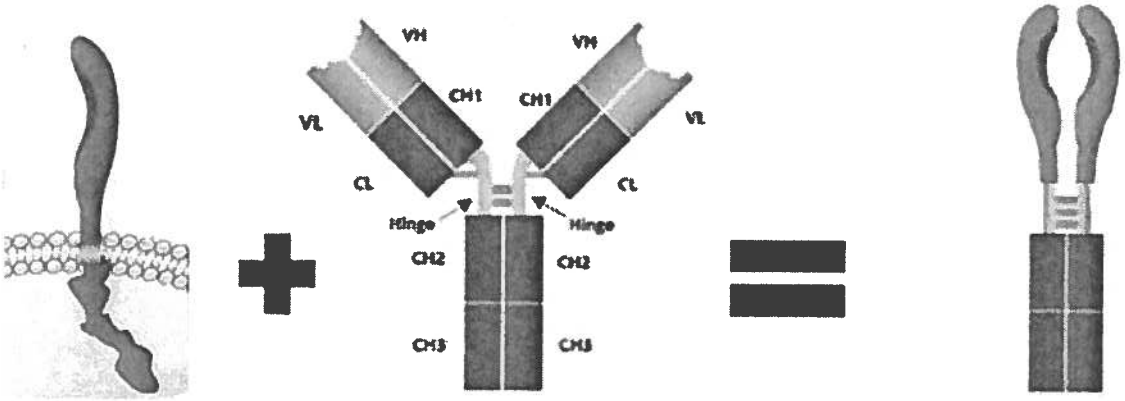


DFOF ¶ 208.

Another component of the immune system, called a cytokine, is a messenger protein that has a wide variety of functions, including to initiate an immune response. PFOF ¶ 27. The body makes dozens of distinct cytokines, one of which is the Human Tumor Necrosis Factor ("TNF"). Id. ¶¶ 27-29. TNF can be found in an insoluble (membrane-bound) or soluble (free-flowing) form. Id. ¶ 28. Originally discovered to kill tumor cells, TNF has many functions and by August 1990, scientists associated it with inflammatory diseases, such as rheumatoid arthritis. Id. ¶¶ 28-33.

TNF plays a significant role in auto-immune disorders. Id. TNF binds to certain proteins called TNF receptors ("TNFRs") that extend beyond the outer membrane of a cell. Id. ¶ 30. TNFRs have three regions: intracellular, transmembrane, and extracellular. Id. The extracellular portion of the TNFR, which is the portion that "protrudes outside the cell," can be split off to produce a "soluble" fragment of the TNFR that can bind to TNF. Id. ¶¶ 30, 76. Two types of TNFRs have been identified, one that has a molecular weight of approximately 55 kilodaltons ("p55 TNFR" or "p55") and one with a molecular weight of approximately 75 kilodaltons ("p75 TNFR" or "p75"). Id. ¶¶ 36-38.

Etanercept, the active ingredient in the biopharmaceutical drug Enbrel® at issue here, is a fusion protein that combines the extracellular region of a p75 TNFR with an IgG1. Id. ¶ 9. "A fusion protein is made by combining DNA sequences encoding parts of different proteins into one sequence, introducing that sequence into host cells, and using their natural internal machinery to produce the desired fusion protein." Id. ¶ 19. Specifically, etanercept is a "dimeric fusion protein consisting of the extracellular region of the p75 TNF receptor" which, as the parties have stipulated, is "fused to the exon-encoded 'hinge-CH2-CH3' of the constant region of a human IgG1 antibody heavy chain." Id. ¶ 9; DFOF ¶ 93; ECF No. 688 at 20 ¶ 68. Etanercept works by binding to and neutralizing excess TNF in patients with rheumatoid arthritis, thereby reducing the auto-immune inflammatory response. PFOF ¶ 244. The graphic below depicts images of a p75 TNFR and an IgG1 on the left-hand side and etanercept on the right-hand side. The Patents-in-Suit cover etanercept and the method of making etanercept. Id. ¶ 76.



p75 TNFR **IgG1 Immunoglobulin** **Etanercept**

DFOF ¶¶ 208, 214.

2. Research and Patent History

By 1990, "there was a high level of interest in studying TNF and investigating whether targeting TNF with a TNF-binding protein would provide a therapeutic benefit by inhibiting the binding of TNF to its cell-bound receptors." DFOF ¶¶ 1, 14. At that time, scientific evidence pointed to at least two TNFRs expressed by the human body: p55 and p75 TNFR. PFOF ¶¶ 37-38; DFOF ¶ 2. In April 1990, researchers at Roche (the "Roche Inventors"[2]) published the complete amino acid sequences for the p55 TNFR and the cDNAs[3] encoding it. PFOF ¶ 39; DFOF ¶¶ 15, 16; JTX-21 at 1. In May 1990, Immunex published an article containing the complete amino acid sequence for p75 and therein stated that the researchers isolated a cDNA clone of the receptor. PFOF ¶ 40; Smith, C.A., et. al., *A Receptor for Tumor Necrosis Factor Defines an Unusual Family of Cellular and Viral Proteins*, Science 248: 1019-23 (1990) (JTX-24) ("Smith 1990"); DFOF ¶ 4. Several months later in July 1990, the Roche Inventors published the complete amino acid sequence for the p75 TNFR and part of its encoding cDNA. PFOF ¶ 39; Dembic, Z. et al., *Two Human TNF Receptors Have Similar Extracellular, But Distinct Intracellular, Domain Sequences*, Cytokine 2(4): 231-37 (1990) (JTX-23) ("Dembic 1990"); DFOF ¶ 30.

Around the same time that the Roche Inventors were publishing studies on the amino acid sequences in p55 and p75 TNFR, they were also exploring the possibility of TNFR-Ig fusion proteins. PFOF ¶ 46. The Roche Inventors were ultimately successful in creating fusion proteins using both p55 and p75 TNFRs. Id. ¶ 49. The initial fusion protein used an IgG3 immunoglobulin,

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[2] The Roche Inventors were Manfred Brockhaus, Reiner Gentz, Zlatko Dembic, Werner Lesslauer, Hansruedi Lötscher, and Ernst-Jurgen Schlaeger.

[3] "cDNA" stands for complementary DNA. The Roche Inventors converted amino acid peptide sequences into DNA sequences and used those DNA sequences as probes to create primers that would allow the Roche Inventors to "fish" out cDNAs encoding TNF receptors out of a cDNA library. PFOF ¶¶ 38-39; DFOF ¶¶ 15-16.

however the Roche Inventors' "pathway of experimental work leading to a TNFR fusion protein" also contemplated fusion proteins with IgG1 and IgG2 immunoglobulins. Id. ¶¶ 50, 58-68.

On August 31, 1990, the Roche Inventors filed a patent application in Europe bearing Application No. 90116707 ("EP '707 Application") and on September 13, 1990, they filed a U.S. Patent with Application No. 07/580,013 ("'013 Application"). Id. ¶ 51. The Patents-in-Suit claim the benefit of the '013 Application and priority to the European '707 Application. Id. The Patents-in-Suit, as well as the EP '707 Application and the '013 Application, encompass a p75 TNFR-IgG1 fusion protein, but because the parties differ in their assessments of the patent specifications and validity of the claimed invention, further details on the Patents-in-Suit will be discussed below. Id. ¶¶ 50-53; DFOF ¶¶ 36-37.

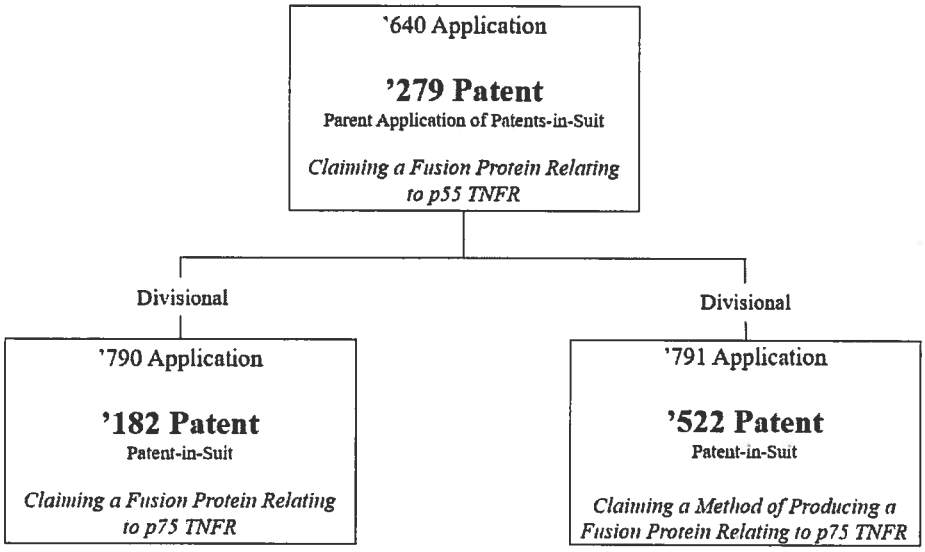
C. Patents-in-Suit and Relevant Prosecution History

1. The '182 Patent

The '182 Patent, entitled "Human TNF Receptor Fusion Protein," issued on November 22, 2011 and expires on November 22, 2028. PFOF ¶ 74; DFOF ¶ 83. The asserted claims "define a fusion protein consisting of parts of two different proteins: the extracellular region of p75 fused to all of the domains of the human IgG1 constant region other than the first domain." PFOF ¶¶ 74-76; *see also* '182 Patent (JTX-1) col. 39:60-67, 42:26-34.

The initial '013 Application was abandoned, and U.S. Application No. 08/965,640 ("'640 Application") was filed on July 21, 1993 as a continuation. PFOF ¶ 57; DFOF ¶¶ 38-39. The '640 Application was subject to a restriction requirement by the United States Patent and Trademark Office ("USPTO") and in response Roche elected to pursue claims related to the p55 fusion protein, which issued as U.S. Patent No. 5,610,279 ("'279 Patent") on March 11, 1997. PFOF ¶ 57; DFOF ¶¶ 39-40; ECF No. 688 at 6 ¶ 9. As a result of the restriction, Roche then filed two divisional applications on May 19, 1995: U.S. Application No. 08/444,790 ("'790 Application"),

which issued as the '182 Patent, and U.S. Application No. 08/444,791 (the '791 Application"), which issued as the '522 Patent. *See* PFOF ¶ 57; DFOF ¶ 41.



In 2004, prior to issuance of the '182 Patent, Amgen and Immunex acquired the exclusive right to prosecute the Patents-in-Suit, among other rights, from Roche pursuant to an Accord and Satisfaction between non-party Amgen Inc., Immunex, and Roche. JTX-12 at 4-6, Article 3, ¶¶ 3.1-3.6; *see also* PFOF ¶ 34; DFOF ¶¶ 54, 58, 62. Those rights were later consolidated in Immunex by a separate agreement. JTX-14. In 2005, Immunex amended the '790 Application in response to a USPTO office action requiring the '790 Application to come into consonance with the restriction requirement. PFOF ¶ 285; DFOF ¶ 73. The '790 Application was again amended in 2006. PFOF ¶ 144; DFOF ¶ 74. Despite the amendments, the '790 Application was rejected "for failing to comply with the written description requirement and as obvious over the applied prior art," and the rejection was appealed to the Board of Patent Appeals and Interferences ("BPAI"). Plaintiffs' Trial Exhibit ("PTX")-6.456 ("BPAI Opinion"). The BPAI reversed the examiner's rejection. PTX-6.456 at 9 (BPAI Opinion reversing rejection by examiner). The '182 Patent then issued on November 22, 2011. *See generally* '182 Patent (JTX-1).

2. The '522 Patent

The '522 Patent, entitled "Human TNF Receptor," issued on April 24, 2012 and expires on April 24, 2029. PFOF ¶ 74; DFOF ¶ 83. The asserted claims "define a method of producing [the] fusion protein" defined in the '182 Patent. '522 Patent (JTX-2) at 47-48 (claims 3, 8, 10); PFOF ¶ 75. The '522 Patent issued from the '791 Application, which was filed on May 19, 1995 as a divisional of the '640 Application, along with the '790 Application which issued as the '182 Patent. PFOF ¶ 57; DFOF ¶ 48.

Prior to the '522 Patent's issuance, Amgen and Immunex amended the '791 Application in 2004, 2007, and 2010 to include several references related to the full amino acid sequence for p75. *See, e.g.*, '522 Patent (JTX-2) col. 3:1-3, Fig. 5; DFOF ¶¶ 78-80. Like the amendments to the '182 Patent, these amendments were triggered by two USPTO actions, which rejected the '791 application for obviousness and insufficient written description. PTX-7.351. Despite the amendments, the '791 Application was still rejected, and that rejection was eventually overcome by citing the '790 Application BPAI Opinion which dealt with similar issues. PFOF ¶ 323; JTX-4 at 4952-53. The '522 Patent then issued on April 24, 2012. *See generally* '522 Patent (JTX-2).

II. ISSUES TO BE DECIDED

Prior to the commencement of trial, Defendants advised that they did not contest infringement of the Patents-in-Suit. ECF No. 619. As discussed above, the parties also stipulated that the term "all of the domains of the constant region of a human immunoglobulin IgG[1] heavy chain other than the first domain of said constant region" is construed as meaning "the exon-encoded 'hinge-CH2-CH3' region of human [IgG/IgG1]." ECF No. 688 at 20 ¶ 68. Accordingly, the question before this Court is whether the '182 and '522 Patents are invalid due to lack of written description and enablement, obviousness, and obviousness-type double patenting.

III. DISCUSSION

Issued patents are presumed valid. *See* 35 U.S.C. § 282(a). To rebut this presumption, Defendants bear the burden of proving invalidity by clear and convincing evidence. *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1376 (Fed. Cir. 2009) ("Because of this presumption, an alleged infringer who raises invalidity as an affirmative defense has the ultimate burden of persuasion to prove invalidity by clear and convincing evidence, as well as the initial burden of going forward with evidence to support its invalidity allegation.").

A. Written Description and Enablement (35 U.S.C. § 112)

A patent specification "shall contain a written description of the invention." 35 U.S.C. § 112. The specification must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm. Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). The test for written description "requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art."[4] *Id.* "[W]hether a patent complies with the written description requirement will necessarily vary depending on the context. Specifically, the level of detail required . . . varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.* (citation omitted). When reviewing the patent according to these principles, "[w]ritten description is a question of fact, judged from the perspective of [a POSA] as of the relevant filing date." *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1363 (Fed. Cir. 2006) (citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991)).

[4] A person of ordinary skill in the art will hereinafter be referred to as a "POSA."

Additionally, as to enablement, a patent specification must describe "the manner and process of making and using [the invention], 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. Moreover, enablement requires that the specification teach a POSA "how to make and use the full scope of the claimed invention without undue experimentation." *Martek Bioscis. Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1378 (Fed. Cir. 2009) (citation omitted). A patentee need not "include in the specification that which is already known and available to [a POSA]" and "not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be." *Koito Mfg. Co. v. Turn-Key-Tech, LLC*, 381 F.3d 1142, 1156 (Fed. Cir. 2004) (citation omitted). "Enablement is a question of law involving underlying factual inquiries." *Falkner*, 448 F.3d at 1363 (citing *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997), *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

Defendants argue that the Patents-in-Suit are invalid because their specifications (1) lack a sufficient written description of the invention and (2) do not enable a POSA to make or use the invention. Defs. Br. at 20-35. By contrast, Plaintiffs contend that the specifications are adequate, and that Defendants failed to prove their written description or enablement claims by clear and convincing evidence. Pls. Br. at 12-21.

In support of their arguments, the parties relied heavily on the testimony of the following four witnesses: (1) Defendants' expert Daniel Capon, Ph.D., (2) Defendants' expert Carl P. Blobel, M.D., Ph.D., (3) Plaintiffs' expert James Naismith, Ph.D, and (4) Plaintiffs' expert Hansruedi Loetscher, Ph.D.[5] For the reasons set forth below, the Court finds that Defendants

[5] Defendants' expert Daniel Capon, Ph.D. has 37 years of experience in the field of biotechnology, including at Genentech, Inc., Cell Genesys, Inc., Xenotech, Inc., and ViroLogic, Inc. Defendants'

failed to prove invalidity based on the written description and enablement requirements by clear and convincing evidence, and therefore the Patents-in-Suit are not invalid under 35 U.S.C. § 112.

1. The Specifications Meet the Written Description Requirement

Defendants argue that the specifications are deficient because they neither sufficiently describe etanercept nor convey that the Roche Inventors had possession of etanercept, and that further, the specifications in conjunction with the claims do not direct a POSA to the specific embodiment of etanercept. Defs. Br. at 20-32. Plaintiffs counter that the necessary elements of the claimed invention are adequately described throughout the specifications, were known and available prior to August of 1990, and that the specifications adequately describe the novel combination of those elements to create etanercept. Pls. Br. at 13-21. Therefore, Plaintiffs contend that the specifications demonstrate possession and the patents properly direct a POSA to etanercept. Id.

The '182 Patent claims a fusion protein consisting of the extracellular portion of the p75, as well as the exon-encoded hinge, CH2 and CH3 domains of human IgG1, while the '522 Patent claims the method of making the fusion protein. '182 Patent (JTX-1) col. 39:14- 42:34; 9/18 AM (Naismith) Tr. at 89:2-12, 91:8-14; '522 Patent (JTX-2) col. 45:44-48:4. The patent specifications of the '182 and '522 Patents identify soluble fragments of p75 TNFR as one of two TNF binding

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expert Carl P. Blobel, M.D., Ph.D. is a Professor of Medicine, Physiology, and Biophysics at the Weil Medical College of Cornell University and Virginia F. and William R. Salomon Chair in Musculoskeletal Research and Director of the Arthritis and Tissue Degeneration Program at the Hospital for Special Surgery. ECF No. 688 at 131 ¶¶ 43-44. Plaintiffs' expert James Naismith, Ph.D. is a Professor of Structural Biology at the University of Oxford in the United Kingdom who has more than 20 years of research experience on the structure and function of proteins. Id. at 126-127 ¶¶ 35-37. Dr. Naismith's post-doctoral research at the Howard Hughes Medical Institute in Dallas, Texas focused on proteins specifically involved in TNF signaling. Id. Plaintiffs' expert Hansruedi Loetscher, Ph.D., an inventor of the Patents-in-Suit, worked at F. Hoffman-La Roche AG from 1984 through 2016, where he most recently served as the Global Head of Neuroscience Discovery. Id. at 117 ¶¶ 1-3.

proteins, i.e. p55 and p75, used in TNFR-IgG fusion proteins and include both figures and examples that are referenced in the parties' arguments. There are multiple figures in the Patents-in-Suit that provide nucleotide sequences for the TNF binding protein. *See generally* '182 Patent (JTX-1); '522 Patent (JTX-2). In analyzing the specifications, it appears that Figure 1 of the specifications relates to a p55 TNFR and Figure 4 relates to a p75 TNFR.[6] Figure 4 is a "[n]ucleotide sequence . . . and deduced amino acid sequence . . . for cDNA clones derived from" a p75 TNFR, which consists of a long combination of letters representing those amino acids and related cDNA combinations. '182 Patent (JTX-1) col. 2:60-62, Fig. 4. The specifications additionally include multiple examples pertaining to a TNFR-IgG fusion protein. In the examples, both the '182 and '522 Patents notably discuss and disclose two nucleotide sequences for portions of p75—SEQ ID NO: 10 (N-terminus) and SEQ ID NO: 7 (C-terminus).

The Patents-in-Suit disclose using "especially preferred vectors" pCD4-Hγ1 (DSM 5314, deposited on Apr. 21, 1989) and pCD4-Hγ3 (DSM 5523, deposited on Sept. 14, 1989) "[f]or the expression of proteins which consist of a soluble fragment of non-soluble TNF-BP [binding protein] and an immunoglobulin fragment, i.e. all domains except the first of the constant region of the heavy chain." '182 Patent (JTX-1) col. 8:56-9:8. The specifications further state that "the present invention embraces not only allelic variants, but also those DNA sequences which result from deletions, substitutions and additions from one or more nucleotides of the sequences given in FIG. 1 or FIG. 4" and yield TNF-binding proteins. '182 Patent (JTX-1) col. 5:17-22; '522 Patent (JTX-2) col. 5:29-34. The Patents-in-Suit also reference the Smith 1990 article—the

[6] In the '522 Patent, Figure 1 is broken down into Figures 1A-1D and Figure 4 is broken down into Figures 4A-4D.

Immunex publication that includes the complete amino acid sequence for p75. '182 Patent (JTX-1) col. 5:22-24; '522 Patent (JTX-2) col. 5:34-37.

a) The Requisite Components of the Fusion Protein Were Disclosed in the Specifications and Known Prior to August 1990

The Court finds that the specifications of the Patents-in-Suit sufficiently describe the components of etanercept. A patent must include sufficient details such that a POSA could understand the subject invention and recognize that the inventor possessed it. *Ariad*, 598 F.3d at 1351. However, this requirement does not necessarily mean that the specification of the patent must include every nuanced detail.[7] Indeed, "[a] patent need not teach, and preferably omits, what is well known in the art." *Falkner*, 448 F.3d at 1365 (quoting *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534 (Fed. Cir. 1987)); *see also Capon v. Eshhar*, 418 F.3d 1349, 1357-58 (Fed. Cir. 2005) (holding that a patent's specifications do not need to reiterate the structure, formula, or chemical name of a claimed invention to satisfy the written description requirement when that information is already known in the field). The Court will first analyze the sufficiency of the description of p75, followed by the sufficiency of the description of the IgG1 portion of the fusion protein.

[7] Defendants contend that Plaintiffs ignore the controlling precedent in *Ariad*, and improperly ask the Court to venture outside of the specifications to find the requisite written description. Defs. Reply Br. at 12-14. In other words, Defendants assume distinct requirements for an adequate written description before and after the *Ariad* decision. However, the precedent is clear that sequences disclosed in the prior art need not be repeated and the standard has not changed in that regard following *Ariad*. *See Falkner*, 448 F.3d 1357; *Capon*, 418 F.3d 1349; *see also Zoltek Corp. v. United States*, 815 F.3d 1302, 1308 (Fed. Cir. 2016) (post-*Ariad* case confirming that "written description need not include information that is already known and available to the experienced public") (internal quotation marks and citation omitted). The Court finds that the specifications meet the requirements of *Falkner* and *Capon*, which are still current and applicable law, and are not inconsistent with *Ariad*.

i. p75 Is Adequately Described

Analyzing the Patents-in-Suit, the Court finds that p75 is sufficiently described. The specifications of the Patents-in-Suit identify two TNF receptors, p55 and p75, and further note that the invention embraces allelic variants and DNA sequences resulting from deletions, substitutions, and additions of one or more nucleotides of the sequences provided in Figure 1 and/or Figure 4. '182 Patent (JTX-1) col. 4:1-5:24. Sequence identification numbers, which correspond to p75, are mentioned throughout the specification (including the examples therein) and in the claims, and Example 6 explains that the inventors isolated the p75 TNFR. Id. col. 15:31-39.

Furthermore, the prior art demonstrates that the p75 amino acid sequence was well known to a POSA at the time of the invention. The Court may look to prior art and trial testimony when determining what a POSA would have known at the time of the invention. *See, e.g.*, *Ariad*, 598 F.3d at 1351 (relying on expert testimony and examples of prior art to make written description determination); *Falkner*, 448 F.3d at 1365-66. The parties agreed that by August 1990, the p75 TNFR was well known to a POSA. PFOF ¶¶ 86-87; DFOF ¶ 2. Both the Immunex Smith article and the Roche Dembic article, which were published in May 1990 and July 1990 respectively, contain a full recitation of the p75 amino acid sequence. PFOF ¶¶ 89-91; Smith 1990 (JTX-24) at 3-4, Fig. 3B; Dembic 1990 (JTX-23) at 1-2. The Smith 1990 article, expressly referenced in the Patents-in-Suit, also notes that "[t]he entire nucleotide sequence is available upon request and has been deposited with GenBank, accession number M32315." Smith 1990 (JTX-24) at 3-4, Fig. 3B. GenBank is an amino acid repository which can match partial amino acid sequences with full corresponding sequences that have been deposited with GenBank. *See* 9/18 AM (Naismith) Tr. at 62:7-16. Sequences are provided to GenBank as "an information deposit" in which the DNA sequence letters are submitted and an "accession number" is the particular

identification number assigned to each submitted sequence. Id. at 73:17-74:1. Similarly, the Dembic 1990 article contains the entire p75 amino acid sequence.[8] *See* Dembic 1990 (JTX-23) at Fig. 1. Ultimately, neither party contests that the prior art "definitively identified two TNF receptors: the p55 and the p75" by August 1990. Defs. Br. at 21; PFOF ¶¶ 36-38. The parties further agree that Immunex scientists in May 1990 and later the Roche Inventors in July 1990 published the full-length p75 TNFR before the related European priority patent application was filed in August 1990.[9] DFOF ¶ 2; PFOF ¶¶ 39-41.

Defendants, however, argue that because the specifications refer to Smith 1990 as an example of a "deletion" when compared to Figure 4 (when it was instead the complete sequence of Figure 4), a POSA would not have considered using the Smith 1990 sequence. Defs. Br. at 25. Upon review of the disclosure, the Court does not believe a POSA would have been deterred from looking to Smith 1990 for use in the fusion protein due to the term "deletion." Just prior to that language in the specification, the invention embraces not only deletions but also all allelic variants including "substitutions and additions." '182 Patent (JTX-1) col. 5:17-24. In fact, a POSA may

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[8] The Dembic 1990 article also explains that TNFRs that have a molecular weight of either 65 kD or 75 kD are both the p75 protein because the 65 kD TNFR is simply a derivative of p75. Dembic 1990 (JTX-23) at 1. The authors of the Dembic 1990 article arrived at this conclusion because both the 65 and 75 kD TNFRs bound "the same monoclonal antibody." Id.; *see also* 9/18 AM (Naismith) Tr. at 80:9-81:5 (Dr. Naismith testifying that proteins can gain or lose weight depending on glycosylation which "is the addition of sugar molecules" and concluding that TNF receptors with molecular weights of either 65 or 75 kD are both the p75 protein used in etanercept).

[9] By April 1990, the Roche Inventors were the first to discover that there were two distinct TNFRs that specifically bound to TNF, p55 and p75. 9/17 (Loetscher) Tr. at 20:1-18, 26:8-28:8; JTX-22 at 1. In May 1990, Immunex scientists published the Smith 1990 article containing the p75's complete amino acid sequence and included a figure caption indicating that a cDNA sequence encoding the p75 had been deposited with GenBank. Smith 1990 (JTX-24) at 3, Fig. 3B; 9/17 (Loetscher) Tr. at 38:6-24; *see also* 9/13 AM (Capon) Tr. at 85:3-11. Two months later, in July 1990, the Roche Inventors published the complete amino acid sequence of p75 and a cDNA sequence encoding part of it, resulting in the Dembic 1990 article. 9/17 (Loetscher) Tr. at 33:1-33:23; Dembic 1990 (JTX-23) at 2, Fig. 1.

have been encouraged to look to an outside reference, such as the Smith 1990 article, that was expressly called out by name in the specification. 9/18 PM (Naismith) Tr. at 52:23-53:8. At trial, Plaintiffs' expert Dr. Naismith credibly testified that the Smith 1990 reference would have communicated to the ordinary artisan that "[i]f you hadn't read the paper, go and read it. They'd think it was a landmark paper."[10] Id. Thus, the Court agrees with Plaintiffs that despite the word "deletion," a POSA would have been directed to Smith 1990 and therefore the full p75 protein.

In further support of Plaintiffs' arguments, Example 7 contains the N-terminus sequence designated SEQ ID NO: 10. '182 Patent (JTX-1) col. 16:22-30. SEQ ID NO: 10 matches the first 18 amino acids at the N-terminus of the known p75 as published in Smith 1990. Id.; Smith 1990 (JTX-24) at 3, Fig. 3B. The Patents-in-Suit also include the 18 amino acid sequences close to the C-terminus of the known p75 protein designated SEQ ID NO: 7. These two disclosed nucleotide sequences for p75 would have, in addition to Figure 4 and the Smith 1990 reference, directed a POSA to the full p75 sequence at the time of the invention. *See* '182 Patent (JTX-1) col. 39:13-42:34 (claims of the '182 Patent specifically requiring the use of the protein that "comprises the amino acid sequence . . . (SEQ ID NO: 10)"), col. 4:18-20, 16:36-38 (identifying SEQ ID NO:7 as a partial amino acid sequence that makes up a preferred protein); '522 Patent (JTX-2) col. 45:44-48:4 (claims of the '522 Patent specifying the amino acid described in SEQ ID NO: 10), col. 4:31-32, 16:57-58 (listing SEQ ID NO:7 as an example of a partial amino acid

[10] Defendants misconstrue part of Dr. Naismith's testimony as indicating that he believed the Smith reference would have discouraged a POSA from using the known complete p75 TNFR sequence. Defs. Br. at 25; 9/18 PM (Naismith) Tr. at 22:19-23, 23:20-24. Plaintiffs correctly counter that because Figure 4 is a smaller sequence than the Smith 1990 sequence, a POSA would have understood the passage to suggest Smith 1990 as a source of p75 TNFR to use in the fusion protein. Pls. Br. at 21; 9/18 PM (Naismith) Tr. at 22:15-24:3, 52:19-53:8 ("I simply went and read the paper to figure out what a scientist would do . . . Smith is a complete sequence, which was known; and Figure 4 is a partial sequence of many less residues.").

sequence to be used in a preferred protein); *see also* '182 Patent (JTX-1) col. 5:17-22. With respect to the sequence identification numbers for SEQ ID NO: 10 and SEQ ID NO: 7, Plaintiffs' expert Dr. Naismith credibly testified that there was less than a one-in-a-million chance that the wrong protein would be produced by GenBank if an inquiry was made to retrieve the complete p75 sequence corresponding to one of the sequence identification numbers. [11] *See* 9/18 AM (Naismith) Tr. at 68:13-16. Moreover, Dr. Naismith testified that there was "zero chance" that any other protein would be returned by GenBank if the request included both SEQ ID NO: 10 and SEQ ID NO: 7 at that time. Id. at 68:17-25; *see also* 9/12 PM (Blobel) Tr. at 14:6-12 (Defendants' expert Dr. Blobel also testifying "if you took a sequence of this receptor, you would presumably get this receptor back. That's how it works.").[12] Accordingly, the Patents-in-Suit sufficiently describe the subject fusion protein using the known full p75 sequence.

ii. IgG1 and the Fusion Protein are Adequately Described

The disclosure of the second necessary part of etanercept was also adequate because the specification clearly refers to use of deposited vectors (including "pCD4-Hγ1") that contain DNA

[11] Defendants cite to *In re Wallach*, 378 F.3d 1330 (2004) to argue that a partial amino acid sequence is insufficient to describe the full protein when it could not be used to obtain the full protein. However, given Dr. Naismith's testimony that the partial sequences as disclosed would allow a POSA to obtain the full-length sequences from Genbank, the Court finds that the instant case is distinguishable from *Wallach.*

[12] Defendants' expert, Dr. Capon, opined that a POSA would not have been able to obtain the correct full p75 sequence from GenBank if provided with the sequence identification number or the accession number as listed in Smith 1990 because there would have been too many results. Dr. Capon, however, stated that he was not qualified to opine in that area and conceded that he had only first accessed GenBank five years after 1990. 9/13 PM (Capon) Tr. at 20:1-6, 20:18-23, 21:10-22:25 (Capon testifying that "I don't know what the requirements of accessing something from GenBank were . . . I'm not qualified to testify [about that]" and "the first time I believe I accessed GenBank was in 1995"). By contrast, Plaintiffs' expert, Dr. Naismith, limited his opinion to what a POSA would have been able to obtain "at [the] time" of the invention. *See* 9/18 AM (Naismith) Tr. at 68:21-25. The timing is significant here because the sequence match is based on the smaller number of deposits GenBank had in 1990. *See* id. at 68:2-9. Thus, the Court accords little weight to Dr. Capon's opinion on this topic.

sequences encoding the exon-defined hinge-CH2-CH3 region of a human IgG1 heavy chain as confirmed by the declaration of Defendants' expert, Jeffery Kittendorf, Ph.D., an expert in biochemistry and a Research Assistant Scientist at the University of Michigan Life Sciences Institute. ECF No. 688 at 132 ¶ 47; JTX-16 at 32-34; *see also* 9/17 (Loetscher) Tr. at 57:4-58:25.

Example 11 then provides a recipe to fuse a soluble TNF-binding fragment directly to that exon-encoded hinge-CH2-CH3 region of an IgG heavy chain, thereby providing a POSA with the full fusion protein. '182 Patent (JTX-1) col. 9:3-8; 9/17 (Loetscher) Tr. at 56:10-57:13, 58:18-59:5; 9/18 AM (Naismith) Tr. at 54:16-21, 90:10-91:7, 92:21-93:8. This example illustrates utilizing a cDNA fragment that encodes the extracellular region of a TNF-binding protein, and describes the process generally using a p55 TNFR as an illustration. 9/17 (Loetscher) Tr. at 56:5-58:24. A POSA would have followed that example and used p75 to create etanercept based on the claims in the Patents-in-Suit and the specification.[13] *See* 9/12 PM (Blobel) Tr. at 8:5-10:2, 14:6-12; 9/17 (Loetscher) Tr. at 56:5-58:24; 9/18 AM (Naismith) Tr. at 67:14-68:25, 72:15-73:1, 73:17-74:8, 94:10-14, 94:20-95:6.

Moreover, the parties agree that the IgG1 hinge-CH2-CH3 was also known in the prior art as of August 1990. DFOF ¶ 167; PFOF ¶¶ 99-100. Thus, because the p75 TNFR sequence and

[13] Defendants claim that *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341 (Fed. Cir. 2011) supports their argument that the Patents-in-Suit are invalid because they contend that the specifications do not describe the claimed fusion protein. Defs. Br. at 31; Defs. Reply Br. at 14. *Centocor* is distinguishable from the instant case for two main reasons. First, unlike in *Centocor*, the Patents-in-Suit issued from divisional applications as a result of a USPTO restriction requirement, so the specification should contain disclosures from the parent application. S*ee Pfizer, Inc. v. Teva Pharms. U.S.A., Inc.*, 518 F.3d 1353, 1359 (Fed. Cir. 2008); *Manual of Patent Examining Procedure* ("MPEP") § 201.06; *see also supra* at I.C. Second, amendments here were made as a result of that restriction requirement and in accordance with an agreement between Plaintiffs Roche, Immunex, and Amgen, and not, as in *Centocor*, in an "attempt to claim as its own the fruit of [Defendants'] innovative work." *Centocor*, 636 F.3d at 1349. Further, *Centocor* is consistent with the Court's analysis above that the written description requirement is satisfied.

the IgG1 sequence were well known and accessible to a POSA, a reproduction of the known sequences was not required to be explicitly included in the Patents-in-Suit in order to claim a novel combination of those sequences. *See Falkner*, 448 F.3d at 1368 (holding that genes and their nucleotide sequences must not be recited or incorporated by reference where "accessible literature sources . . . as of the relevant date" contain such information, because "forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification").

b) The Patents-in-Suit Demonstrate Possession

To the extent Defendants assert that Roche[14] never made the claimed p75-IgG1 fusion protein, such contention is legally insignificant. *Ariad* holds that "the written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." 598 F.3d at 1352 (citing *Falkner*, 448 F.3d at 1366-67). Here, as discussed, the claim language identifies the requisite elements of the subject invention—the p75 fusion protein combined with the hinge-CH2-CH3 domains of IgG1—and, in conjunction with the specification, provides support of possession. Many of the examples in the Patents-in-Suit further demonstrate that the Roche Inventors had possession.[15] Accordingly, the Court is persuaded that

[14] As mentioned above (I.C.1.), Immunex acquired the rights to prosecute the Patents-in-Suit pursuant to a 2004 Accord and Satisfaction agreement between Roche and Immunex, which will be discussed in further detail below in Section III.C.2.a.

[15] Defendants assert that a POSA would not believe that the Roche Inventors had possession of a p75 fusion protein because none of the examples in the Patents-in-Suit are directed to a p75 TNFR or a p75-IgG1 fusion protein. Defs. Br. at 26-27. In opposition, Plaintiffs contend that the specifications, including the examples, disclose the known p75 protein and the p75 TNFR-IgG1 fusion protein "because [the specification in each Patent-in-Suit] identifies both parts of the claimed p75-IgG1 fusion protein . . . and describes how to combine them as the claims specify." Pls. Br. at 14-18.

the Roche Inventors had possession of the invention based on the specifications of the Patents-in-Suit, including the examples within the specifications, and the claims.

c) Amendments to the Prosecution File History Did Not Add New Material

The Court will now consider two amendments to the Patents-in-Suit, both of which were approved by the USPTO. First, in 2006, Amgen and Immunex, with assistance from Roche, deposited a plasmid containing a p75 cDNA with American Tissue Culture Collection ("ATCC")[16], and gave it a designation of PTA 7942. PFOF ¶¶ 93-94; DFOF ¶ 75; *see also* JTX-81 at 19-20 (Plaintiffs' witness Dr. Werner Lesslauer, one of the Roche Inventors involved in this project, testifying that Amgen deposited the p75 plasmid, Roche assisted in the deposit, and it was designated PTA 7942). That same year, Immunex amended the specification of the '790 application (which resulted in the '182 Patent) to include a reference to Immunex's PTA 7942 plasmid deposit. 9/13 AM (Capon) Tr. at 50:9-51:1; JTX-16 at 29-31. The cDNA for the PTA 7942 plasmid encodes the full-length p75 TNFR, which is identical to the sequence reported in Smith 1990. JTX-16 at 29-31. Second, in 2007, Immunex amended the specification of the '791 application (which resulted in the '522 Patent) to expressly incorporate the Smith 1990 protein by reference. Defs. Br. at 33. Immunex also inserted a new figure, Figure 5, that included the Smith 1990 sequence (in addition to the reference previously included). Id.

Defendants assert that Immunex's decision to take over the prosecution and amend the specifications of the Patents-in-Suit is a clear indication that the original specifications as filed by Roche were deficient. Id. at 32-33. In addition, Defendants assert that the USPTO did not have

[16] ATCC is a public depository where cell structures and microorganisms are deposited and made available for public access. *See* "*Who We Are*," https://lgcstandards-atcc.org/en/About/About_ATCC/Who_We_Are.aspx (last visited August 9, 2019).

complete information when it approved the amendments because the Plaintiffs informed the USPTO that the Smith 1990 protein was "99% identical" to Figure 4, when in fact Defendants contend the two proteins are meaningfully different. Id. at 33-34. Defendants argue that Plaintiffs' amendments added what amounts to "new matter" not previously included in the application, which is a ground for a patent rejection.[17] *See* 35 U.S.C. § 132 ("No amendment shall introduce new matter into the disclosure of the invention."); *see also* Defs. Reply Br. at 16 n.13.

By contrast, Plaintiffs contend that each amendment did not contain new matter and that the USPTO properly approved the valid amendments. Pls. Br. at 16 n.2, 18 n.3; PFOF ¶¶ 11-14. Plaintiffs maintain that the amendment to include the PTA 7942 plasmid, which encodes the sequence reported in Smith 1990, complies with USPTO rules because the plasmid (1) contains p75 cDNA that was identified in the original specification as variants of a "DNA sequence[] encoding the 75/65 kD," (2) was made prior to August 1990, and (3) was properly deposited with the ATCC in 2006. Pls. Br. at 16 n.2; PFOF ¶¶ 11-14.

The Court concludes that the deposited PTA 7942 plasmid was properly made part of the Patents-in-Suit and did not add new matter. The Federal Circuit has held that where information

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[17] Defendants appear to have relinquished their anticipation argument, which focused on PTA 7942, because their expert on the topic, Dr. Blobel, did not provide related testimony at trial and their post-trial briefs relegate the substance of the argument to a footnote. *See* Defs. Br. at 35 n.5. Invalidity based on anticipation "requires that the same invention, including each element and limitation of the claims, was known or used by others before it was invented by the patentee." *Hoover Grp., Inc. v. Custom Metalcraft, Inc.*, 66 F.3d 299, 302 (Fed. Cir. 1995). To the extent they maintain an anticipation argument, Defendants argue that claims 35-36 of the '182 Patent, which specifically claim the 2006 PTA 7942 plasmid deposit, are invalid for anticipation because Enbrel® had been on sale and publicly available for 8 years at the time of the amendment. Defs. Br. at 35 n.5. The USPTO Board's allowance of the amendment and specific finding that it did not add new matter is "entitled to an especially weighty presumption of correctness in a subsequent validity challenge based on the alleged introduction of new matter." *See Commonwealth Sci. & Indus. Research Org. v. Buffalo Tech. (USA), Inc.*, 542 F. 3d 1363, 1380 (Fed. Cir. 2008) (quotation marks omitted); *see also* Pls. Br. at 16 n.2. Accordingly, insofar as Defendants maintain this anticipation argument, it has not been proven by clear and convincing evidence.

is properly deposited with an independent source, "[a]n accession number and deposit date add nothing to the written description of the invention" and are therefore, not considered new matter. *In re Lundak,* 773 F.2d 1216, 1223 (Fed. Cir. 1985). Further, the deposited plasmid was appropriately made part of the Patents-in-Suit as of their 1990 priority dates because as long as the plasmid was described in the application as-filed, it is not considered new and may be deposited at any time before issuance. *See In re Lundak*, 773 F.2d at 1222-23 ("Lundak's deposit with the ATCC, which was made after filing but prior to issuance of his patent, and which is referred to in his specification, meets the statutory requirements."); *see also* 37 C.F.R. § 1.804(a) (" . . . an original deposit . . . may be made . . . subject to § 1.809, during pendency of the application for patent.").[18] The Court agrees with the USPTO and finds that the properly deposited plasmid reflected one of these variants and did not add new matter. Accordingly, the Court finds that Plaintiffs' amendments adequately described the inventive concept at the time of the invention.

As to the Smith 1990 incorporation, the Court does not find that Immunex's decision to amend is proof that the original specifications were deficient. As discussed above, the Court finds that the Smith 1990 protein was sufficiently described when it was originally referred to and did not need to be amended to expressly incorporate it by reference. *See, e.g.*, *Falkner*, 448 F.3d at 1365 (finding that "the absence of incorporation by reference is not problematic."). The Court therefore finds that the amendments to the Patents-in-Suit were proper and do not alter the written description analysis.

[18] Defendants argue that the amendment occurred much sooner in time in *Lundak* than in the instant case, however, the Court has not been provided with any legal authority to suggest a time limit on specification amendments during the course of prosecution of a patent. *See* Defs. Br. at 13 n.11.

2. The Specification Enables Etanercept

Finally, Defendants argue that the claims of the Patents-in-Suit are not enabled. DFOF ¶ 180; Defs. Br. at 35. Plaintiffs assert that Defendants' enablement challenge fails because the Patents-in-Suit identify both p75 TNFR and IgG1 (which were well-known), sufficiently describe how to combine them to enable a POSA to produce etanercept, and Defendants' own experts concede that a POSA could have produced the claimed fusion protein without undue experimentation by using known methods as of August 1990. *See* Pls. Br. at 2, 21-22; *see also* 9/12 PM (Blobel) Tr. at 53:19-56:13; 9/13 PM (Capon) Tr. at 61:22-62:16.

To be enabling, "[t]he specification must 'enable one of ordinary skill in the art to practice the claimed invention without undue experimentation.'" *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1305 (Fed. Cir. 2010) (quoting *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999)). "Enablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, 858 F.2d at 736-37. However, the experimentation needed to practice the art must not be undue. *Id.* at 737. The test for undue experimentation "is not merely quantitative, since 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." *Id.* To determine whether a disclosure would require undue experimentation, courts should consider the *Wands* factors, which 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. *Id.*

The Court finds that Defendants have failed to show by clear and convincing evidence that the Patents-in-Suit do not meet the enablement standard. Preliminarily, both parties agree to a POSA's relative skill in the art, and each party used nearly identical definitions and qualifications for their respective hypothetical POSA. *Compare* 9/11 PM (Blobel) Tr. at 30:24-32:5 *with* 9/20 AM (Wall) Tr. at 18:6-25.[19] Specifically, the parties' experts agreed that the p75 protein and the exon-encoded hinge-CH2-CH3 portion of the IgG1 immunoglobulin sequences were known before August of 1990, which is the initial date of the applications. 9/11 PM (Blobel) Tr. at 14:19-15:5 (Dr. Blobel noting that the claims in the '182 Patent were directed at "essentially etanercept"); 9/20 AM (Wall) Tr. at 19:2-12, 92:16-93:2 (Dr. Wall explaining that the components of etanercept were known by August 1990). Both of Defendants' experts, namely Dr. Blobel and Dr. Capon, agreed that a POSA in 1990 would have been able to produce a fusion protein that is similar to etanercept. 9/12 PM (Blobel) Tr. at 55:20-56:5 (Dr. Blobel testifying that a POSA would have been able to produce a fusion protein similar to etanercept using "ordinary and routine methods utilized in the art"); 9/13 PM (Capon) Tr. at 73:5-14 (Dr. Capon testifying to the same). These experts also testified that the claim scope is both limited to and covers etanercept. 9/11 PM (Blobel) Tr. at 14:19-15:5; 9/13 PM (Capon) Tr. at 82:22-83:3. Regarding the state of the art at the time of the invention, the parties explicitly agreed that technology relating to recombinant DNA was developed by 1990 and allowed for the creation of fusion proteins like etanercept. 9/12 PM (Blobel) Tr. at 54:13-56:13 (Dr. Blobel testifying regarding the state of the art in August 1990); *see also* ECF No. 688 at 65 ¶ 247.

[19] Plaintiffs cite to expert Randolph Wall, Ph.D. as part of their enablement argument. Dr. Wall is an expert in the fields of immunology, molecular biology, and antibody engineering. (ECF No. 688 at 122 ¶ 22). Plaintiffs more heavily rely on his testimony on obviousness and therefore he is fully introduced in the obviousness section of this Opinion.

Furthermore, the Patents-in-Suit, and in particular the '522 Patent, provide a POSA with sufficient guidance on how to make etanercept. Specifically, both Patents-in-Suit explain to a POSA how to prepare a cDNA encoding the extracellular region of the known p75 protein. '182 Patent (JTX-1) col. 16:22-48, 5:22-24, 7:24-46; 9/18 AM (Naismith) Tr. at 60:13-62:6; 9/18 PM (Naismith) Tr. at 53:12-54:6; 9/20 AM (Wall) Tr. at 93:14-94:16. The specifications also provide a POSA with information regarding how to prepare a cDNA encoding all of the domains of a human IgG1 constant region, except the first, including identifying a publicly accessible exemplary vector pCD4-Hγ1. '182 Patent (JTX-1) col. 8:56-9:3; 9/20 AM (Wall) Tr. at 94:17-95:19.

Finally, Plaintiffs' witnesses Dr. Naismith and Dr. Loetscher credibly testified that the '182 Patent directs a POSA to follow the recipe set forth in Example 11 contained in the specification. 9/17 (Loetscher) Tr. at 56:5-9 (Dr. Loetscher noting that the example "describe[s] the process [of] how to make TNF receptor fusion proteins"); 9/18 AM (Naismith) Tr. at 53:22-54:2. Defendants' expert Dr. Capon even appeared to acknowledge that Example 11 in conjunction with the prior art would have enabled a POSA to construct etanercept. *See* 9/13 PM (Capon) Tr. at 72:3-73:14. Hence, as Plaintiffs submit, a POSA could have easily made the claimed fusion protein (i.e., a fusion protein that had the extracellular region of the p75 receptor with an exon-encoded hinge and the CH2-CH3 region of the IgG1 immunoglobulin) of the '182 Patent in or before August 1990 with only routine experimentation by adapting Example 11 to make the claimed fusion protein. 9/17 (Loetscher) Tr. at 58:18-59:5; 9/18 AM (Naismith) Tr. at 93:12-22 (Dr. Naismith explaining that a POSA would have been able to make Example 11 in August of 1990); 9/20 AM (Wall) Tr. at 95:17-19 (Dr. Wall testifying that a POSA would have "been able to adapt Example 11 to make the claimed fusion protein."); JTX-82 (Lesslauer Deposition) at 298:11-14, 17. The

Court finds that based on this evidence, Defendants have not met their burden of proving by clear and convincing evidence that the Patents-in-Suit fail to meet the enablement standard.

B. Obviousness (35 U.S.C. § 103)

To prove that an asserted claim of a patent is invalid as obvious under 35 U.S.C. § 103, a patent challenger bears the burden of establishing by clear and convincing evidence that 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 [POSA]."[20] 35 U.S.C. § 103(a); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360-61 (Fed. Cir. 2007). Obviousness is a question of law that is predicated on several factual inquiries. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966). Specifically, there are four basic factual inquiries which concern: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art;[21] (3) the differences between the claimed subject matter and the prior art; and (4) objective indicia (secondary considerations) of non-obviousness, including unexpected results, success and praise in the industry, long-felt but unsolved need, failure of others, and other indicia. *See id.*

Defendants assert that the Patents-in-Suit are invalid because they are obvious in view of prior art that would have motivated a POSA to create etanercept prior to the relevant patent

[20] The pre-America Invents Act version of 35 U.S.C. § 103 applies to the Patents-in-Suit.

[21] The parties agree as to the level of ordinary skill in the art. Defendants present that a POSA is "a scientist with an M.D. or a Ph.D. degree in biology, molecular biology, biochemistry, chemistry, or a similar field." 9/11 PM (Blobel) Tr. at 30:14-31:18. Such a person would "have one to two years of experience in the field of immunology or molecular immunology, including experience with cloning and expression of DNA, protein biochemistry on cell culture, protein purification, and immunological assays." Id. Plaintiffs offered a definition that is not materially different. *See* 9/20 AM (Wall) Tr. at 18:5-22; Pls. Br. at 24.

applications.[22] Defs. Br. at 35-43; *see also* Defs. Reply Br. at 19-22. At trial, Defendants asserted six obviousness combinations of prior art references, two of which disclose the protein sequence of, and the DNA sequence that encodes, the p75 extracellular region (Smith 1990 and Immunex's U.S. Patent No. 5,395,760 (JTX-65) (the "Smith '760 Patent")). PFOF ¶ 147. The other asserted prior art references disclose Ig fusion proteins, which combine a receptor protein with various portions of an Ig heavy chain. Id. Specifically, the first five (5) combinations are the Smith '760 in view of: (1) the Seed European Patent Application No. 0325262 ("Seed '262"); (2) Byrn, R. et al., *Biological Properties of a CD4 Immunoadhesin*, Nature 344: 667-70 (1990) ("Bryn 1990"); (3) Watson, S. et al., *A Homing Receptor-IgG Chimera as a Probe for Adhesive Ligands of Lymph Node High Endothelial Venules*, J. Cell. Bio. 110: 2221-2229 (1990) ("Watson 1990"); (4) the Karjalainen European Patent Application No. 0394827 ("Karjalainen '827"); and (5) the Capon U.S. Patent No. 5,116,964 ("Capon '964") in further view of Traunecker, A. et al., *Highly Efficient Neutralization of HIV with Recombinant CD4-immunogloblin Molecules*, Nature 339: 68-70 (1989) ("Traunecker 1989"). The sixth combination was Smith 1990 in view of Watson. Id. ¶ 147 n.3. Defendants' post-trial arguments regarding these prior art references focus on motivation. Defs. Br. at 35 ("[T]he only real dispute as to obviousness of the asserted claims concerned motivation."). The Court has examined the asserted prior art references both alone and in combination, as discussed below, to determine motivation and whether it would have been obvious to a POSA to create etanercept.

In addition, Defendants argue that certain secondary considerations prove, rather than refute, that the Patents-in-Suit are invalid for obviousness. Id. at 44-50. In support of their

[22] The Court notes that the USPTO considered these prior art references and concluded that the Patents-in-Suit were not obvious in light of these references. 9/12 AM (Blobel) Tr. at 33:25-39:4; PTX-1089 at 19; PTX-6.456 at 7-8.

obviousness arguments, Defendants primarily rely on (1) Dr. Blobel, introduced above; and (2) Arne Skerra, Ph.D, Chair of Biological Chemistry at the Technical University of Munich, Center of Life Sciences at Weihenstephan, Freising, Germany. ECF No. 688 at 131-32 ¶¶ 43, 49.[23]

Plaintiffs contend that Defendants' obviousness arguments fail because a POSA would not have been motivated to create etanercept based on the prior art and, in fact, would have actually been dissuaded by the prior art to create a TNFR-Ig fusion protein to treat inflammation. Pls. Br. at 22-23. Further, Plaintiffs counter each of Defendants' secondary consideration arguments as set forth below and contend that the secondary considerations support nonobviousness. Id. at 33-39. Plaintiffs rely on (1) Randolph Wall, Ph.D., a Distinguished Professor in the Department of Microbiology, Immunology, and Molecular Genetics at the Molecular Institute, University of California at Los Angeles (UCLA) and the David Geffen School of Medicine at UCLA, as an expert on obviousness (ECF No. 688 at 122 ¶ 22); and (2) Warner C. Greene, M.D., Ph.D., the Founder and Director of the Gladstone Institute of Virology and Immunology in San Francisco and a Distinguished Professor of Translational Medicine with over 40 years of experience in biomedical research, as an expert on etanercept's effect on the immune system (Id. at 124-25 ¶ 29).

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[23] Plaintiffs assert that the testimony of Defendants' expert Dr. Blobel should be completely disregarded because he ignored the agreed upon claim construction. Pls. Br. at 23-24; ECF No. 688 at 20 ¶ 68. While the parties agreed to construe the claim term "all of the domains of the constant region of a human immunoglobulin IgG[1] heavy chain other than the first domain of said constant region" as having a three-cysteine hinge ("the exon-encoded-hinge-CH2-CH3 region of human [IgG/IgG1]"), Dr. Blobel inconsistently testified that a two-cysteine hinge would be within the scope of the claims of the Patents-in-Suit. 9/12 AM (Blobel) Tr. at 30:19-24; ECF No. 688 at 20 ¶ 68. Although an obviousness analysis based on "an incorrect understanding of the claim construction" may be disregarded, the Court will still consider Dr. Blobel's testimony to the extent it is not inconsistent with the agreed upon claim construction, including his testimony about other fusion proteins referenced in the prior art and testimony about what would have motivated a POSA to create etanercept before August 1990. *See Cordis Corp. v. Bos. Sci. Corp.*, 658 F.3d 1347, 1357-58 (Fed. Cir. 2011).

For the reasons discussed below, the Court finds that Defendants have failed to prove by clear and convincing evidence that the Patents-in-Suit are invalid based on obviousness pursuant to 35 U.S.C. § 103.

1. Scope of the Prior Art and Differences Between the Prior Art and the Claimed Invention

The Patents-in-Suit provide for a fusion protein, etanercept ('182 Patent), consisting of the extracellular portion of a p75 TNFR combined with a three-cysteine, exon-encoded hinge-CH2-CH3 portion of an IgG1, and a method of making this fusion protein ('522 Patent). *See generally* '182 Patent (JTX-1) and '522 Patent (JTX-2). Therefore, to prove obviousness, Defendants have to show by clear and convincing evidence that the claimed invention, which consists of a precise combination of specific portions of p75 TNFR and IgG1, would have been obvious to a POSA.

Defendants point to various scientific publications and patent applications that they contend render the claimed invention obvious. Some of these prior art references relate to p75 TNFRs—Smith 1990 and Smith '760—and others disclose Ig fusion proteins without p75—Capon 1989, Traunecker 1989, Seed '262, Capon '964, Byrn 1990, and Watson 1990. DFOF ¶¶ 208-09, 217-20. Defendants contend that a POSA would have been motivated, when viewing these references alone and in combination, to select p75 and IgG1 and combine them to create etanercept. Id.; Defs. Br. at 37-41. According to Plaintiffs, these references would not have motivated a POSA to make the precise construct of etanercept because there was no clear direction in the prior art, and in fact, the prior art would have taught away from creating etanercept. Pls. Br. at 24-29. The Court will address the prior art concerning both TNFRs and Ig fusion proteins individually and then discuss the motivation to combine the two elements in the specific way necessary to create the claimed invention.

a) *The Prior Art Would Not Have Motivated a POSA to Select the Individual Components of Etanercept, and in Fact Taught Away from Using these Components*

i. *Selecting p75 TNFR*

The Patents-in-Suit identify p75 TNFR as one of the two components of etanercept, a fusion protein used to treat rheumatoid arthritis. As noted above, rheumatoid arthritis is an inflammatory autoimmune disease that arises when an overactive immune system attacks a person's own body. PFOF ¶ 32; 9/12 AM (Blobel) Tr. at 39:24-40:2. Chronic inflammation in rheumatoid arthritis patients causes bone erosion and also destroys tendons and ligaments. PFOF ¶¶ 33-34. As such, scientists studying auto-immune disorders, such as rheumatoid arthritis, in 1990 were seeking to reduce inflammation by interrupting the body's immune system. 9/20 AM (Wall) Tr. at 39:24-40:3.

According to scientists, there was a prevailing view at the time that many cytokines, including TNF, were thought to be involved in excess inflammation. PTX-34 at 6 ("It is a misconception to think that TNF[] was an obvious therapeutic target in the early 1990s since it is pro-inflammatory. . ."). As previously discussed, cytokines are messenger proteins with a wide variety of functions in the body. PFOF ¶ 27. TNF was one of dozens of cytokines known in 1990. Id. ¶ 28. Critically, the prior art demonstrates that researchers at the time were concerned that TNFRs could aggravate pro-inflammatory responses by binding TNF and then releasing it back into the body in active form, causing inflammation. 9/20 AM (Wall) Tr. at 28:24-33:15. At trial, Dr. Wall testified that this would be "a very undesirable outcome" for a POSA trying to block inflammation possibly caused by excess TNF. Id. Because the treatment of auto-immune disorders was based on trying to inhibit inflammation caused by the TNF response, a POSA would have been discouraged from using TNFR as a treatment option.

Additionally, a POSA in 1990 would have considered cytokines to be "poor therapeutic targets" and therefore TNFR would not have been an obvious choice. PFOF ¶ 149; 9/20 AM (Wall) Tr. at 20:4-10. By August of 1990, the art had identified several cytokines and discovered that these cytokines were redundant, which means that they had "overlapping functions." 9/20 AM (Wall) Tr. at 37:16-25. Because of this redundancy, a POSA would not have considered any individual cytokine to be a good therapeutic target because it was understood that if you blocked one cytokine, another cytokine would be able to fill in the missing function, thereby eliminating any beneficial effect. Id. Moreover, cytokines, including TNF, were difficult to study due to their many different roles in the body, causing their function in treating various diseases to remain unclear. Id. at 21:7-22:18. Furthermore, if a POSA targeted cytokines at all, a POSA would have looked to a different cytokine, called IL-1, to treat inflammatory diseases because IL-1 was known in August 1990 to have stronger potential as a mediator in rheumatic diseases. Id. at 23:17-24:14; PTX-10 at 8.

However, even if TNFR were chosen as the starting point, it would not have been obvious to use a p75 TNFR. The parties agree that at least two TNF receptors were known as of August 1990, namely p55 and p75. PFOF ¶¶ 36-37; DFOF ¶ 2. Much of the literature at the time showed that p55 bound TNF with five times greater strength than p75 and was superior in neutralizing TNF. PFOF ¶ 153; JTX-47 at 3; 9/18 PM (Greene) Tr. at 108:21-109:24. Equipped with this knowledge, a POSA deciding to select TNFR to treat pro-inflammatory diseases would have likely used p55. Id. Finally, even assuming a POSA decided to use p75 instead of p55, a POSA would have also had to decide between the soluble and insoluble form of p75, which could be a partial or full-length extracellular region of the p75 TNFR. PFOF ¶¶ 154, 157; 9/12 PM (Blobel) 15:21-17:6; Smith 1990 (JTX-24) at 4; Smith '760 Patent (JTX-65) col. 4:12-21, 9:17-60.

ii. Selecting IgG1

The second necessary element of etanercept is the exon-encoded, three-cysteine hinge-CH2-CH3 domain of an IgG1. At the time etanercept was being created as a possible treatment for auto-immune disorders like rheumatoid arthritis, researchers were also studying Ig fusion proteins as a viable treatment option to combat the HIV/AIDS epidemic. PFOF ¶ 171. HIV/AIDS is a disease that greatly weakens or destroys the immune system so that the immune system becomes unable to kill HIV-infected cells on its own. Id. ¶¶ 171-72. Therefore, the goal of HIV/AIDS treatment was to trigger pro-inflammatory responses in the immune system to kill the HIV-infected cells within the body. Id. ¶ 173.

By August of 1990, prior art related to HIV/AIDS research demonstrated that Ig caused increased inflammation and aggregation, the opposite objective of treatment for auto-immune conditions. According to the prior art, Ig fusion proteins were effective in eliciting pro-inflammatory responses in the body, known as effector functions. Id. ¶¶ 173-75; 9/18 PM (Greene) Tr. at 72:13-74:13, 77:17-78:2. There are two pro-inflammatory effector functions, which are separate, complex pathways by which the immune system kills other cells. PFOF ¶ 26. First, the pathway known as complement dependent cytotoxicity ("CDC") pertains to the effector functions trigged by the CH2 domain. Id. ¶ 174. Second, the pathway known as antibody dependent cellular cytotoxicity ("ADCC") refers to the effector functions triggered by the junction between the CH2 domain and the hinge. Id. The HIV/AIDS research at the time demonstrated that Ig fragments in fusion proteins successfully triggered both CDC and ADCC effector functions within the immune system. Id. ¶ 173; 9/18 PM (Greene) Tr. at 76:8-77:2.

Against this backdrop, a POSA studying auto-immune diseases would have avoided Ig because the inflammatory immune response elicited by Ig fusion proteins was extremely

undesirable. In fact, six of the asserted prior art references cited by Defendants, all of which discuss using Ig to increase inflammatory responses in the body, would have taught a POSA to look away from Ig fusion proteins as a potential treatment option for auto-immune disorders. *See* Capon 1989 (JTX-58), Traunecker 1989 (JTX-25), Seed '262 (JTX-57), Capon '964 (JTX-61), Byrn 1990 (JTX-56), and Watson 1990 (JTX-59).[24]

For example, in his 1989 article, Defendants' expert Dr. Capon reported experimental results of CD4-Ig fusion proteins that successfully triggered pro-inflammatory immune responses in HIV-infected patients by eliciting effector functions. JTX-58 at 4 (demonstrating that effector functions were "found in the constant region of the heavy chain"). The Traunecker 1989 prior art reference found a similar result with CD4-Ig fusion proteins using mouse IgG2a and mouse IgM sequences. JTX-25 at 1-2; 9/12 AM (Blobel) Tr. at 51:11-16; 9/18 PM (Greene) Tr. at 84:12-19; 9/20 AM (Wall) Tr. at 56:24-57:13. Published in July 1989, Seed '262 described CD4-Ig fusion proteins designed to treat HIV/AIDS patients and emphasized the importance of preserving

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[24] Although Watson 1990 (JTX-59) concerned studies outside of the body for which effector functions would not be relevant and therefore were not specifically discussed, similar constructs to those discussed in Watson 1990 (*e.g.*, Byrn 1990) were demonstrated through experimental evidence to have retained cell-killing effector functions. 9/20 AM (Wall) Tr. at 61:9-13, 259:12-22; JTX 59 at 3, 8.

Defendants also cite to Karjalainen '827, a European patent application published in October 1990. JTX-60 at 1; PFOF ¶ 191. The parties' experts agreed that this reference is not prior art for purposes of their analysis. 9/12 AM (Blobel) Tr. at 84:3-12; 9/20 AM (Wall) Tr. at 84:11-16. Moreover, Karjalainen '827 is exempt as prior art under § 103(c)(1) because the inventors of Karjalainen '827 and the Patents-in-Suit "were at the time the claimed invention was made . . . [both] subject to an obligation of assignment to the same person," F. Hoffmann-La Roche AG. 35 U.S.C. § 103(c)(1) ("Subject matter developed by another person . . . shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person."); 9/17 (Loetscher) Tr. at 21:11-13; JTX-3 at 875-79; JTX-4 at 706-10; JTX-60 at 1. In any event, Karjalainen '827 also taught use of a CD4-Ig fusion protein to elicit effector functions to treat AIDS. PFOF ¶ 192.

effector functions to properly combat HIV-infected cells. JTX-57 at 5. Similarly, Capon '964 described many different Ig fusion protein configurations that were intended to retain effector functions. JTX-61 col. 4:43-47; 9/12 AM (Blobel) Tr. at 60:24-61:13; PFOF ¶¶ 185-86. Moreover, Byrn 1990 provided experimental evidence demonstrating that a protein with only a partial Ig hinge would still successfully induce ADCC effector functions. JTX 56 at 1-2; 9/12 AM (Blobel) Tr. at 70:18-71:16; 9/18 PM (Greene) Tr. at 87:5-19. Based on these prior references, a POSA would have refrained from using Ig fusion proteins for anti-inflammatory treatments, which sought to reduce effector functions in the body.

Defendants also assert that the Patents-in-Suit are obvious in light of the combination of Watson 1990 and Smith 1990. PFOF ¶ 147 n.3. Smith 1990 disclosed the amino acid sequence of p75 TNFR but did not suggest using p75 TNFR in a fusion protein. DFOF ¶ 4. Moreover, Watson 1990 also did not contemplate a TNFR-Ig fusion protein and instead discussed a construct with a partial region of an Ig fused with a receptor known as a lymphocyte homing receptor. JTX-59 at 1-3; 9/20 AM (Wall) Tr. at 61:9-13; PFOF ¶ 194. Therefore, a POSA looking to these two prior art references either individually or in combination would not have been motivated to create etanercept.

Defendants further point to Capon '964 and additional prior art, namely Brennan 1989, to assert that researchers at the time were not concerned about the negative effects from effector functions. DFOF ¶ 226-27.[25] However, prior art published in June 1990 shows that effector functions were in fact a concern with Ig fusion proteins at the time of the invention. *See* Gerd

[25] It appears that many of the prior art references cited by the Defendants used to support the modification of Smith '760 were published prior to Smith '760. Pls. Reply Br. at 12 (noting that Traunecker 1989, Seed '262, Capon '964, and Byrn 1990 were published before Smith '760 and did not motivate the Smith '760 inventors to remove the light chain or CH1 domain).

Zettlmeissl, et al., *Expression and Characterization of Human CD4: Immunoglobulin Fusion Proteins,* DNA & Cell Biology 9: 347-53 (1990) (PTX-26 at 5-10) (discussing CD4-Ig fusion proteins created to treat HIV/AIDS and reporting that "one of the most important issues confronting" Ig fusion proteins was "the extent of autoimmune damage" caused by effector functions); *see also* 9/12 AM (Blobel) Tr. at 81:15-83:13. Additionally, a well-known immunology textbook by William E. Paul and Dr. Wall's credible testimony further demonstrate that a POSA would have expected that pro-inflammatory effector functions would have been triggered when a fusion protein, like etanercept, attached to a soluble TNF. *See* Paul, William E., *Fundamental Immunology* (2d ed., Raven Press 1989) (PTX-3); 9/20 AM (Wall) Tr. at 46:18-48:22, 49:6-53:8. Furthermore, the fact that the papers cited by Defendants did not report effector functions as problematic is reasonable in the context of HIV/AIDS research where effector functions were a desired result, rather than an obstacle. Thus, the Court finds that a POSA would have expected from the prior art that an Ig fusion protein could lead to autoimmune damage caused by effector functions. 9/20 AM (Wall) Tr. at 39:14-40:9, 59:3-18; 9/18 PM (Greene) Tr. at 90:25-91:16.

The prior art also taught that Ig fusion proteins would cause another detrimental effect, known as aggregation, in patients with inflammatory conditions. Plaintiffs' expert in immunology, Dr. Greene, opined that an Ig fusion protein would likely cause aggregation—the formation of large immune complexes in the human body—that would then lead to increased inflammation in the kidney, skin, and joints. 9/18 PM (Greene) Tr. at 98:1-16, 137:4-12. Based on the prior art, a POSA would have believed that an Ig fusion protein, like etanercept, would have likely aggregated and caused an inflammatory response, as Defendants' expert Dr. Blobel similarly opined. 9/18 PM (Greene) Tr. at 70:17-71:2; *see also* 9/12 AM (Blobel) Tr. at 53:23-54:24 (testifying that

researchers at the time were intentionally creating CD4-Ig fusion proteins to cause aggregation and attack infected cells). Therefore, a POSA would have refrained from selecting Ig for the treatment of auto-immune disorders because it was shown to increase aggregation, resulting in heightened inflammation.

Additionally, a POSA seeking to avoid using Ig at the time would have had a number of non-Ig options to achieve desirable outcomes while avoiding effector functions. PFOF ¶ 155. In fact, prior art at the time suggested joining proteins with polyethelene glycol ("PEG"), a non-Ig option that did not cause effector functions and was also associated with longer half-lives and better drug properties at that time. Id.; 9/20 AM (Wall) Tr. at 68:19-70:24; *see, e.g.,* Smith '760 Patent (JTX-65) col. 10:39-44. By August 1990, numerous PEG-modified proteins were in clinical trials and at least one PEGylated compound had been approved by the FDA. PFOF ¶ 155; 9/20 AM (Wall) Tr. at 68:22-70:24; *see* Smith '760 Patent (JTX-65) col. 10:35-53. Given that the prior art showed that Ig was increasing inflammation, PEG was a more obvious choice to use in a fusion protein than Ig.

Nevertheless, even if a POSA was undeterred by the research that predicted an inflammatory response and decided to create an Ig fusion protein, a POSA would have had numerous options when determining what type and conformation of Ig to select. While etanercept used IgG1, there were many alternative Ig constructions that a POSA could have selected, none of which was more obvious than the other. For example, a POSA would have had to choose from many known classes of immunoglobulins (Ig), such as IgG, and further choose between the subclasses of IgG, including IgG1, IgG2, IgG3, and IgG4. 9/18 AM (Naismith) Tr. at 51:11-13; *see supra* I.B.1. Moreover, a POSA would have had to consider and decide between the variety of Ig conformations in the prior art including a full hinge, an exon-encoded hinge, a two-cysteine

hinge, or no hinge. PFOF ¶ 159; 9/20 AM (Wall) Tr. at 82:24-83:8; *see also* 9/12 PM (Blobel) Tr. at 34:5-13, 39:24-40:11 (Dr. Blobel testifying that it was "not so obvious" to use a three-cysteine hinge as opposed to a two-cysteine hinge). Finally, as reflected in the prior art above, a POSA selecting Ig would have had to decide whether to use a linker, and if so, would have also had to determine which length to use. PFOF ¶ 159; 9/20 AM (Wall) Tr. at 82:1-4, 88:17-90:1. Accordingly, a POSA choosing to select Ig, despite the scientific research teaching that this was not a desirable option, would still have had many different variations and configurations of Ig to opt for when creating the fusion protein. Defendants have failed to sufficiently prove by clear and convincing evidence that it was obvious for a POSA to select IgG1, as used in etanercept, among all of these alternatives.

b) It Would Not Have Been Obvious to a POSA to Combine p75 with the Exon-Encoded Hinge-CH2-CH3 Region of IgG1

Furthermore, even assuming it was obvious to select both p75 TNFR and IgG1, a claim cannot be held obvious merely because its elements were independently known in the prior art. *KSR Int'l Co. v. Teleflex, Inv.*, 550 U.S. 398, 418-19 (2007); *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1068 (Fed. Cir. 2018) (stating that the "genius of invention is often a combination of known elements which in hindsight seems preordained"). Defendants must prove by clear and convincing evidence that a POSA would have been motivated to combine the essential components from the prior art teachings to create the claimed invention, and would have had a reasonable expectation of success in doing so. *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1359-61 (Fed. Cir. 2017).

Moreover, Defendants must show by clear and convincing evidence that a POSA would have been motivated to combine the specific parts of each component that make up the claimed invention, rather than only showing it was obvious to combine p75 and IgG1. *See id.* (finding that

the required motivation is a motivation to combine prior art to achieve ***the particular claimed invention***). Merely combining p75 TNFR and IgG1 would not have resulted in etanercept because the claimed invention specifically joins the extracellular region of p75 and only a portion of IgG1, namely the exon-encoded hinge-CH2-CH3 domain. '182 Patent (JTX-1);'522 Patent (JTX-2). Therefore, Defendants must demonstrate that a POSA would have been motivated to create the precise TNRF-IgG1 construct that is etanercept.

As addressed above, the prior art cited by Defendants taught that Ig fusion proteins activated effector functions leading to inflammation in the body. *See supra* III.B.1.a.ii. Given this prior art, a POSA would have expected a fusion protein combining TNFR and IgG1 to lead to autoimmune damage caused by effector functions. 9/20 AM (Wall) Tr. at 39:14-40:9, 56:7-16; 9/18 PM (Greene) Tr. at 90:25-91:16. Therefore, for all of the reasons stated above, a POSA looking to treat an autoimmune condition, such as rheumatoid arthritis, would have been dissuaded from combining TNFR with IgG1.

Despite the prior art, Defendants assert that a POSA would have been motivated to combine p75 and IgG1 to produce etanercept because this combination was already described in the Smith '760 Patent. Defs. Br. at 37. However, this argument fails because, as discussed below, (1) Smith '760 was an unconstructed, untested chimeric antibody that would not have been an obvious starting point; (2) the Smith '760 construct was distinct from etanercept; and (3) a POSA would not have been motivated to modify Smith '760 in the precise ways necessary to create etanercept.

i. A POSA Would Not Have Ignored the Prior Art Concerning Effector Functions in Ig Fusion Proteins Because of the Smith '760's Hypothetical Antibody

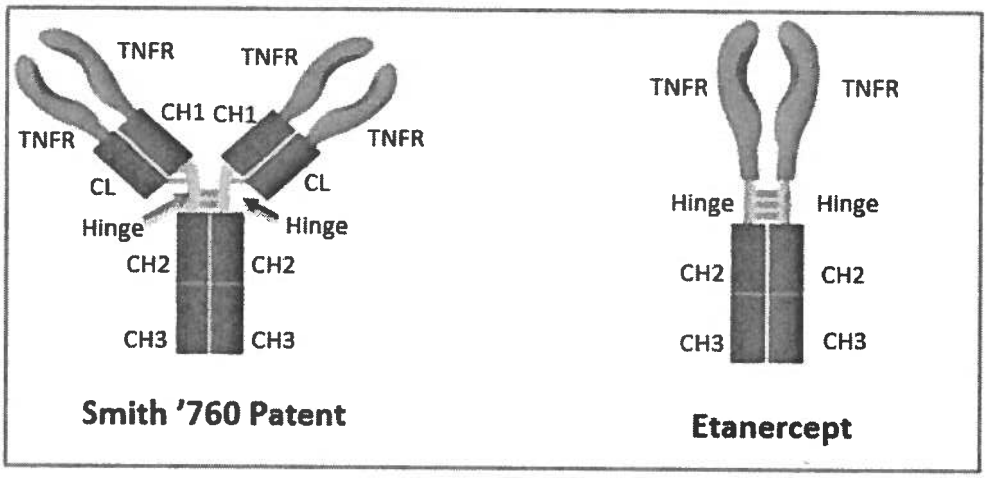
First, the Smith '760 Patent, filed in May 1990, described a hypothetical construction of a TNFR-IgG1 chimeric antibody that was never made. PFOF ¶ 164; DFOF ¶ 210; 9/12 PM (Blobel) Tr. at 84:5-7. There is no prior art that suggests exactly how the Smith '760's construct may have

been used, much less that it was known to have desirable therapeutic properties. Defendants argue that a POSA would have obviously looked to the Smith '760 fusion protein because this protein was expected to have advantageous properties, including an "extended *in vivo* half-life, ease of purification, and enhanced TNF binding." Defs. Br. at 38. However, as outlined above, the prior art actually taught away from using an Ig fusion protein, such as the one proposed in Smith '760, to treat auto-immune diseases because such a construct would have likely elicited an inflammatory response in the body. *See supra* III.B.1.a.ii. The speculative expectations of Smith '760's unconstructed chimeric antibody would not have been enough to compel a POSA to ignore the numerous experimental studies that revealed that Ig proteins elicited an inflammatory response and use the Smith '760's fusion protein as a starting point to create an anti-inflammatory drug. It is not obvious that a POSA would have selected this idea as a possible solution for patients with pro-inflammatory conditions when the therapeutic effects of this chimeric antibody were uncertain, at best.

ii. Etanercept Is Distinct from Smith '760 Such That it Cannot Render the Patents-in-Suit Obvious

Second, etanercept is not an obvious variant of the Smith '760 Patent because the Patents-in-Suit claim a distinct fusion protein. Smith '760 teaches fusing a portion of TNFR to a human IgG1 containing both the CH1 and the light chain (*see generally* Smith '760 Patent (JTX-65)), whereas the Patents-in-Suit require the removal of the CH1 and the light chain from the constant region domain of IgG1 (*see* '182 Patent (JTX-1) col. 39:12-42:34; '522 Patent (JTX-2) col. 45:44-48:4). The Smith '760 Patent also discussed a number of ways to construct the fusion site of the TNFR, none of which suggested directly fusing the TNFR to the hinge. *See* Smith '760 Patent (JTX-65) col. 10:33-56; PFOF ¶ 166. The Patents-in-Suit directly fused the extracellular region

of p75 to the exon-encoded hinge-CH2-CH3 region of IgG1. '182 Patent (JTX-1) col. 39:12-42:34; '522 Patent (JTX-2) col. 45:44-48:4.



In contrast to Smith '760, etanercept specifically uses only a portion of IgG1, namely the partial exon-encoded hinge-CH2-CH3. Defendants have not pointed to any prior art that recommends using the exon-encoded hinge-CH2-CH3 of IgG1 for such a fusion protein, or any reference that advises fusing this portion to the extracellular region of p75. This concept was not taught in the prior art, rendering etanercept a distinct, nonobvious construction from Smith '760. *Compare* '182 Patent (JTX-1) and '522 Patent (JTX-2) *with* Smith '760 Patent (JTX-65) at 10:53-68. Defendants have failed to show why a POSA would have been motivated to combine the specific parts of IgG1 and p75 that make up the claimed invention.

Moreover, the specific construct within Smith '760 that Defendants compare to the distinct construct of etanercept, as pictured above, was only one of many contemplated in Smith '760. In hindsight, Defendants assert that this one construct contemplated in Smith '760 would have obviously motivated a POSA to create etanercept. This assertion ignores the fact that had a POSA looked to Smith '760 in its entirety, the POSA would have had to consider and select among a broad array of options as the patent suggested a variety of different constructs to pursue, none of

which were ever actually constructed or determined to be preferred. The Smith '760 Patent embraces many variations, including both monovalent and polyvalent forms of TNFR, and further reports a wide variety of choices for the polyvalent forms. *See* Smith '760 Patent (JTX-65) at 13; PFOF ¶¶ 165-67. Among these possibilities was combining p75 with PEG, which as mentioned above was a widely used and FDA approved non-Ig construct. It appears Defendants focused on a single construct "out of the sea" of alternatives based on hindsight reasoning notwithstanding other potential constructs contemplated in Smith '760 that refuted their assertions. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1337 (Fed. Cir. 2016). Therefore, Defendants have failed to show by clear and convincing evidence that a POSA looking to Smith '760 for motivation would have decided on the specific construct of p75 and IgG1.

iii. A POSA Would Not Have Been Motivated to Modify Smith '760 by Removing the Light Chain, Removing the CH1 Domain, and Directly Fusing the p75 Protein to the Exon-Encoded Hinge-CH2-CH3 Region

Third, a POSA would not have been motivated to alter the Smith '760 fusion protein in the specific ways necessary to create etanercept. To modify Smith '760 and construct etanercept, a POSA would need to have been motivated to remove the CH1 domain, eliminate the light chain, and directly fuse the extracellular region of p75 to the exon-encoded hinge-CH2-CH3.

As to the removal of the CH1 domain and the light chain, a POSA would not have been motivated to make these modifications to Smith '760 based on the patent itself. First, Smith '760 specifically states that its construct must have "unmodified constant region domains[,]" signifying to a POSA that the light chain and CH1 should not be modified if the POSA wished to maintain all of the alleged advantageous properties of Smith '760. *See* Smith '760 Patent (JTX-65) col. 10:53-57; Defs. Br. at 38. Accordingly, a POSA looking to Smith '760 for motivation would have been discouraged from altering the constant region by removing the light chain and CH1.

However, even if a POSA were to ignore this statement, there was no clear evolution in the prior art that would have taught a POSA to eliminate the light chain or the CHI domain. If anything, the prior art would have dissuaded a POSA from making these modifications to Smith '760 based on their proven increase in effector functions.

Furthermore, in analyzing the cited prior art beyond Smith '760, it would not have been obvious to a POSA to remove the CH1 and light chain because there was no clear direction in the prior art. When the prior art provides no reason to select, among several unpredictable alternatives, the exact route that would guide and/or motivate a POSA to the patented invention, then it is not obvious. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). Researchers at the time, many of whom were seeking treatment for HIV/AIDS patients, were modifying fusion proteins in a number of different ways and no one way was known to definitively work better than the other. For example, with respect to removal of the light chain, Defendants point to Dr. Capon's 1989 article, mentioned above, that disclosed several CD4-Ig fusion proteins, including proteins that retained the light chains and those that lacked the light chain. DFOF ¶ 216; JTX-58 at 1-2. Additionally, prior art references that contemplated removing the CH1 domain, such as the Seed '262 and Capon '964 publications, disclosed a variety of constructs, including proteins with the CH1 domain and those that deleted it. JTX-57 at 10; JTX-61 at 28; 9/20 AM (Wall) Tr. at 79:12-21. No one arrangement could have been considered to be predictable in its effect as even Dr. Capon found the results of his own constructs to be "surprising." JTX-58 at 4-5; 9/12 AM (Blobel) Tr. at 46:8-11. Therefore, the prior art was in a state of uncertainty and had many variables, such that creating etanercept using only the CH2-CH3 domain of the IgG1 immunoglobulin would not have been obvious.

In fact, a POSA would have been disincentivized to remove the CH1 chain because the prior art established that Ig fusion proteins without the CH1 domain created additional effector functions, thereby intensifying the inflammatory response. 9/20 AM (Wall) Tr. at 78:20-79:6. According to the prior art, HIV/AIDS researchers were removing CH1 to successfully *increase* the effector functions—an undesired response for an anti-inflammatory drug. 9/18 PM (Greene) Tr. at 84:12-19 (Dr. Greene explaining that removal of the CH1 domain was shown to cause an inflammatory response). For example, Byrn 1990 provided experimental evidence that CD4-Ig fusion proteins lacking CH1 would trigger the ADCC effector function as desired for HIV/AIDS treatments. JTX-56 at 1-2; 9/12 AM (Blobel) 70:18-71:15. Such a result would have been contrary to a goal of reducing inflammation, and therefore a POSA would have been dissuaded to alter the Smith '760 protein in this way. Moreover, Defendants point to Traunecker 1989, which found that the pro-inflammatory response of the Ig fusion protein remained strong despite eliminating the CH1 domain in mouse fusion proteins. JTX-25; 9/20 AM (Wall) Tr. at 78:18-79:1. Based on this finding, a POSA seeking new therapies for auto-immune disorders would not have been motivated to remove the CH1 domain because Traunecker 1989 showed that removing CH1 retained the inflammatory effects. *See* 9/20 AM (Wall) Tr. at 78:20-79:1.

Defendants specifically aver that a POSA would have been motivated to eliminate the CH1 domain and the light chain of the Smith '760 protein, as was done in etanercept, because these deletions were known to improve the secretion of fusion proteins, a desirable feature because it allowed the fusion protein to leave the cell. *See* Defs. Br. at 39; DFOF ¶ 325. However, Dr. Capon's 1989 paper that Defendants use to support this argument reported that secretion problems actually arose when the light chain was removed from CD4 fusion proteins. JTX-58 at 2. Furthermore, even if the deletion of the CH1 domain did increase secretion, a POSA would have

likely avoided eliminating the CH1 domain because removal was known to elicit effector functions and increase inflammation, as discussed above.

Lastly, a POSA would not have been motivated to remove the linker and directly fuse the p75 extracellular region to the full exon-encoded hinge. Again, Defendants cite to a number of references teaching multiple variations of what fragments a POSA could use, including many references that recommend using a partial hinge and/or a linker. *See, e.g.*, JTX-57 at 10:57-11:2 (Seed '262 describing the use of a five amino acid linker); JTX-56 at 1-2 (Byrn 1990 using a partial two-cysteine hinge); JTX-25 at 1 (Traunecker 1989 contemplating the removal of the entire hinge). Based on the uncertainty in the art, it would not have been obvious to a POSA to remove the linker or to use the full exon-encoded hinge. *See Ortho-McNeil Pharm.*, 520 F.3d at 1364 (holding that the patented invention was not obvious where a POSA had no reason to select the exact route among several unpredictable alternatives).

Defendants have failed to show by clear and convincing evidence that it would have been obvious to a POSA to create etanercept by precisely combining specific portions of TNFR and IgG1 prior to August 1990.

2. Objective Indicia of Nonobviousness

As part of its obviousness analysis, the Court must also consider evidence regarding objective considerations of nonobviousness when present. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075-77 (Fed. Cir. 2012). Secondary considerations such as unexpected results, success, long felt but unsolved needs, and the failure of others may be relevant indicia of nonobviousness. *See Graham*, 383 U.S. at 17-18; *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006). Moreover, evidence of copying, simultaneous invention, and licensing may also be considered. *See Diamond Rubber Co. v. Consol. Rubber Tire Co.*, 220 U.S. 428, 441 (1911); *Geo. M. Martin Co. v. Alliance Mach. Sys.*

Int'l LLC, 618 F.3d 1294, 1304 (Fed. Cir. 2010); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1539 (Fed. Cir. 1983).

The parties have both presented evidence of certain objective indicia that they argue support their obviousness arguments, all of which are discussed below. A number of witnesses opined on these objective indicia including, for the Plaintiffs, (1) Dr. Naismith, as mentioned above; (2) Dr. Greene, as mentioned above; and (3) Dr. Fleischmann, an expert in the field of rheumatic diseases and disorders, who is the Founder and Co-Medical Director of the Metroplex Clinical Research Center in Dallas, Texas, and a Clinical Professor in the Department of Internal Medicine at the University of Texas, Southwestern Medical Center at Dallas (ECF No. 688 at 121 ¶¶ 19-21); and for the Defendants, (1) Dr. Blobel, as mentioned above; and (2) Dr. Skerra, as mentioned above. While both parties offered evidence of objective indicia to support their positions, the burden always remains on Defendants to prove by clear and convincing evidence that the claimed invention is obvious. *In re Cyclobenzaprine Hydrochloride,* 676 F.3d at 1075-79 (concluding that, when considering secondary considerations of nonobviousness, the burden never shifts to the patentee to prove nonobviousness and instead always remains on the party challenging the patent to prove by clear and convincing evidence that the patent at issue is obvious).

As to the objective indicia, Defendants challenge whether there is a sufficient nexus between the merits of the claimed invention and the objective evidence. Plaintiffs contend that the appropriate nexus is present and such evidence is commensurate in scope with the claims. *See Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369-70 (Fed. Cir. 2011) (concluding that, to establish a nexus to the merits of a claimed invention, the offered secondary consideration must actually result from what is both claimed and novel in the patent); *see also Dome Patent L.P. v. Rea*, 59 F. Supp. 3d 52, 86 (Fed. Cir. 2014) (holding that objective evidence of secondary

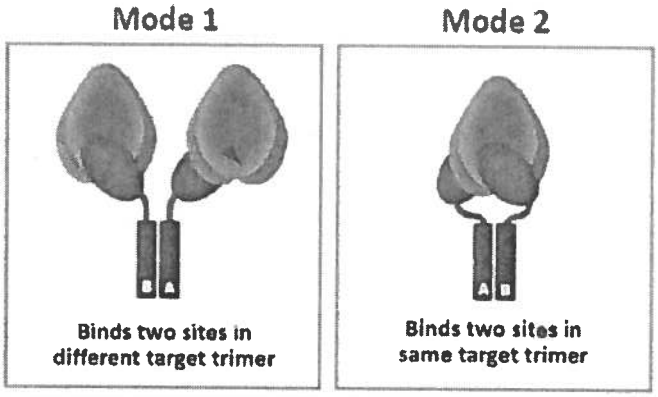
considerations must be proportional to the scope of the claims to be probative of nonobviousness). Here, the Court finds that the secondary considerations discussed below have a sufficient nexus to, and are commensurate in scope with, the claimed invention because the proffered evidence is linked to etanercept, which the Court has found was adequately described in the Patents-in-Suit. To the extent more specific arguments concerning nexus and scope were made by the parties, such assertions are addressed in the relevant sections below.

a) Unexpected Results

Unexpected or surprising results can support nonobviousness. To demonstrate unexpected results, a party must "show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). "The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results." *Id.* Plaintiffs assert that etanercept exhibits three unexpected properties: (1) a lack of aggregation with TNF due to Mode 2 binding; (2) a superior binding affinity to, and inhibition of, TNF; and (3) little to no effector functions. Pls. Br. at 33. Defendants disagree that these properties were unexpected. Defs. Br. at 45-48.

First, the Court finds that etanercept's ability to bind in Mode 2 with little to no aggregation was an unexpected result. For background, in order for etanercept to be effective, the TNFR in etanercept has to bind to TNF. 9/20 PM (Fleischmann) Tr. at 149:11-17. Etanercept is a bivalent fusion protein, which means that it has two binding sites. DFOF ¶ 238. Dr. Naismith explained that fusion proteins like etanercept can potentially bind to TNF in either one of two ways: (1) Mode 1 binding, which occurs when a bivalent fusion protein binds two TNF cytokines at each of its two separate binding sites, (9/18 AM (Naismith) Tr. at 110:13-21 (explaining that etanercept has two "hand[s]," and that in "Mode 1" binding each hand would attach to a different TNF

molecule)); or (2) Mode 2 binding, which occurs when a bivalent fusion protein binds one TNF with both binding sites.[26] DFOF ¶ 238; 9/24 AM (Skerra) Tr. at 39:25-41:24; 9/18 AM (Naismith) Tr. at 110:10-111:13; Defendants' Trial Exhibit-84 at 5. While Mode 1 binding is very common in protein constructs similar to etanercept, (*see* 9/18 AM (Naismith) Tr. at 112:1-5), Mode 2 binding, which occurs in etanercept, is much rarer because the receptors have to be precisely arranged for Mode 2 binding to work. *See* id. at 110:22-111:8.



DFOF ¶ 238.

Despite the fact that Mode 2 binding was uncommon in proteins similar to etanercept, etanercept surprisingly engages in Mode 2 binding, which is one of the reasons why it effectively treats rheumatoid arthritis.[27] 9/18 AM (Naismith) Tr. at 114:19-115:23. Plaintiffs' expert Dr. Naismith credibly explained that a POSA in 1990 would have expected etanercept to bind in Mode 1 because Mode 1 had fewer limitations and, as a result, was much more likely in antibodies similar

[26] The Court notes that the parties' experts also discussed Mode 3 binding, which is an intermediate or transient step that could lead to either Mode 1 or Mode 2 binding. *See* 9/24 AM (Skerra) Tr. at 39:25-41:24; 9/18 AM (Naismith) Tr. at 111:9-13; DFOF ¶ 238.

[27] Defendants' expert, Dr. Skerra, who testified that a POSA would not have expected aggregation, was later impeached on this point because he based his opinions on a molecule that was different from etanercept and ultimately agreed that a POSA would have expected a molecule with etanercept's exact construction to have caused aggregation. 9/24 AM (Skerra) Tr. at 81:6-84:1.

to etanercept. Id. at 111:14-114:25. Etanercept's unexpected ability to bind in Mode 2 has important consequences. If etanercept had engaged in Mode 1 binding, aggregation would have resulted in the body—an undesired result for rheumatoid arthritis treatment as it leads to further inflammation. Id. at 112:13-19, 114:21-25. Mode 2 binding, however, results in little to no aggregation. 9/18 AM (Naismith) Tr. at 110:22-111:8. Hence, based on the state of the art in 1990, the Court finds that there is sufficient evidence to support the fact that etanercept's lack of aggregation due to Mode 2 binding was an unexpected and crucial result.

Second, a POSA would not have expected etanercept to bind fifty times stronger to TNF or to exhibit superior TNF-neutralizing properties. PFOF ¶ 254; PTX-73 at 4; 9/18 AM (Naismith) Tr. at 116:7-118:3. According to Defendants' expert, Dr. Capon, a POSA at the time would have thought that the binding power of an Ig fusion protein, such as etanercept, would have been weak. [28] JTX-58 at 2 (stating that Ig fusion proteins exhibit binding that is "indistinguishable" from binding as exhibited by soluble receptors, which were known to have weak binding strength at the time). Therefore, the fact that etanercept has strong binding capabilities would have been surprising to a POSA at the time. Moreover, etanercept's Mode 2 binding led to increased neutralization of TNF because etanercept bound to TNF more efficiently, reducing the amount of TNF left in the cells and thereby decreasing TNF's inflammatory effect. 9/18 AM (Naismith) Tr. at 117:17-118:3. A POSA would have also been surprised by etanercept's ability to powerfully neutralize TNF given that etanercept's ability to bind without aggregation was unexpected. Id. at 117:9-19 (Dr. Naismith concluding that prior to August 1990, a POSA would not have expected

[28] Defendants, relying on *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013), argue that etanercept's ability to strongly bind to, and effectively neutralize, TNF was not unexpected because TNF was already known to bind and neutralize soluble TNFRs. Defs. Br. at 46. However, this argument fails because the ability of TNF to effectively bind to *etanercept*—a TNFR-Ig fusion protein—rather than to a soluble TNFR, was unknown and unexpected. *See* JTX-58 at 2; 9/18 AM (Naismith) Tr. at 116:10-16, 117:7-118:3.

etanercept to produce the 1000-fold efficacy in TNF neutralization that etanercept is now known to produce).

Third, prior to August 1990, a POSA would not have expected etanercept to produce little to no undesired effector functions. 9/18 PM (Greene) Tr. at 91:17-93:12, 100:10-101:10 (Dr. Greene testifying that it was a "surprise" and "unexpected result" that etanercept produced little or no CDC or ADCC effector functions. As discussed at length above, this result would have been unknown to a POSA prior to August 1990 and supports the assertion that etanercept produced unexpected results. Id. at 70:17-71:2 (Dr. Greene comparing etanercept to the prior art and testifying that, given the results of the testing with the CD4 fusion proteins, a POSA would have expected etanercept to exhibit effector functions); *see also supra* III.B.1.a. Accordingly, the Court concludes that this evidence of unexpected results weighs in favor of finding that the claims of the Patents-in-Suit are nonobvious.

b) Praise and Clinical Success

"Evidence that the industry praised a claimed invention or a product which embodies the patent claims weighs against an assertion that the same claim would have been obvious. Industry participants, especially competitors, are not likely to praise an obvious advance over the known art." *WBIP, LLC*, 829 F.3d at 1334. The Court may also look to evidence of Enbrel®'s clinical success. *See KSR*, 550 U.S. at 415 (concluding that with respect to the question of obviousness, courts should take "an expansive and flexible approach[,]" and noting that *Graham* "set forth a broad inquiry and invited courts, where appropriate, to look at any secondary considerations that would prove instructive"). Here, Plaintiffs offered ample evidence of praise and clinical success. In fact, Defendants' counsel conceded this at the beginning of trial. 9/11 AM (Opening) Tr. at 49:20-25 (Defendants' counsel stating that they were "not going to dispute that Enbrel[®], the product, the etanercept product . . . has not been . . . commercially successful[,] . . . clinically

successful[,] ... [and] praised."). In any event, the evidence at trial confirmed that etanercept has been highly praised as a drug that has "changed the practice of medicine." 9/14 (McCamish) Tr. at 41:13-17. Enbrel® has been widely prescribed since its approval in 1998 and the number of prescriptions rose rapidly through 2008, despite shortages in supply and the entry of two major competitors into the market. 9/21 (Vellturo) Tr. at 14:22-15:19.

Nevertheless, Defendants assert that Enbrel®'s success and praise is unpersuasive because Enbrel®'s achievements are not sufficiently connected to the asserted claims of the Patents-in-Suit. *See* DFOF ¶ 335; 9/11 AM (Opening) Tr. at 49:25-50:10. The testimony at trial, however, established that Enbrel®'s success was largely rooted in the unexpected ability of etanercept, the claimed invention, to bind and neutralize TNF and its stability in the human body. 9/20 PM (Fleischmann) Tr. at 148:16-149:20 (Dr. Fleischmann testifying that the success of etanercept was due to its molecular properties and efficacy). Therefore, the Court concludes that there is a sufficient nexus between the claimed invention, etanercept, and Enbrel® because the drug's successes result from the effectiveness and novelty of etanercept, Enbrel®'s active ingredient. *WBIP, LLC*, 829 F.3d at 1331 (holding that a nexus can be presumed when the asserted objective indicia is tied to a specific product and the product is the invention claimed in the patent).

Moreover, as to whether this secondary consideration is reasonably commensurate in scope with the claims, Defendants contend that the evidence of Enbrel®'s success and praise ignores etanercept's failures in treating other conditions, such as Crohn's disease. Defs. Br. at 49. The Court has considered this argument and nonetheless concludes that Enbrel®'s success in treating rheumatoid arthritis—the focus of the litigation and the only use for which etanercept was FDA-approved in 1998—is probative of nonobviousness as etanercept was highly praised and extremely

successful in helping vast numbers of rheumatoid arthritis patients.[29] 9/20 PM (Fleischmann) Tr. at 148:16-150:20. Thus, praise and clinical success also weighs in favor of nonobviousness.

c) Long-Felt Need and Failure of Others

"Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1082-83. In order to show satisfaction of long-felt need, one must establish that (1) a POSA recognized a problem that existed for a long period of time without a solution, (2) the long felt need had not been satisfied by another before the claimed invention, and (3) the invention in fact satisfied the long-felt need. *See Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988); *In re Cavanagh*, 436 F.2d 491, 495-96 (C.C.P.A. 1971); *In re Gershon*, 372 F.2d 535, 538-39 (C.C.P.A. 1967).

The trial testimony showed that there was a long-felt need for a better treatment for rheumatoid arthritis and that Enbrel® was the first drug to successfully satisfy this need. Prior to Immunex's sale of Enbrel®, a drug known as methotrexate "was a drug of choice" to treat rheumatoid arthritis. 9/20 PM (Fleischmann) Tr. at 131:22-24, 135:21-136:3 (Dr. Fleischmann testifying that methotrexate was the best drug available to treat rheumatoid arthritis in the mid-1990s, and that it was "the gold standard"). However, methotrexate could help only a small minority of patients. Pls. Br. at 35; 9/20 PM (Fleischmann) Tr. at 146:20-147:9. Although other research groups tried for decades to inhibit inflammation in the body, they failed to develop an effective solution before the claimed invention. 9/11 PM (Blobel) Tr. at 66:13-67:6. After

[29] The Court has similarly considered that Plaintiffs presented data focusing on Enbrel®'s success during its first ten years on the market. The Court has weighed this evidence accordingly and finds that the evidence of Enbrel®'s success over this ten-year span is persuasive of nonobviousness. *See* Defs. Br. at 49-50.

Enbrel® was introduced into the market, approximately 70% of patients with rheumatoid arthritis found relief from this treatment. 9/20 PM (Fleischmann) Tr. at 139:2-17.

In analyzing Plaintiffs' evidence as to this factor, the Court finds that a nexus is established because the community's long-felt need for an effective, wide-reaching rheumatoid arthritis drug was satisfied by the claimed invention itself. *See* id. at 139:8-24, 149:2-9, 146:20-147:9, 151:3-17. Enbrel® was able to satisfy this need because of etanercept's ability to effectively neutralize and bind TNF while suppressing pro-inflammatory effector functions. 9/20 AM (Wall) Tr. at 87:11-24. Accordingly, the Court finds that Plaintiffs have presented sufficient evidence to show that etanercept met a long-felt need that many others failed to successfully address prior to etanercept.

d) Copying

There is no dispute that Defendants' biosimilar has the same amino acid sequences and structure as Enbrel®. *See* DFOF ¶¶ 258-59. Plaintiffs ask the Court to find Defendants' copying as probative of nonobviousness. Pls. Br. at 12. Defendants draw a comparison to Hatch-Waxman Act Abbreviated New Drug Application ("ANDA") cases with generic drugs, and counter that copying a biologic drug should not be evidence of nonobviousness for creation of a biosimilar because "copying by Sandoz reflects its efforts to meet the FDA standards for approval of biosimilar products." Defs. Br. at 50, DFOF ¶¶ 258-59, 337.

It is well settled that the copying of an invention can be indicative of nonobviousness. *Diamond Rubber*, 220 U.S. at 440-41 (finding "imitation" of a certain tire as a "concession to its advance beyond the prior art and of its novelty and utility"). In the pharmaceutical realm, however, copying is generally not considered evidence of nonobviousness for matters in the ANDA context. *See, e.g.*, *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir.

2013) ("evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval") (citation omitted).[30]

In order to obtain FDA approval for a biosimilar under the Biologics Price Competition and Innovation Act ("BPCIA"), "the applicant may piggyback on the showing made by the [original] manufacturer of a previously licensed biologic (reference product)" if the applicant can "show that its product is 'highly similar' to the reference product and that there are no 'clinically meaningful differences' between the two in terms of 'safety, purity, and potency.'" *Sandoz Inc. v. Amgen Inc.*, 137 S. Ct. 1664, 1670 (2017) (quoting 42 U.S.C. § 262(i)(2)(A), (B) and citing § 262(k)(2)(A)(i)(l)). Specifically, as compared to the original biologic, the biosimilar is permitted to have "minor differences in clinically inactive components," but must be "interchangeable with the reference product." 42 U.S.C. § 262(i)(2)(A), (k)(4). This is similar to the ANDA process for FDA approval of generic drugs, which requires "a generic drug company [to] submit information to show, inter alia, that its generic drug and the relevant listed drug share the same active ingredients and are bioequivalent." *Caraco Pharm. Labs., Ltd. v. Forest Labs., Inc.*, 527 F.3d 1278, 1282 (Fed. Cir. 2008) (citing 21 U.S.C. § 355(j)(2)(A)(ii), (iv)). At trial, Plaintiffs presented testimony by deposition from Graham B. Jones, Ph.D., their expert on the FDA's practices and policies regarding demonstrating biosimilarity, which was not inconsistent with the Court's

[30] Plaintiffs cite to *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, an ANDA case in which the Federal Circuit found copying evidence of nonobviousness where the alleged infringer copied the "process of ***manufacturing*** the drug" in the patent. 874 F.3d 724, 726, 731 (Fed. Cir. 2017) (emphasis in original). The Court finds the facts of this case distinguishable from *Merck*. Here, Defendants presented credible testimony that they began developing their biosimilar in 2006, prior to the issuance of the Patents-in-Suit and prior to the BPCIA, and that they developed the biosimilar by utilizing etanercept's amino acid sequence directly from the commercial product Enbrel® due to an understanding that the amino acid sequence would need to be identical to etanercept for approval as a biosimilar. *See* 9/14 (McCamish) Tr. at 17:17-18:15, 84:15-85:6; JTX-83 (Alliger Deposition) at 9:85-10:90; DFOF ¶¶ 258-59; Defs. Br. at 50.

analysis in this Opinion. *See generally* JTX-87 (Jones Deposition); DFOF at xv.[31] Given the BPCIA abbreviated pathway for FDA approval and the testimony on the active ingredient at issue here, the Court finds that the same logic for not considering copying in ANDA cases would apply in this circumstance.[32] Thus, this factor cannot be used herein as evidence of nonobviousness.

e) Simultaneous Invention

Evidence of an independently made, simultaneous invention may be used in "some rare instances" to provide objective indicia of obviousness by showing that persons of ordinary skill in the art identified the same particular solution to a known problem. *Geo. M. Martin*, 618 F.3d at 1304 (citations and internal quotations omitted); *see Lindemann Maschinenfabrik GmbH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1460 (Fed. Cir. 1984). "Unlike the ultimate determination of obviousness, which requires courts to answer the hypothetical question of whether an invention 'would have been obvious,' 35 U.S.C. § 103, simultaneous invention demonstrates what others in the field ***actually accomplished***." *Trustees of Columbia Univ. v. Illumina, Inc.*, 620 F. App'x 916, 930 (Fed. Cir. 2015) (emphasis in original). Defendants assert four instances of alleged simultaneous invention of etanercept by: (1) Dr. Beutler at the University of Texas; (2) Dr.

[31] Jones testified that theoretically a proposed biosimilar could "encode a different primary amino acid sequence than the reference product," however the FDA guidance calls for evaluation "on a case-by-case basis." JTX-87 (Jones Deposition) at 5:33-34, 7:49-50, 8:54. Jones confirmed that he had not reviewed either of the Patents-in-Suit nor was he offering an opinion on whether Sandoz specifically "was required to use the same primary amino acid sequence as Enbrel® to obtain licensure of its etanercept product under the abbreviated pathway." Id. at 4:28. Furthermore, Jones could not "provide any examples of a biosimilar drug that's been approved by the FDA with an expression construct that encodes a different primary amino acid sequence as its reference product." Id. at 8:56.

[32] The Court notes that even if this factor could be used as evidence of nonobviousness in favor of Plaintiffs, such finding would not have any material impact on the outcome of the Court's obviousness analysis.

Ashkenazi at Genentech; (3) Dr. Lauffer of Behringwerke, who was working in collaboration with Immunex; and (4) Dr. Goodwin of Immunex. *See* DFOF ¶¶ 10, 223, 228, 233.

Dr. Beutler, Dr. Ashkenazi, and Dr. Lauffer did not make etanercept, but rather different fusion proteins, and therefore their constructs cannot be used as evidence of simultaneous invention. *See Endo Pharms. Inc. v. Actavis Pharms., LLC*, 922 F.3d 1365, 1378 n.14 (Fed. Cir. 2019), *aff'g Endo Pharms. Inc. v. Amneal Pharms., LLC*, 224 F. Supp. 3d 368, 381 (D. Del. 2016) (finding that alleged evidence of simultaneous invention can be disregarded for obviousness if it is not the same compound as the claimed invention); *see also Shire Orphan Therapies LLC v. Fresenius Kabi USA, LLC*, No. 15-1102, 2018 WL 2684097, at *20 (D. Del. June 5, 2018). Dr. Beutler of the University of Texas was working on a fusion protein that consisted of the extracellular region of p55 fused to a mouse IgG1 with a two-cysteine hinge. *See* JTX-67 col. 7:5-8; DFOF ¶ 235; 9/18 PM (Greene) Tr. at 103:12-21; *see also* 9/20 AM (Wall) Tr. at 89:19-90:1. Dr. Ashkenazi at Genentech similarly constructed a fusion protein with p55 and a partial two-cysteine hinge. JTX-69 at 1; PFOF ¶ 267; DFOF ¶ 233. Behringwerke's Dr. Lauffer made a fusion protein with p75 and a three-cysteine hinge but deleted the last five amino acids of the C-terminus of the TNFR and also added a linker. PFOF ¶¶ 269-71. The record does not demonstrate that Dr. Lauffer or anyone at Behringwerke contemplated using the full extracellular region of p75 or removing the linker, as was done in etanercept. Based on the evidence presented, the Court finds that the constructs of Dr. Beutler, Dr. Ashkenazi, and Dr. Lauffer do not support a finding of obviousness because these inventions did not contemplate etanercept.

Roche's patent applications were already pending when Immunex created etanercept in November or December 1990. PFOF ¶¶ 51, 263. Immunex's subsequent decision to license the Patents-in-Suit from Roche demonstrates etanercept's inventive nature and undermines an

obviousness finding. *See* id. ¶¶ 69-70; DFOF ¶ 228. Moreover, a single instance of simultaneous invention cannot alone support a finding of obviousness for the following reasons. First, if one instance of simultaneous invention were sufficient to show obviousness, any claims involved in an interference would be unpatentable for obviousness, making interference proceedings futile. *Lindemann Maschinenfabrik GmbH*, 730 F.2d at 1460 (Fed. Cir. 1984) (concluding that because the statute governing interference "recognizes the possibility of near simultaneous invention by two or more equally talented inventors working independently, that occurrence may or may not be an indication of obviousness when considered in light of all the circumstances"). Second, even when evidence of simultaneous invention exists, the unexpected success of the claimed invention can preclude a finding of obviousness because surprising results demonstrate the true novelty of the invention, even if multiple inventors happened to discover it within a similar time period. *See Regents of Univ. of Cal. v. Broad Inst., Inc.*, 903 F.3d 1286, 1291, 1295-96 (Fed. Cir. 2018) (declining to find obviousness despite strong evidence of six different simultaneous inventions because the results of the claimed invention were unpredictable and unexpected, thereby outweighing any potential probativeness of the simultaneous inventions). Accordingly, the Court finds that the Defendants' argument concerning the factor of simultaneous invention fails to support obviousness.

f) Licensing

The licensing of a patent is also objective indicia that a patent is not obvious. *See Stratoflex*, 713 F.2d at 1539 ("Recognition and acceptance of the patent by competitors who take licenses under it to avail themselves of the merits of the invention is evidence of nonobviousness."). Here, Defendants concede that Immunex obtained a license for the Patents-in-Suit from Roche in 1998. DFOF ¶ 52; JTX-13. As such, the Court finds that the licensing factor also weighs in favor of nonobviousness.

Accordingly, for all of the above reasons, the Court finds that Defendants have failed to prove by clear and convincing evidence that the Patents-in-Suit are obvious.

C. Obviousness-Type Double Patenting

The judicially-created doctrine of obviousness-type double patenting prevents a party from extending their right to exclude by obtaining a later patent with claims that are not patentably distinct from claims in a commonly-owned previous patent. *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985). "The purpose of the rule against double patenting is to prevent an inventor from effectively extending the term of exclusivity by the subsequent patenting of variations that are not patentably distinct from the first-patented invention." *Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc.*, 98 F.3d 1563, 1568 (Fed. Cir. 1996); *see also Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 999 (Fed. Cir. 2009). Thus, a preliminary step to find that the rule against obviousness-type double patenting was violated is to assess whether the patents or patent applications have a common inventor or common ownership. *See Applied Materials, Inc.*, 98 F.3d at 1568; *In re Longi*, 759 F.2d at 895.

Double patenting entails a two-pronged analysis. "First, as a matter of law, a court construes the claim in the earlier patent and the claim in the later patent and determines the differences." *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001) (citing *Ga.-Pac. Corp. v. U.S. Gypsum Co.*, 195 F.3d 1322, 1326 (Fed. Cir. 1999)). "Second, the court determines whether the differences in subject matter between the two claims render the claims patentably distinct." *Id.* (citing *Ga.-Pac. Corp.*, 195 F.3d at 1327). If the later claim is an "obvious variant" or obvious modification of the earlier claim, then the later claim is invalid for double patenting. *In re Basell Poliolefine Italia S.P.A.*, 547 F.3d 1371, 1378-79 (Fed. Cir. 2008).

An analysis of step two requires a determination of whether or not the claims are "patentably distinct," by "ask[ing] whether the identified difference renders the claims of the . . .

[two] patents non-obvious to a person of ordinary skill in the art in light of the prior art." *Amgen Inc. v. F. Hoffmann-La Roche, Ltd.*, 580 F.3d 1340, 1361 (Fed. Cir. 2009); *see also Pfizer, Inc. v. Teva Pharms. USA, Inc.*, 518 F.3d 1353, 1363 (Fed. Cir. 2008); *In re Kaplan*, 789 F.2d 1574, 1580 (Fed. Cir. 1986). "This part of the obviousness-type double patenting analysis is analogous to an obviousness analysis under 35 U.S.C. § 103, except that" the alleged invalidating reference patent itself "is not considered prior art" for purposes of the analysis. *Amgen*, 580 F.3d at 1361. Specifically, an obviousness-type double patenting analysis requires an inquiry into the scope and content of the prior art, the level of skill in the art, and what would have been obvious to a POSA. *See Studiengesellschaft Kohle mbH v. N. Petrochemical Co.*, 784 F.2d 351, 355 (Fed. Cir. 1986).

Defendants argue that the Patents-in-Suit (*i.e.*, the '182 and '522 Patents) should be invalidated because Immunex has used the Patents-in-Suit to "obtain[] an unjustified timewise extension of its etanercept monopoly" in violation of 35 U.S.C. § 121. Defs. Br. at 6-15. Specifically, Defendants contend that the Patents-in-Suit are invalid for obviousness-type double patenting over (1) Roche's '279 Patent; (2) Immunex's U.S. Patent No. 5,605,690 ("the '690 Patent"); and (3) three Immunex patents aimed at psoriasis and psoriatic arthritis, U.S. Patent Nos. 7,915,225 ("'225 Patent"), 8,119,605 ("'605 Patent"), and 8,722,631 ("'631 Patent") (collectively, "the Finck Patents"). Id. Plaintiffs counter that Defendants' challenges fail because (1) a safe harbor provision applies to the Roche '279 Patent, preventing an obviousness-type double patenting violation; (2) Defendants employ an incorrect doctrine to find common ownership over Immunex's '690 Patent and Finck Patents, which is required before even conducting the traditional two-step analysis; and (3) the Patents-in-Suit are patentably distinct from the Roche '279 Patent, Immunex's '690 Patent, and Immunex's Finck Patents. Pls. Br. at 39-50.

In support of their arguments on obviousness-type double patenting, Defendants relied, to a large extent, on the following two of their witnesses: (1) Dr. Blobel, previously introduced in sections III.A and III.B, who is an expert in biophysics, particularly focusing on arthritis and tissue degeneration; and (2) John Parise, who testified via deposition and was Roche's former Senior Counsel and Managing Attorney involved in drafting and negotiating the 2004 Accord and Satisfaction on behalf of Roche. ECF No. 688 at 131 ¶ 43, 137 at ¶ 71; DFOF ¶¶ xvi, 66. Plaintiffs relied heavily on (1) expert Stephen G. Kunin, J.D., an attorney who is the former Deputy Commissioner for Patent Examination Policy in the Office of the Commissioner for Patents in the USPTO and an expert in USPTO policies, practices, and procedures; and (2) Stuart Watt, former Vice President of Law and Intellectual Property Officer at Amgen, who was involved in the prosecution of the Patents-in-Suit and the negotiation and drafting of licensing agreements for the company. ECF No. 688 at 128 ¶ 39, 137 ¶ 73.

The Court will first address Defendants' arguments with respect to Roche's '279 Patent, followed by Immunex's '690 Patent, and finally Immunex's Finck Patents. For the reasons set forth, the Court agrees with Plaintiffs that the Patents-in-Suit are not invalid for obviousness-type double patenting.

1. The '182 Patent Is Not Invalid in View of Roche's '279 Patent

Defendants argue that the '182 Patent should be invalidated based on Roche's '279 Patent.[33] Defs. Br. at 6-15. There is no dispute that Roche is the owner of both the '279 Patent and the '182 Patent and therefore common ownership exists. However, Plaintiffs contend that any

[33] Defendants stipulated at trial that the Safe Harbor provision of 35 U.S.C. § 121 protects the '522 Patent against a challenge based on Roche's '279 Patent. Pls. Br. at 39; 9/21 Tr. at 9:7-16 (defense counsel acknowledging, at trial, that the Safe Harbor provision protects the '522 Patent from any challenge based on the '279 Patent). The analysis herein will therefore solely focus on the validity of the '182 Patent as it relates to Roche's '279 Patent.

challenge based on the '279 Patent must fail because of the safe harbor provision in 35 U.S.C. § 121 ("Safe Harbor"). The Safe Harbor provision protects applicants from obviousness-type double patenting invalidity when they are forced to pursue inventions in separate patent applications as a result of a "restriction requirement" set by the USPTO, here in the filing of related divisional applications. *See* 35 U.S.C. § 121; Pls. Br. at 39-41. The Court will first examine Plaintiffs' argument that the Safe Harbor provision protects the '182 Patent from being invalidated by Roche's '279 Patent for obviousness-type double patenting and then go through the traditional obviousness-type double patenting analysis comparing the asserted claims of the '182 Patent to Roche's '279 Patent claims.

a) Roche's '279 Patent

i. Background on the '279 Patent

Roche's first patent application covering the claimed invention, the '013 Application, was filed in September 1990. PFOF ¶ 51; DFOF ¶ 38. That application was abandoned and the '640 Application, which also covered the claimed invention, was filed in July 1993. PFOF ¶ 57; DFOF ¶¶ 38-39. During patent prosecution, the USPTO placed a restriction requirement on the '640 Application, requiring Roche to "elect one of three distinct inventions" and choose "between the p55 and p75 protein." DFOF ¶ 40. Roche elected to pursue claims related to the p55 fusion protein, which resulted in the '279 Patent being issued in March 1997. PFOF ¶ 57; DFOF ¶¶ 39-40. In order to pursue the non-elected claims, i.e. those related to the p75 fusion protein, Roche was required to file separate divisional applications. In May 1995, Roche filed the '790 Application, which eventually issued as the '182 Patent. PFOF ¶ 57.

ii. The Safe Harbor Provision Protects the Claims of the '182 Patent in View of the '279 Patent

The Court finds that the Safe Harbor provision protects the claims of the '182 Patent from Defendants' invalidity argument based on the '279 Patent. Under the Safe Harbor provision, a patent cannot be invalidated for obviousness-type double patenting if the subject patent was issued from a divisional application that was filed as a result of a requirement for restriction. 35 U.S.C. § 121; *see Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1579 (Fed. Cir. 1991). There are three requirements for invoking the protection of the Safe Harbor provision: (1) a restriction requirement, (2) a divisional application filed as a result of the restriction requirement, and (3) consonance with the restriction requirement. 35 U.S.C. § 121.

At trial, Plaintiffs' expert Steven G. Kunin explained the USPTO's policy, practice, and procedure related to the Safe Harbor protection afforded to "applicants who are forced to file multiple patent applications." 9/21 (Kunin) Tr. at 69:18-20. Based on his experience with the USPTO for more than thirty-four years, ten of which were spent as the Deputy Commissioner, Mr. Kunin described the procedure for restriction requirements and divisional applications. Id. at 66:5-68:9, 69:21-70:24. He explained that if an "applicant claimed more than one independent and distinct invention" in a parent application, the applicant would be forced to file a divisional patent application to ensure "administrative efficiency and effectiveness." Id. at 69:23-70:7. If the applicant still wished to obtain a patent for the other inventions initially included in the parent application, the applicant would need to file a "divisional application." Id. at 70:8-24. This divisional application would be prohibited from rejection on obviousness-type double patenting grounds over the claims of the parent application based on the Safe Harbor provision. Id. The Safe Harbor provision was created for the specific purpose of preventing "unfairness by penalizing the applicant who would do . . . what the examiner had requested by electing an invention, filing

a divisional and seeking the examination of the withdrawn claims in the parent in the divisional." Id. at 70:25-71:7.

As to the instant case, Mr. Kunin testified that the USPTO placed a restriction requirement on the '640 Application (which became the '279 Patent) during its prosecution. PFOF ¶¶ 278-82; DFOF ¶¶ 40-41; *see also* 9/21 (Kunin) Tr. at 69:23-70:2 (Mr. Kunin testifying generally that when "the examiner required the applicant to elect only one of those inventions for search and examination" it is "known as a restriction requirement"). According to the restriction requirement, Roche was obligated to choose between prosecuting claims of either p55 or p75 TNFR. PFOF ¶ 280; DFOF ¶ 50. Roche elected claims relating to p55 TNFR, which resulted in the '279 Patent. PFOF ¶ 285; DFOF ¶ 50. Thereafter, the p75 TNFR claims were pursued in a divisional application that led to the '182 Patent. PFOF ¶ 285. Plaintiffs therefore meet the first two requirements because there was both a restriction on the application underlying the '279 Patent and a divisional application filed as a result of that restriction.

Defendants do not challenge the fact that there was a restriction on the application for the '279 Patent and that the Patents-in-Suit were the result of divisional applications filed based on that restriction. DFOF ¶¶ 40-41, 45 ("[d]uring the prosecution of the '279 patent, the examiner issued a restriction requirement" and "[f]ollowing the restriction requirement, Roche filed divisional applications from the '279 patent application," one of "which led to the '182 patent"). The focus of Defendants' Safe Harbor challenge for the '182 Patent therefore appears to be based on the third requirement of consonance. Id. ¶¶ 298-301. Consonance is a judge-made principle that states that the divisional application cannot reclaim the invention, which was elected and examined in the parent. *See Symbol Techs.*, 935 F.2d at 1579 ("Consonance requires that the line of demarcation between the 'independent and distinct inventions' that prompted the restriction

requirement be maintained.") (quoting *Gerber Garment Tech., Inc. v. Lectra Sys., Inc.*, 916 F.2d 683, 688 (Fed. Cir. 1990)); *see also* 9/21 (Kunin) Tr. at 76:5-8. In other words, just as the parent patent application must elect a distinct invention as a result of the restriction requirement, so too must the subsequent divisional application refrain from claiming the elected invention from the parent application. Where the principle of consonance is violated, the Safe Harbor provision "will not apply to remove the parent [patent] as a reference" in an obviousness-type double patenting analysis. *See Symbol Techs.*, 935 F.2d at 1579.

Here, Roche's '279 Patent elected claims relate to p55 TNFR from the original patent application as a result of the restriction requirement. Immunex and Amgen then amended the subsequent '790 Application (a divisional of the '279 Patent application) which became the '182 Patent, to include claims for p75. *See* PTX-6.280. That amendment was made in response to a rejection by the USPTO, approximately ten years after the application for the '182 Patent was originally filed[34] and brought the claims into consonance with the restriction requirement. PTX-6.332; 9/21 (Kunin) Tr. at 87:19-90:9 (Mr. Kunin explaining the patent prosecution history and when the patent applications were brought into consonance). Defendants take the position that the amount of time it took for Roche to amend the claims of the '182 Patent to bring them into consonance with the restriction requirement should result in invalidity of the patent, "because the applicants failed to maintain consonance throughout the prosecution of the '182 patent application." (DFOF ¶¶ 298-99).

[34] As discussed further below, the Court notes that Plaintiffs' expert Mr. Kunin testified that he reviewed the prosecution history and prior to the amendment, there "was something like three years, in which the applicant submitted like six status requests because the Office hadn't been working on them" and also "the '182 patent . . . was lost for a couple of years" by the USPTO. 9/21 (Kunin) Tr. at 104:15-105:18.

The USPTO allows application amendments at any time and does not provide temporal limits for the Safe Harbor provision to apply. *See* 35 U.S.C.§ 121 (including no time limits as to when Safe Harbor applies, so long as "divisional application is filed before the issuance of the patent on the other application"); *see also* 9/21 Tr. (Kunin) at 90:22-91:5 (Mr. Kunin testifying that "[t]here's nothing in [the relevant section that] talks about time limits. So long as the applicant is still permitted to amend claims, then if the claims during that period prior to issuance are amended to bring them back into consonance, then the safe harbor will apply."). Moreover, an inquiry into whether the Safe Harbor rule applies requires analysis of the issued claims. *Boehringer Ingelheim Int'l GmbH v. Barr Labs, Inc.*, 592 F.3d 1340, 1354 (Fed. Cir. 2010) (explaining that, when doing a Safe Harbor analysis, the proper inquiry is on the issued claims). Defendants have not presented case law or trial testimony to indicate by clear and convincing evidence that the timing of the amendment or the content of pre-amendment application claims bear any legal significance. Based on its analysis of the issued claims, the Court concludes that the Safe Harbor provision protects the '182 Patent such that it cannot be invalidated for obviousness-type double patenting because the '182 Patent was (1) the result of a divisional application, (2) based on a restriction requirement issued by the USPTO, and (3) in consonance with that restriction requirement.

b) The Claims of the '279 Patent Are Patentably Distinct from the '182 Patent

Even assuming the Safe Harbor provision did not protect the '182 Patent from invalidity based on obviousness-type double patenting, the Court nonetheless finds that the '182 Patent is patentably distinct from the '279 Patent and therefore not invalid for obviousness-type double patenting. To determine whether the claims are patentably distinct, the Court must compare the two patents at issue and decide whether the '182 Patent is an obvious modification of the earlier-

issued '279 Patent. If the later claim is an "obvious variant" or obvious modification of the earlier claim, according to a POSA, then the later claim is invalid for non-statutory double patenting. *In re Basell Poliolefine Italia S.P.A.*, 547 F.3d at 1378-79. The Court concludes that the claims of the '182 Patent are patentably distinct from the '279 Patent for the reasons stated herein.

The '279 Patent relates to an "invention [that] is concerned with non-soluble proteins and soluble or insoluble fragments thereof, which bind TNF, in homogenous form." '279 Patent (JTX-5) at "Abstract". All claims of the '279 Patent relate to a p55 TNFR. Id. at col. 24:11-21. Claim 1 is for a p55 TNFR and all of the remaining claims in the '279 Patent depend on Claim 1. Hence, the '279 Patent involves a p55 TNFR that is fused to an immunoglobulin. Id.

In contrast, the '182 Patent claims, in part, an insoluble human TNFR that "has an apparent molecular weight of about 75 kilodaltons," which specifically binds human TNF. '182 Patent (JTX-1) col. 39:18-19. Throughout Defendants' contentions regarding the patent specification, Defendants acknowledge that p55 TNFR is distinct from p75 TNFR. DFOF ¶ 125. During prosecution of the '279 Patent application, the USPTO required Roche to elect either the p55 or the p75, acknowledging that p55 and p75 were patentably distinct. JTX-9 at 118 ("The proteins are unobvious in view of each other . . . ."); *see also* 9/21 (Kunin) Tr. at 83:5-84:19. Accordingly, the Court finds that there are significant distinctions between the '279 and '182 Patents such that the patents would not have been modifications obvious to a POSA in 1990. Therefore, the Court concludes that the '182 Patent is not invalid for obviousness-type double patenting based on the '279 Patent.

2. The Patents-in-Suit Are Not Invalid over the '690 Patent and the Finck Patents

Defendants argue that the Patents-in-Suit are obvious over Immunex's '690 Patent and Immunex's Finck Patents (consisting of the '225, '605, and '631 Patents) (collectively, the

"Immunex Patents"). Defs. Br. at 6-20. However, common ownership is required for obviousness-type double patenting. *In re Longi*, 759 F.2d at 893-95. While Roche is the recorded owner of the Patents-in-Suit, Defendants contend that the 2004 Accord and Satisfaction was tantamount to an assignment to Immunex, making Immunex a common owner of the Patents-in-Suit and the Immunex Patents. Defs. Br. at 6-15. Specifically, Defendants claim that the Accord and Satisfaction transferred "all substantial rights" from Roche to Immunex, resulting in Immunex's ownership of the Patents-in-Suit and an impermissible extension of Plaintiffs' monopoly over etanercept. Id. at 7-14. Plaintiffs argue that the Accord and Satisfaction did not transfer ownership from Roche to Immunex, and instead granted a license. Pls. Br. at 41-47. Plaintiffs further aver that even if the Patents-in-Suit were commonly owned, Defendants have not met their burden to show that the Patents-in-Suit are patentably indistinct from the Immunex Patents. Id. at 47-50.

The Court will first address the common ownership issue and then discuss the '690 Patent and the Finck Patents.

a) The Accord and Satisfaction Does Not Create Common Ownership

In 1999, Immunex licensed Roche's pending patent applications, which became the Patents-in-Suit, effective back to the FDA approval date of Enbrel® in 1998. PFOF ¶ 70. Under the license, Immunex was required to pay Roche "tens of millions of dollars." Id. Non-party Amgen Inc. acquired Immunex in 2002. Id. ¶ 71. Later, Roche entered into the Accord and Satisfaction with Amgen Inc. and its affiliates, including Immunex, which was executed on June 7, 2004. JTX-12; PFOF ¶ 71. Thereunder, Amgen Inc. and Immunex fully paid their outstanding royalty obligations to Roche and received an exclusive license to the Patents-in-Suit.[35] PFOF ¶

[35] At that time, the applications for the Patents-in-Suit were still pending and had not yet been issued.

71. Immunex and Amgen Inc. received the following rights as they pertained to the eventual Patents-in-Suit and their then-pending applications: (1) an "irrevocable, exclusive license, with the sole right to grant sublicenses" of the Patents-in-Suit; (2) the exclusive right to practice under the Patents-in-Suit in North America; (3) the exclusive right to prosecute the Patents-in-Suit; (4) the right to select outside counsel for the prosecution of the Patents-in-Suit; (5) the first right to bring an infringement action in connection with the Patents-in-Suit; and (6) the right to retain all profits that result from any infringement litigation brought by Amgen Inc. or Immunex. JTX-12 at 4-7 (§§ 3.1-3.6). Roche retained the rights to (1) sue for infringement if Amgen Inc. does not, (2) choose its partners under the license agreement, and (3) use the inventions for non-clinical research. PFOF ¶¶ 304-06; DFOF ¶¶ 53, 62. The rights conferred by Roche through the Accord and Satisfaction were later consolidated in Immunex by a separate agreement, and Immunex "sublicensed exclusive rights related to Enbrel®'s commercialization to Amgen."[36] JTX-14; 9/24 PM (Watt) Tr. at 28:20-29:8; JTX-15 at 3; PFOF ¶¶ 4-5.

To use the Immunex Patents to invalidate the Patents-in-Suit, Immunex must first be a common owner to both sets of patents, in accordance with the obviousness-type double patenting doctrine. *In re Longi*, 759 F.2d at 892. Defendants' argument of common ownership is that the 2004 Accord and Satisfaction transferred "all substantial rights" from Roche to Amgen and Immunex and any rights that Roche did retain were illusory. Defs. Br. at 7-20; *see also Speedplay, Inc. v. BeBop, Inc.*, 211 F.3d 1245, 1249-50 (Fed. Cir. 2000). Defendants therefore ask the Court to find first that the transfer of all substantial rights is the legal equivalent of common ownership,

[36] While the Accord and Satisfaction was negotiated with non-party Amgen Inc., the rights were later consolidated in Immunex. JTX-14. For ease of reference the Court will refer to Immunex, which is a party to this action and currently retains the rights discussed in the Accord and Satisfaction.

which is necessary for obviousness-type double patenting invalidation, and second that the Accord and Satisfaction transferred all substantial rights.

Defendants' cases in support of their common ownership argument all analyze indicia of common ownership for the purpose of determining whether a party had what is referred to as "prudential standing" to sue, and not ownership for the purpose of obviousness-type double patenting. *See Diamond Coating Techs., LLC v. Hyundai Motor Am.*, 823 F.3d 615, 618-19 (Fed. Cir. 2016); *Luminara Worldwide, LLC v. Liown Elecs. Co.*, 814 F.3d 1343, 1349-50 (Fed. Cir. 2016); *Speedplay*, 211 F.3d at 1249-50; *Vaupel Textlimaschinen KG v. Meccanica Euro Italia SPA*, 944 F.2d 870, 875 (Fed. Cir. 1991); *EMC Corp. v. Pure Storage, Inc.*, 165 F. Supp. 3d 170, 178 (D. Del. 2016). For example, although the Federal Circuit in *Diamond Coating* made observations about what constitutes ownership, Defendants correctly concede that the observations were made in the context of deciding whether the plaintiff had standing or the right to sue under the subject patent, which is not the question currently before this Court.[37] *See Diamond Coating*, 823 F.3d at 617-19; s*ee also Speedplay*, 211 F.3d at 1250.

Here, the matter is not within the "standing to sue" context, and thus the ownership caselaw presented by Defendants is not directly applicable. However, even assuming those cases apply, the Court finds that Roche remained the owner of the Patents-in-Suit because the Accord and Satisfaction did not confer all substantial rights on Immunex. First, the Court finds that the parties specifically intended for the Accord and Satisfaction to be a license such that Roche would remain

[37] Defendants have not cited to, nor has this Court found, any caselaw that has extended or applied the "all substantial rights" test to render a patent *invalid* pursuant to the obviousness-type double patenting doctrine. The purpose of the doctrine of obviousness-type double patenting is to prevent the same inventor and/or owner of an invention from extending their patent terms over the same invention or an obvious variant thereof. *Gilead Scis., Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1212 (Fed. Cir. 2014) ("[T]he doctrine of double patenting was primarily designed to prevent . . . harm [to the public] by limiting a patentee to one patent term per invention or improvement.").

the owner of the Patents-in-Suit. "To determine whether an exclusive license is tantamount to an assignment, [the Court] 'must ascertain the intention of the parties [to the license agreement] and examine the substance of what was granted.'" *Alfred E. Mann Found. For Sci. Research v. Cochlear Corp.*, 604 F.3d 1354, 1359 (Fed. Cir. 2010) (quoting *Mentor H/S, Inc. v. Med. Device All., Inc.*, 240 F.3d 1016, 1017 (Fed. Cir. 2001)); *see also AsymmetRx, Inc. v. Biocare Med., LLC*, 582 F.3d 1314, 1319 (Fed. Cir. 2009) ("To determine whether an assignment of patent rights was made, we must examine whether the agreement transferred all substantial rights to the patents and whether the surrounding circumstances indicated an intent to do so.") (internal citations omitted)). A district court's interpretation of a contract presents a question of law. *Alfred E. Mann*, 604 F.3d at 1359. To the extent that determining the intention of the parties to the license agreement requires evaluation of evidence outside of the contract, the district court's evaluation presents a question of fact. *Id.*

The evidence during trial demonstrated that the parties agreed to draft the Accord and Satisfaction as a license, and not an assignment of all rights. On the face of the Accord and Satisfaction itself, the transfer of rights in North America to Amgen is expressly called a "[l]icense," in contrast to the transfer of rights outside of North America to non-party Wyeth BV, which is expressly called an "[a]ssignment." *Compare* JTX-12 at 4 ("Article 3 License to Amgen" granting "to Amgen and its Affiliates a paid-up, irrevocable, exclusive license, with the sole right to grant sublicenses") *with* id. at 3 ("Article 2 Assignment to Wyeth BV" stating Roche "hereby agrees to assign, and will cause its Affiliates to assign"). Under the Accord and Satisfaction with respect to the Patents-in-Suit in North America, Roche maintained a second right to sue for infringement, including a right to determine whether an assignment or sublicence would be granted to cure the infringement, and retained the right to practice the invention. PFOF ¶¶ 304-05; DFOF

¶¶ 53, 62. In contrast, the Accord and Satisfaction expressly assigned to non-party Wyeth BV "all right, title and interest in and to" the Patents-in-Suit outside of North America and acknowledges that "Wyeth BV has succeeded to all of Roche's and its Affiliates' right, title, interest, benefit, and standing to receive all rights and benefits" pertaining to the Patents-in-Suit outside of North America. JTX-12 at 3-4.

Moreover, the Court heard the testimony of Stuart Watt, Amgen's Vice President of Law and Intellectual Property Officer, who engaged in negotiations with Roche on behalf of Immunex and Amgen. *See* 9/24 PM (Watt) Tr. at 20:21-23, 25:15-18. Watt credibly testified that it was more valuable to Immunex for Roche to remain as the owner of the Patents-in-Suit. *See* id. at 29:11-22. Watt stated that, based on his past litigation experience, it was important for Roche to have an obligation to participate in litigation as a party, rather than have the mere contractual duty, which could easily be breached. Id. at 29:15-31:14. The fact that the parties thoughtfully negotiated and ultimately agreed to draft the portion of the Accord and Satisfaction pertaining to North America and Amgen as a license presents strong evidence that the parties intended for the Accord and Satisfaction to be treated as a license, rather than an assignment.

While Defendants believe the rights retained by Roche for the Patents-in-Suit in North America are "illusory" or insignificant, the Court disagrees. As explained at trial, Roche still possessed the power to bring a patent infringement action if the Immunex Plaintiffs failed to do so. *See* 9/24 PM (Watt) Tr. at 39:2-25. The Federal Circuit has found that a second right to sue is in fact a substantial right retained. *Alfred E. Mann*, 604 F.3d at 1361-62. According to the language of the Accord and Satisfaction, if Roche initiates a suit for infringement, the suit is solely within the control of Roche but Immunex has a duty to cooperate during the suit. *See* JTX-12 at 6 (§ 3.6). Importantly, while Immunex had the right to sublicense, Immunex could *not* end a

Roche-initiated lawsuit by granting a sublicense on its own. *See* id. Moreover, Roche could veto the assignment of Immunex's rights to a third party, which suggests that the parties envisioned the agreement to be a license. *See* id. at 14 (§ 11.4). This scenario is distinguishable from a situation where the licensee can grant a license to end a licensor-initiated lawsuit. *See, e.g.*, *Speedplay*, 211 F.3d at 1251. Ultimately, Roche's own enforcement capabilities, in the event Immunex chooses not to sue, are not nullified by Immunex's separate right to sublicense.

Furthermore, Roche maintained the right to practice the invention. JTX-12 at 4 (§ 3.2) (Roche "reserves for itself and its Affiliates the right to practice" the invention in North America "for internal, non-clinical research"). In *AsymmetRx, Inc.*, the licensor also retained the right to practice the patents "for academic research" and the court noted that as one factor in finding that the licensor did not transfer all substantial rights. 582 F.3d at 1320 (considering the retained "right to make and use the [patented compound] for its own academic research purposes," in ultimate conclusion that rights conveyed were a license). Because Roche retained not only a right to sue for infringement, but a right to veto assignments or sublicenses, and the right to practice the patent, the Court finds that Roche did not convey all substantial rights.

In sum, should the "all substantial rights" test have a place in this case, Roche has nonetheless retained certain substantial rights and accordingly, ownership of the Patents-in-Suit did not transfer to Immunex. As stated above, common ownership or having at least one common inventor is a required element for the Patents-in-Suit to be invalid under the obviousness-type double patenting doctrine. *In re Longi*, 759 F.2d at 893-95. Hence, Defendants cannot establish common ownership and/or inventorship to support invalidity of the Patents-in-Suit pursuant to the doctrine of double patenting over the '690 and the Finck Patents based on Defendants' all substantial rights argument.

b) *The Claims of the Immunex Patents Are Patentably Distinct from the Patents-in-Suit*

Due to the Court's finding of no common ownership, the remaining portions of this Opinion are not necessary to the Court's ultimate conclusion on obviousness-type double patenting. Nevertheless, even assuming the Court had found common ownership, the Court finds that the Immunex Patents (the '690 and Finck Patents) are patentably distinct from the Patents-in-Suit and therefore the Patents-in-Suit are not invalid. According to the law of double patenting, the Court must first ask: "[i]s the same invention being claimed twice?" *Gen. Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1278 (Fed. Cir. 1992) (citing *In re Vogel*, 422 F.2d 438, 442 (C.C.P.A. 1970)). If the answer to the first question is no, then the Court must ask: "[d]oes any claim in the application define merely an obvious variation of an invention claimed in the patent asserted as supporting double patenting?" *Id.* If the answer to that question is no, there is no double patenting. *Id.* That is, if the claim at issue "defines *more* than an obvious variation, it is *patentably distinct*" and any double patenting argument would fail. *Id.* When conducting this analysis, the claims must be read as a whole. *Id.*

When construing a claim in an earlier patent against a claim in a later patent, the Court needs to determine whether the differences in subject matter between the two claims render the claims patentably distinct. *Eli Lilly & Co.*, 251 F.3d at 968 (citing *Ga.-Pac. Corp.*, 195 F.3d at 1326). If, according to a POSA, the later claim is an obvious modification of the earlier claim, then the later claim is invalid for non-statutory double patenting. *In re Basell Poliolefine Italia S.P.A.*, 547 F.3d at 1378-79.

The Court will first address Defendants' claims as to the '690 Patent, and then will examine the claims regarding the Finck Patents.

i. The '690 Patent Is Patentably Distinct from the Patents-in-Suit

The '690 Patent, entitled "Methods of Lowering Active TNF-α Levels in Mammals Using Tumor Necrosis Factor Receptor," issued on February 25, 1997 and expired on February 25, 2014. '690 Patent (JTX-42); DFOF ¶ 97. There is no dispute that Immunex is the proper owner of the '690 Patent. ECF No. 688 at 36 ¶¶ 147-48. The parties dispute whether the asserted claims from the Patents-in-Suit are invalid in view of Claim 3 of the '690 Patent. Primarily, the parties dispute the meaning of the term "fused to the constant domain of an immunoglobulin" contained in the '690 Patent. Defendants argue that the '690 Patent's claim scope includes etanercept because the claimed chimeric antibody could have been fused to an immunoglobulin in the same way described in the Patents-in-Suit. Defs. Br. at 17. Plaintiffs disagree and state that the Patents-in-Suit do not cover the fusion of a TNFR to "the constant domain of an immunoglobulin" because etanercept's construction requires the removal of a portion of the constant domain, namely CH1 and the light chain of the IgG1 immunoglobulin. Pls. Br. at 48. In the alternative, Defendants assert that even if the claim is not construed to cover etanercept exactly, the prior art would have led a POSA to modify the claimed protein to create etanercept. Defs. Br. at 15. By contrast, Plaintiffs contend that Claim 3 of the '690 Patent does not include etanercept and therefore the inventions claimed in the Patents-in-Suit are patentably distinct. Pls. Br. at 48. The Court finds that Defendants have not demonstrated by clear and convincing evidence that the claims in the '690 Patent are patentably indistinct from the claims in the Patents-in-Suit—the '182 and '522 Patents.

Claim 3 of the '690 Patent is directed to "a method for lowering the levels of active TNF-α" by using a chimeric antibody[38] consisting of "a TNF receptor comprising the sequence of amino acids 3-163 of SEQ ID NO:1 fused to the constant domain of an immunoglobulin molecule." '690 Patent (JTX-42) col. 33:66-34:54. In other words, Claim 3 "requires that the p75 TNF receptor has to be fused to the constant domain of an immunoglobulin molecule" which "would include CH1, the hinge, CH2, CH3 and the constant region on the variable region." 9/12 PM (Blobel) Tr. at 69:15-18, 70:2-7. In fact, the specification of the '690 Patent describes a chimeric antibody as a molecule "having TNFR sequences substituted for the variable domains of either or both of the immunoglobulin heavy and light chains and having *unmodified* constant region domains." '690 Patent (JTX-42) col. 7:42-46 (emphasis added).

In comparison, the Patents-in-Suit claim a fusion protein with "all of the domains of the constant region of a human immunoglobulin IgG heavy chain *other than the first domain of said constant region*" ('182 Patent (JTX-1) col. 39:13-25) (emphasis added) and methods of making it ('522 Patent (JTX-2)). Critically, both the '182 and the '522 Patents exclude the CH1 and the light chain of the IgG1 immunoglobulin. *See* '182 Patent (JTX-1) col. 39:13-25; '522 Patent (JTX-2) col. 46:59-47:3. The Patents-in-Suit cover the fusion of p75 to the hinge-CH2-CH3 of the constant domain of IgG1. Id.

Therefore, the Court finds that the chimeric antibody of the '690 Patent could not have been etanercept because the constant region domains include CH1. In other words, the '690 Patent requires the use of the CH1 domain and light chain of the IgG1, while the Patents-in-Suit specifically require the removal of both of these items. *Compare* '690 Patent (JTX-42) col. 33:66-

[38] As defined in the '690 Patent, a chimeric antibody is a "molecule having TNFR sequences substituted for the variable domains of either or both of the immunoglobulin heavy and light chains and having unmodified constant region domains." 9/12 (Blobel) AM Tr. at 24:9-18.

34:54 *with* '182 Patent (JTX-1) col. 39:46-49 and '522 Patent (JTX-2) col. 45:57-60. Thus, the Patents-in-Suit are patentably distinct from the '690 Patent.

Lastly, Defendants argue that even if Claim 3 of the '690 Patent was strictly construed to include the complete constant domain for the light chain and the heavy chains, etanercept only differs in the removal of the light chain and the CH1 domain from the IgG1, which would have been obvious to a POSA. Defs. Br. at 15. However, as the Court previously stated above, it would not have been obvious to a POSA to modify the constant region domain in this way and combine it with a p75 TNFR. *See supra* III.B.

For these reasons, the Court finds that Defendants have failed to prove by clear and convincing evidence that the Patents-in-Suit are invalid in light of the '690 Patent based on obviousness type double patenting.

ii. The Patents-in-Suit Are Not Invalid In View of the Finck Patents

The patents referred to collectively as the Finck Patents are comprised of the following three patents: (1) the '225 Patent entitled "Soluble Tumor Necrosis Factor Receptor Treatment of Medical Disorders," issued on March 29, 2011; (2) the '605 Patent entitled "Soluble Tumor Necrosis Factor Receptor Treatment of Medical Disorders," issued on February 21, 2012; and (3) the '631 Patent entitled "Soluble Tumor Necrosis Factor Receptor Treatment of Medical Disorders," issued on May 13, 2014. JTX-39 ("'225 Patent"); JTX-40 ("'605 Patent"); JTX-41 ("'631 Patent"). The Finck Patents will expire on August 13, 2019 and there is no dispute that Immunex is the proper owner.[39] Defendants claim that the Patents-in-Suit are invalid for obviousness-type double patenting in view of the Finck patents. Defs. Br. at 14-15. The parties

[39] The Finck Patents expire on the same day because each is subject to a terminal disclaimer pursuant to 37 CFR § 1.321.

disagree as to whether the one-way test or two-way test shall be used to compare the Finck Patents and the Patents-in-Suit.[40] Part of that issue is a question of how and to what extent the amendments to the General Agreement on Tariffs and Trade ("GATT") impact an obviousness-type double patenting analysis.[41] Next, the parties disagree as to whether the Patents-in-Suit are patentably distinct from the Finck Patents. These arguments will be addressed in turn.

a. The Two-Way Test Shall Apply to Analysis of the Finck Patents

Invalidity for obviousness-type double patenting is a question of law based on underlying factual inquiries. *See Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 689 F.3d 1368, 1376 (Fed. Cir. 2012). Under the "one-way" test, the court determines whether the asserted patent claim is patentably distinct from—i.e., obvious over or anticipated by—the reference patent claim. *See In re Berg*, 140 F.3d 1428, 1432 (Fed. Cir. 1998). For purposes of the two-way analysis, "the order of issuance is, in effect ignored, and the relevant determination becomes whether the improvement is patentably distinct from the generic invention." *In re Braat*, 937 F.2d 589, 593-94 (Fed. Cir. 1991); *see also In re Hubbell*, 709 F.3d 1140, 1149 (Fed. Cir. 2013). The two-way test is a "narrow exception to the general rule of the one-way test" and is only applied when "(1) a second-filed application issues prior to a first-filed application, and (2) 'the [US]PTO is solely responsible for

[40] Plaintiffs alternatively argue that even under the one-way test, Defendants have failed to prove by clear and convincing evidence that any claims in the Patents-in-Suit are invalid for obviousness-type double patenting over the Finck Patents. PFOF ¶ 325. Plaintiffs contend that even if the Finck Patents were proper obviousness-type double patenting references, their claims could not have been rendered invalid given that the Finck Patents' claims are directed to a method of treatment with etanercept whereas the claims of the Patents-in-Suit are directed to a compound and the method of composition. Pls. Br. at 49. The facts on patentable distinctness, discussed infra, may be considered in accordance with either test.

[41] The Uruguay Round Agreements Act was enacted on December 8, 1994. *See* Pub. L. No. 103-465, 108 Stat. 4809. This Act implemented various agreements during the Uruguay Round of General Agreement on Tariffs and Trade. *Id.* The Act is commonly referred to as "GATT."

the delay' in the issuance of the first-filed application." *In re Janssen Biotech, Inc.*, 880 F.3d 1315, 1325 (Fed. Cir. 2018); *see also Smith & Nephew, Inc. v. Arthrex, Inc.*, 355 F. App'x 384, 388 n.4 (Fed. Cir. 2009).

The two-way test arose to "prevent rejections for obviousness-type double patenting when the applicants filed first for a basic invention and later for an improvement, but, through no fault of the applicants, the [US]PTO decided the applications in the reverse order of filing." *In re Hubbell*, 709 F.3d at 1149 (quoting *In re Berg*, 140 F.3d at 1432). "The two-way exception can only apply when the applicant could not avoid separate filings, and even then, only if the [US]PTO controlled the rates of prosecution to cause the later filed species claims to issue before the claims for a genus in an earlier application." *In re Berg*, 140 F.3d at 1435. Whether the one-way or two-way test applies is a question of law, but the determination can be based on underlying factual findings.[42] *See In re Emert*, 124 F.3d 1458, 1460 (Fed. Cir. 1997).

The applications for the Patents-in-Suit were both filed in May 1995, however the '182 Patent issued in November 2011, and the '522 Patent issued in April 2012. The Finck Patent applications, which describe a method of treating psoriasis and psoriatic conditions, were filed four years after the applications for the Patents-in-Suit, in August 1999. However, the '225 Finck Patent issued in March 2011 prior to the issuance of the Patents-in-Suit, the '605 Finck Patent issued in February 2012, after the '182 Patent but prior to the '522 Patent, and the '631 Finck Patent issued in May 2014, after the Patents-in-Suit. As the Court has already determined that the Patents-in-Suit and Finck Patents lack the requisite common ownership for an obviousness-type

[42] The Court notes that the Finck Patents are the only patents as to which a two-way test argument has been made. The other patents analyzed for obviousness-type double patenting were all earlier-filed and earlier-issued compared to the Patents-in-Suit and therefore were evaluated under a one-way test.

double patenting analysis, the Court need not look any further to address the issue of patentable distinctness. Nevertheless, the Court has reviewed the evidence presented at trial and the prosecution file history and determines that if common ownership existed, the two-way test should apply.

At trial, Plaintiffs' expert Mr. Kunin reviewed the prosecution history for the Patents-in-Suit and testified that there was a period of "something like three years" where Roche submitted "six status requests because the Office hadn't been working" on the applications for the Patents-in-Suit. 9/21 (Kunin) Tr. at 104:21-105:1; *see also* JTX-4 at 354-55. He later testified that the application for the "'182 Patent . . . was lost for a couple of years" by the USPTO. 9/21 (Kunin) Tr. at 105:2-18. Then, in August 2010, a Director at the relevant USPTO Technology Center sent a letter to Plaintiffs' legal representative acknowledging that a petition decision mailed in August 2007 "relied upon an image file wrapper which mistakenly contained papers from an unrelated application." JTX-4 at 4239. The letter additionally acknowledged that "only one substantive office action has been set forth in the last five years" and therefore "the Examiner has been advised to treat this application as special and expedite its prosecution to conclusion." Id. at 4240. Further, the applications for the Patents-in-Suit faced several rejections from the patent examiners, which ultimately were found to be unjustified and reversed by the BPAI on appeal. *See* BPAI Opinion, PTX-6.456 (reversing all of the Examiner's rejections, and finding Plaintiffs' "evidence . . . convincing to rebut the Examiner's . . . rejection" as well as stating the BPAI was "persuaded by Appellants' argument"); PFOF ¶¶ 321-22. While Plaintiffs did make several proper requests for extensions, the Court finds that, to the extent the earlier-filed Patents-in-Suit were issued after the later-filed Finck Patents, as a matter of fact the USPTO was solely responsible for the delay that resulted. *See* PFOF ¶¶ 321-25. The Court additionally finds that, based on the record presented,

Plaintiffs acted in good faith to diligently prosecute the Patents-in-Suit. Therefore, the Court will apply the two-way test.

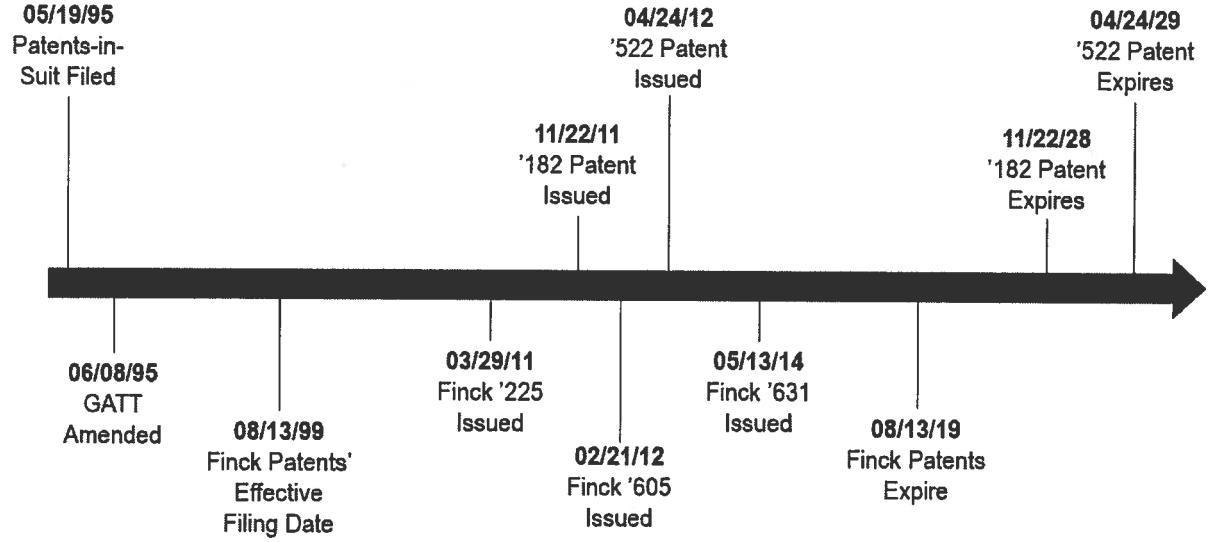
b. Impact of GATT on the Patents-in-Suit

The parties also disagree about the impact of GATT on the obviousness-type double patenting analysis. In particular, the parties argue as to whether an earlier-expiring post-GATT patent can cut short the statutory term of a pre-GATT later-expiring patent. Pls. Br. at 47-48; Defs. Reply Br. at 9-10. Among other things, GATT changed the term of a patent and how to calculate its expiration. *See Avanir Pharms., Inc. v. Actavis S. Atl. LLC*, 987 F. Supp. 2d 504, 516 n.20 (D. Del. 2013). Prior to GATT, "[p]atents claiming priority to applications filed ***before*** June 8, 1995, . . . have a patent term which is the greater of 20 years from the date of the filing of the application or 17 years from the date of the grant of the patent, subject to any terminal disclaimers." *Id.* (citing 35 U.S.C. § 154(a)(2)) (emphasis in original). However, due to the GATT amendment, "[p]atents that issued from applications filed ***after*** June 8, 1995 receive a 20-year term" from the effective filing date. *Id.* (citing 35 U.S.C. § 154(a)(2)) (emphasis in original).

Here, the applications for the Patents-in-Suit were filed pre-GATT in May 1995, and therefore were granted a patent term of seventeen years from the date of issuance (from November 2011 until November 2028 for the '182 Patent and from April 2012 to April 2029 for the '522 Patent). The Finck Patents, however, were filed post-GATT, and therefore will expire in August 2019, twenty years from the earliest effective filing date of August 1999 for the applications. Defendants' arguments focus on Claim 1 and the term TNFR:Fc in the Finck Patents, which is identical in each Finck Patent. Based on the times of filing, issuance, and expiration, at least one Finck Patent would properly serve as a reference patent for the Patents-in-Suit for an obviousness-

type double patenting analysis, which is all that is needed because the claim terms at issue in the Finck Patents are identical in each one.[43]

Next, because obviousness-type double patenting is "intended to address *unjustifiable* extensions of patent terms," a post-GATT later-granted and earlier-expiring patent cannot cut short the term of a pre-GATT "valid, earlier-granted patent with a longer term." *Abbott Labs. v. Lupin Ltd.*, No. 09-152, 2011 WL 1897322, at *9-10 (D. Del. May 19, 2011) (citing *Brigham & Women's Hosp. Inc. v. Teva Pharms. USA Inc.*, 2011 WL 63895 (D. Del. Jan. 7, 2011). Here as in *Abbott*, an act of Congress, rather than "improper gamesmanship by the patentee" or "strategic abuse of



[43] An obviousness-type double patenting analysis requires a comparison between the earlier patent, referred to as the reference patent, and the later patent. *See Eli Lilly & Co.*, 251 F.3d at 968. For patent applications filed pre-GATT, the ***issuing date*** is used to ascertain which patent was earlier and which was later. *Gilead,* 753 F.3d at 1214-15 (Fed. Cir. 2014). For applications filed post-GATT, however, the patent ***expiration date*** determines the earlier and later patents. *Id.* at 1216. In the instant matter, because the validity challenge is to the Patents-in-Suit, which are not subject to GATT, the issuance date should determine the reference patent. *See id.* at 1214-15 (finding that issuing date is used in an obviousness-type double patenting analysis for patents to which GATT does not apply). Looking to the issuance dates, the '225 Finck Patent is the only one which issued prior to both of the Patents-in-Suit and therefore is the only Finck Patent which could be properly considered an "earlier patent" for an obviousness-type double patenting analysis. The Court notes that alternatively looking to expiration date, all of the Finck Patents could serve as reference patents because they expire prior to the Patents-in-Suit, and therefore under either analysis at least one Finck Patent properly serves as the reference patent.

the patent system[,]" led to the Patents-in-Suit having a longer patent term and the expiration date for the Patents-in-Suit is "the same as it would have been had the [Finck Patents] never issued." *Id.* The Court therefore finds that the statutory term for the Patents-in-Suit may not be cut short to mirror the statutory term for the Finck Patents.

c. The Finck Patents Are Patentably Distinct from the Patents-in-Suit

At issue here is the patentable distinctness of Claims 11 and 35 of the '182 Patent and Claims 3 and 8 of the '522 Patent in comparison to Claim 1 of the Finck Patents in light of the definition of etanercept in the Finck specification. DFOF ¶¶ 92-95. The Patents-in-Suit claim etanercept itself and the method of making it. *See generally* '182 Patent (JTX-1); '522 Patent (JTX-2). In contrast, the Finck Patents cover a method of treating psoriasis and psoriatic conditions with etanercept. *See, e.g.,* '225 Patent (JTX-39) col. 21:33-36. For example, Claim 1 of the '225 Finck Patent claims "a method for treating a patient having psoriasis comprising administering to the patient a therapeutically effective dose of TNFR:Fc [i.e. etanercept], wherein the patient attains at least fifty percent improvement in PASI score." *See, e.g.,* id.

The Court first notes that a biologic manufacturer "may hold multiple patents covering the biologic, its therapeutic uses, and the processes used to manufacture it." *Sandoz*, 137 S. Ct. at 1670. Here, the '182 Patent claims the compound etanercept, the '522 Patent claims a process used to manufacture etanercept, and the Finck Patents claim a therapeutic use of treating psoriasis and psoriatic variants using etanercept. In support of their argument that the Finck Patents and the Patents-in-Suit are not patentably distinct, Defendants cite to *Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373 (Fed. Cir. 2003), wherein the court found that a claimed compound for which a POSA "would recognize a single use" was not distinct from a patent that "simply claims that use as a method." *See id.* at 1385-86; *see also Astellas Pharma, Inc. v.*

Ranbaxy Inc., No. 05-2563, 2007 WL 576341, at *6 (D.N.J. Feb. 21, 2007). In that case, however, the court determined that the claimed use of the compound was not only an inherent property of the compound but its sole use. *Geneva Pharm.*, 349 F.3d at 1385. *Geneva* is distinguishable from the instant case because, while the Finck Patents use etanercept for the treatment of psoriasis and related conditions, psoriasis treatment is neither an inherent property nor the sole use of etanercept.[44] *See* PFOF ¶ 316; *cf. Geneva Pharm.*, 349 F.3d at 1385.

Plaintiffs contend that practicing the claimed invention of the Patents-in-Suit to make etanercept would not result in the practice of the Finck Patents, because merely making etanercept would not result in treating psoriasis. *See* PFOF ¶ 316. Reviewing the Finck Patents and the Patents-in-Suit, the treatment methods for psoriasis and psoriatic conditions contained in the Finck Patents are not found in the Patents-in-Suit. Therefore, based on the Court's analysis, the Finck Patents' claim to a psoriasis treatment method using etanercept cannot be used to invalidate the Patents-in-Suit. *See In re Braat*, 937 F.2d at 593-94. Furthermore, the Finck Patents and the Patents-in-Suit could not have been combined into a single application because they do not share common owners. *See supra* III.C.2.a. Accordingly, the Court finds that Defendants have not demonstrated by clear and convincing evidence that the Patents-in-Suit are invalid for obviousness type double patenting.

[44] Furthermore, Plaintiffs argue that etanercept can be made using methods other than the one detailed in the '522 Patent, namely "by using a host cell" other than the type specified in the patent and therefore the Finck Patents' treatment method could be accomplished without infringing on the '522 Patent. *See* PFOF ¶ 316.

IV. CONCLUSION

For the foregoing reasons, the Court finds that Defendants have failed to show by clear and convincing evidence that the Patents-in-Suit are invalid. An appropriate Order accompanies this Opinion.

Dated: August 9, 2019

HON. CLAIRE C. CECCHI
United States District Judge