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

IMMUNEX CORPORATION, AMGEN MANUFACTURING, LIMITED, and HOFFMANN-LA ROCHE INC., Plaintiffs, v. SANDOZ INC., SANDOZ INTERNATIONAL GMBH, and SANDOZ GMBH, Defendants.	Honorable Claire C. Cecchi, U.S.D.J. Civil Action No.: 2:16-cv-01118-CCC-MF

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Term	Definition
’182 patent	U.S. Patent No. 8,063,182 (JTX-1)
’522 patent	U.S. Patent No. 8,163,522 (JTX-2)
Patents-in-suit	The ’182 and ’522 patents
’029 patent	U.S. Patent No. 5,808,029 (PTX-1035)
ADCC	Antibody dependent cellular cytotoxicity
Amended specification	The specification of the ’182 and ’522 patents, as amended by Immunex on Nov. 10, 2006, and Aug. 30, 2007, respectively
Amgen	Plaintiff Amgen Manufacturing, Ltd.
Arora 2009	Arora, T., et al., Differences in binding and effector functions between classes of TNF antagonists, Cytokine 45:124-131(2009) (PTX-130)
Ashkenazi 1991	Ashkenazi, A., et al., Protection against endotoxic shock by a tumor necrosis factor receptor immunoadhesin, Proc. Natl. Acad. Sci. 88:10535-39 (1991) (JTX-69)
Asserted claims	Claims 11-12 and 35-36 of the ’182 patent and claims 3, 8, and 10 of the ’522 patent
BPCIA	The Biologics Price Competition and Innovation Act
Brennan 1989	Brennan FM et al., Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis, Lancet, 2 (8657):244-47, 247 (1989) (DTX-75)
Brockhaus ’279 patent	U.S. Patent 5,610,279 (JTX-5)
Byrn 1990	Byrn, R.A., et al., Biological properties of a CD4 immunoadhesion, Nature 344:667-670 (1990) (JTX-56)
Capon 1989	Capon, D., et al., Designing CD4 immunoadhesins for AIDS therapy, Nature 337:525-30 (1989) (JTX-58)

Term	Definition
Capon '964 patent	U.S. Patent No. 5,116,964 (JTX-61)
CDC	Complement dependent cytotoxicity
Dembic 1990	Dembic et al., Two Human TNF Receptors Have Similar Extracellular, But Distinct Intracellular, Domain Sequences, Cytokine, 2(4): 231-237 (July 1990) (JTX-23)
Exon-encoded hinge-CH2-CH3 of a human IgG1	Hinge-CH2-CH3 of a human IgG1, as defined by Dr. Tonegawa according to the DNA that encodes a human IgG1
Figure 1	Figure 1 of the patents-in-suit
Figure 4	Figure 4 of the patents-in-suit
Finck '225 patent	U.S. Patent No. 7,915,225 (JTX-39)
Finck '605 patent	U.S. Patent No. 8,119,605 (JTX-40)
Finck '631 patent	U.S. Patent No. 8,722,631 (JTX-41)
IgG	Immunoglobulin of class G
IgG1	IgG subclass 1
IgG3	IgG subclass 3
Immunex	Plaintiff Immunex Corp.
Jacobs '690 patent	U.S. Patent 5,605,690 (JTX-42)
Karjalainen '827 publication	European Patent Application Publication No. 0 394 827 (JTX-60)
Kohno 2007	Kohno, *et al.*, Binding Characteristics of Tumor Necrosis Factor Receptor-Fc Fusion Proteins vs Anti-Tumor Necrosis Factor mAbs, Journal of Investigative Dermatology Symposium Proceedings (2007) (PTX-140)
Mitoma 2008	Mitoma H, et al., Mechanisms for Cytotoxic Effects of Anti-Tumor Necrosis Factor Agents on Transmembrane Tumor Necrosis Factor a-Expressing-Cells, Arthritis & Rheumatism, Vol. 58 No. 5, 1248-57 (May 2008) (DTX-213)

Term	Definition
p55 TNFR	A human TNF receptor having an apparent molecular weight of 55 kilodaltons on a non-reducing SDS-polyacrylamide gel
p75 TNFR	A human TNF receptor having an apparent molecular weight of 75 kilodaltons on a non-reducing SDS-polyacrylamide gel
p75 extracellular region	The portion of the p75 TNFR that protrudes outside the cell, which is amino acids 1-235 of the p75 TNFR
Peppel 1991	Peppel, K., et al., A tumor necrosis factor (TNF) receptor-IgG heavy chain chimeric protein as a bivalent antagonist of TNF activity, J. Exp. Med. 174:1483-89 (1991) (JTX-68)
POSA	Person of ordinary skill in the art
Psoriasis patents	The ’225, ’605, and ’631 patents
PTO	U.S. Patent and Trademark Office
Roche	Plaintiff Hoffmann-La Roche Inc.
Sandoz	Defendants Sandoz Inc., Sandoz International GmbH, and Sandoz GmbH
Seed ’262 publication	European Patent Application Publication No. 0 325 262 (JTX-57)
Smith 1990	Smith, C.A., et al., A receptor for tumor necrosis factor defines an unusual family of cellular and viral proteins, Science 248:1019-1023 (1990) (JTX-24)
Smith ’760 patent	U.S. Patent No. 5,395,760 (JTX-65)
Smith ’760 patent’s chimeric antibody	The “recombinant chimeric antibody molecule” described in the Smith ’760 patent at col. 10, ll. 53-68.
Smith protein	The p80 TNFR protein encoded by the amino acid sequence published by Immunex as Figure 3 in Smith 1990, now known as the full-length p75 TNFR

Term	Definition
Specification	The original specification of EP 90116707, the priority application of the patents-in-suit, as filed on August 31, 1990
TNF	Tumor necrosis factor
TNFR	TNF receptor
Traunecker 1989	Traunecker, A., et al., Highly efficient neutralization of HIV with recombinant CD4-immunoglobulin molecules, Nature 339:68-70 (1989) (JTX-25)
Watson 1990	Watson, S.R., et al., A Homing Receptor-IgG Chimera as a Probe for Adhesive Ligands of Lymph Node High Endothelial Venules, J. Cell Biol., 110:2221-29 (1990) (JTX-59)

TABLE OF WITNESSES

Witness	Live or By Deposition	Description
Peter Alliger, Ph.D.	By Deposition	Dr. Alliger is technical project leader at Sandoz for its GP2015 project
Taruna Arora, Ph.D.	By Deposition	Dr. Arora is a former principal scientist at Amgen who was involved in research related to etanercept. Dr. Arora submitted a declaration to the USPTO in support of the prosecution of the patents-in-suit
Carl P. Blobel, M.D., Ph.D.	Live	Dr. Blobel is Defendants' expert on obviousness, obviousness-type double patenting, and anticipation
Manfred Brockhaus, Ph.D.	By Deposition	Dr. Brockhaus is a named inventor on the patents-in-suit and a former employee of Hoffmann La-Roche
Daniel Capon, Ph.D.	Live	Dr. Capon is Defendants' expert on written description and enablement
Zlatko Dembic, Ph.D.	By Deposition	Dr. Dembic is a former senior scientist at Hoffman-LaRoche who is involved in research relating to TNF receptor. Dr. Dembic is a named inventor of the patents-in-suit
Roy Fleischmann, M.D.	Live	Dr. Fleischmann is Plaintiffs' expert on clinical success
Stephen Gillis, Ph.D.	By Deposition	Dr. Gillis is a former employee of Immunex. He served as Immunex's executive vice president and director of research and development during the development of etanercept

Witness	Live or By Deposition	Description
Raymond G. Goodwin, Ph.D.	By Deposition	Dr. Goodwin is a former employee of Immunex and was involved in the development of etanercept
Graham B. Jones, Ph.D.	By Deposition	Dr. Jones is Plaintiffs' expert on FDA's practices and policies regarding demonstrating biosimilarity
Warner C. Greene, M.D., Ph.D.	Live	Dr. Greene is Plaintiffs' expert on etanercept's properties with respect to aggregation, and CDC, and ADCC pathways
Ueli Gubler, Ph.D.	By Deposition	Dr. Gubler is a former senior research leader at Hoffmann-LaRoche, who was involved in research relating to TNF receptors
Johann Gudjonsson, M.D.	By Deposition	Dr. Gudjonsson is Plaintiffs' expert in dermatology
Jeffrey Kittendorf, Ph.D.	By Deposition	Dr. Kittendorf is Defendants' expert in biochemistry
Michael K. Kirschner	By Deposition	Mr. Kirschner is an intellectual property attorney who was formerly employed by Immunex and Amgen
Stephen G. Kunin	Live	Mr. Kunin is Plaintiffs' expert on USPTO patent policy, practice, and procedure
Leandre Lauffer, Ph.D.	By Deposition	Dr. Lauffer was a research scientist and former employee of Behringwerke. During his time there he was involved in the development of fusion proteins
Werner K.	By Deposition	Dr. Lesslauer is a named inventor of the

Witness	Live or By Deposition	Description
Lesslauer, Ph.D.		patents-in-suit. He was a research scientist and former employee of Hoffmann-LaRoche
Stewart Lyman, Ph.D.	By Deposition	Dr. Lyman is a former director at Extramural Research at Immunex. Dr. Lyman submitted declarations to the United States Patent and Trademark Office in support of the patents-in-suit.
Mark A. McCamish, M.D., Ph.D.	Live	Dr. McCamish was the Global Head of the Biopharmaceutical Development at the Biopharmaceutical Division of Sandoz from 2009-2016
DeForest McDuff, Ph.D.	Live	Dr. McDuff is Defendants' expert responding to Dr. Vullturo's opinion on commercial success
James H. Naismith, Ph.D.	Live	Dr. Naismith is Plaintiffs' expert on written description and binding properties of etanercept
John P. Parise	By Deposition	Mr. Parise is the former senior counsel and managing attorney at Hoffman LaRoche who was involved in the negotiation and drafting of license agreements
Arne Skerra, Ph.D.	Live	Dr. Skerra is Defendants' expert on binding properties, aggregation, and CDC and ADCC activities of etanercept
Christopher A. Vellturo, Ph.D.	Live	Dr. Vellturo is Plaintiffs' expert on commercial success
Thomas R. Wall, Ph.D.	Live	Dr. Wall is Plaintiffs' expert on obviousness and enablement

Witness	Live or By Deposition	Description
Stuart Watt	Live	Mr. Watt is Amgen's Vice President, Law and Intellectual Property Officer

INTRODUCTION

The question at the heart of the case is whether Immunex, the holder of all substantial rights to the patents-in-suit, is entitled to an over thirty-year monopoly on etanercept simply because it refused a formal assignment of the patents-in-suit from Roche. It is not. The patent laws, and specifically the doctrine of double patenting, were designed to prevent precisely this kind of gamesmanship. Furthermore, Immunex cannot use its own invention of etanercept to overcome the patents-in-suit's problems with written description and enablement. The patents-in-suit were filed by Roche, but Roche did not discover the p75 TNF receptor and never made etanercept. The application as originally filed reflects those facts. Immunex's attempt, after purchasing Roche's applications, to repurpose the applications to describe its etanercept invention fails the test for written description and enablement. Finally, Immunex's invention of etanercept prevents it from now taking the position that no person skilled in the art other than the Roche inventors would have thought to do so. All elements of the claimed invention were disclosed in the prior art, and the inventions of other scientists at the time make clear that persons of skill in the art were motivated to combine the elements, making the patents-in-suit obvious. Indeed, the real world evidence is that Immunex succeeded in inventing etanercept. Roche failed. The patents-in-suit are invalid, and Sandoz should be permitted to launch its biosimilar etanercept product and deliver on the promise of

competition that Congress encouraged pursuant to the BPCIA. 42 U.S.C. § 262.

Immunex obtained multiple patents covering the etanercept compound and its use and launched Enbrel in 1998. Around the time of Enbrel's launch, Immunex obtained a non-exclusive license from Roche for Roche's applications to the patents-in-suit, as it was at the time unsure whether Roche was going to be able to obtain patents that covered etanercept. This license allowed Immunex to sell Enbrel without the threat of potential patent infringement lawsuits by Roche, and at a royalty rate of less than 5%.

In 2004, faced with expiry of its main compound patent in 2014, Immunex recognized an opportunity to extend its patent protection. To that end, it executed a new agreement giving it—among other things—complete control of Roche's pending patent applications, which at the time were directed primarily to its p55 fusion protein and secondarily to a different TNF receptor than Immunex's p75 TNF receptor, and not to etanercept. Among the many rights that Immunex received, the unfettered right to control the prosecutions allowed Immunex to repurpose Roche's applications to cover etanercept. Roche retained no substantial rights in the applications, and did not even retain a license to commercialize a product itself, including the p55 fusion protein it invented.

Immunex knew that the 2004 Agreement would present double-patenting problems. So, although Roche wanted to assign the patent applications to Immunex,

Immunex insisted on calling the transfer a "license," despite the fact that it was, in operation, an assignment. Now, Immunex seeks to avoid the bedrock principle of patent ownership by arguing that it does not own the patents-in-suit because, despite controlling all substantial rights in those patents, it insisted on calling its agreement with Roche a "license." The label Immunex selected is irrelevant under the law. What matters is the substantive effect of the agreement. Immunex obtained complete control of all substantive rights, as Mr. Watt, who negotiated the agreement on behalf of Immunex, admitted at trial. Under the only test for patent ownership the Federal Circuit has ever adopted, Immunex owns the patents-in-suit as a matter of law.

This, alone, ends the case because Immunex makes no serious argument that the patents-in-suit are not obvious in view of its psoriasis patents. Moreover, Immunex's argument that the patents-in-suit are not obvious in view of its '690 patent is based on a deliberate misreading of that patent, which Immunex told the world for sixteen years covered etanercept, but is now—to avoid obviousness type double patenting—arguing it does not. Under the proper interpretation of the '690 patent, it claims etanercept and renders the patents-in-suit obvious.

Furthermore, the patents-in-suit are invalid for failing to meet the requirements of Section 112. As a factual matter, Roche did not conceive of and never made etanercept. As a result, the description of the invention in the specification of the patents initially filed by Roche does not include etanercept.

Rather, it describes a fusion protein that uses the p55 receptor and provides some disclosure of a truncated, mutated p75 receptor. On acquiring the Roche patent applications, Immunex promptly amended the specification to expressly describe its etanercept product, a recognition that etanercept had not been described in the original applications. But Roche's failure to describe etanercept in the original specification dooms the asserted claims under the written description analysis.

Finally, even if the patent specification is determined to satisfy the written description requirement, the claims are still invalid as obvious. All elements of the claimed invention were present in the prior art and Immunex concedes that there was a reasonable expectation that they would work if combined. The only remaining issue is whether a POSA would have been motivated to combine the elements. The prior art expressly encouraged that combination, as evidenced by work done by real world scientists. One third party, Immunex, actually invented etanercept with no assistance from Roche, and others created very similar fusion proteins using the same components. Indeed, even the PTO found that the combination was obvious, but issued the patents-in-suit in reliance on Immunex's one-sided presentation of alleged unexpected results that are, when examined closely in this Court, wholly expected and unsurprising.

The relevant facts were either undisputed at trial or were disputed only by witnesses affiliated with or retained by Immunex. While Sandoz consistently

presented evidence of what actually happened, Immunex created a hypothetical universe in which Immunex's witnesses, including its main negotiator of the 2004 Agreement and its lead expert, among others, ignored the real world facts and created issues that simply did not exist.

Immunex has received the full benefit of its own patents, making over $35 billion in sales through their expiration in 2014, and seeks to make billions more by using the patents it obtained from Roche to extend its monopoly through 2029. Immunex's position throughout this case has been driven solely by an effort to defend the patents-in-suit, in contradiction to its prior position that it invented etanercept, all in an effort to obtain over 30 years of market exclusivity for its product. This Court end Immunex's scheme and hold the patents-in-suit invalid.

ARGUMENT

I. The Patents-in-Suit Are Invalid for Obviousness-Type Double Patenting.

Obviousness-type double patenting "is a judicially created doctrine grounded in public policy." *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985). The purpose of the doctrine is to prevent the unjustified timewise extension of the right to exclude, and there are two requirements: (1) the patents-in-suit and the reference patents must be commonly owned or assigned, or have at least one common inventor, and (2) the asserted claims must be obvious variations of the reference patent claims. *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001); *In re Hubbell*, 709

F.3d 1140, 1149 (Fed. Cir. 2013).

There is no question that Immunex has obtained an unjustified timewise extension of its etanercept monopoly. Immunex enjoyed the full benefit of its original etanercept patents, including its main patent on the etanercept molecule which protected Enbrel from its launch in 1998 until the patent expired in 2014, and, pursuant to the 1998 Agreement with Roche, was free to market Enbrel without fear of being sued by Roche. FOF ¶¶ 12-13, 52-53, 57, 82. Nonetheless, in 2004, Immunex negotiated to acquire complete control of the Roche applications leading to the patents-in-suit. *Id*. ¶¶ 54, 57-65. Fully aware of the double patenting doctrine, Immunex deliberately insisted upon calling its transaction with Roche a "license," which, unlike the formal assignment that Roche wanted to grant, would not have to be reported to the PTO. *Id*. ¶¶ 55-56, 66-67. Immunex then obtained claims that, if upheld, will extend its etanercept monopoly by an additional 15 years, giving it a total of 30 years of market exclusivity for Enbrel. *Id*. ¶¶ 82-83. Federal Circuit case law makes clear that this "extension of the term of a patent, even where an express statutory basis for the rejection is missing" is precisely the conduct that the equitable doctrine of obviousness type double patenting is designed to prevent. *Longi*, 759 F.2d at 892.

Under all controlling Federal Circuit case law on patent ownership, there is no question Immunex owns the patents-in-suit. And if the Court concludes that

Immunex owns the patents-in-suit, there is no dispute that they are obvious in view of the psoriasis patents and therefore invalid. Moreover, Immunex's '690 patent, which was its primary patent covering etanercept until its expiration in 2014, also renders obvious the asserted claims of the patents-in-suit.

A. Immunex Owns The Patents-In-Suit.

1. Under Controlling Federal Circuit Law, Immunex Is The Owner Of The Patents-In-Suit.

The Federal Circuit has well-settled rules for determining who is the owner of a patent, and has set them out in a series of cases addressing standing (*i.e.*, who has the right to exclude another from practicing the patented invention) under the Patent Act. *See, e.g.*, *Diamond Coating Techs., LLC v. Hyundai Motor Am.*, 823 F.3d 615, 618 (Fed. Cir. 2016); *Luminara Worldwide, LLC v. Liown Elecs. Co.*, 814 F.3d 1343, 1349 (Fed. Cir. 2016); *Speedplay, Inc. v. BeBop, Inc.*, 211 F.3d 1245, 1249 (Fed. Cir. 2000). Under these rules, if a licensee to a patent has received "all substantial rights" in the patent from the licensor, it becomes the patent owner or assignee "regardless of how the parties characterize the transaction that conveyed those rights." *Speedplay*, 211 F.3d at 1250.

The two most critical substantial rights in determining patent ownership are the exclusive right to make, use, and sell the patented product and the right to sue for infringement. *Diamond Coating Techs.*, 823 F.3d at 619. It is undisputed that Immunex holds both of these critical rights.

Under the 2004 Agreement, Immunex has the exclusive right to make, use, sell, offer for sale, and import the claimed invention. FOF ¶ 59. Moreover, Immunex has the sole right to sublicense the patents, without restriction. *Id*. In addition, Immunex has the first right to rectify any alleged infringement, either by suing, sublicensing, or causing the alleged infringement to cease. *Id*. ¶¶ 59, 64. If Immunex sues, it exclusively finances and controls the litigation, including settlement, and obtains all, if any, proceeds from such a lawsuit. *Id*. Importantly, Immunex holds these rights to patent expiration and Roche has no right whatsoever to terminate the agreement for any reason. *Id*. ¶ 60.

These are the hallmarks of patent ownership. *Diamond Coating Techs.*, 823 F.3d at 619 ("[W]e have observed that (1) 'the exclusive right to make, use, and sell . . . is *vitally important*,' and (2) 'the nature and scope of the [patentee's] retained right to sue accused infringers [and to license the patent are] the most important factor[s] in determining whether an [agreement] . . . transfers sufficient rights to render the [other party] the owner of the patent.'"); *EMC Corp. v. Pure Storage, Inc.*, 165 F. Supp. 3d 170, 178 (D. Del. 2016) ("A party's right to sue for infringement is complete if it includes the 'right to indulge infringements.'"); *Vaupel Textilmaschinen KG v. Meccanica Euro Italia SPA*, 944 F.2d 870, 875 (Fed. Cir. 1992) (finding assignment even though licensor retained "a veto right on sublicensing"); *Speedplay*, 211 F.3d at 1250 (finding assignment where licensee

obtained exclusive right to make, use, and sell, and right to enforce the patents).

In addition, Immunex obtained another critical right: the exclusive right to control the prosecution of the patents-in-suit. FOF ¶¶ 59, 61. Roche did not even retain a right to review or comment on any patent prosecution submissions. *Id.* ¶ 72. Immunex had the unfettered right to draft patent claims and amend the specification to cover etanercept and extend its monopoly over the product. *Id.* ¶¶ 54-55, 72-83.

The extent of Immunex's control of the patents-in-suit is made more stark by the illusory rights that Roche retained. First, Roche only retained the right to practice the invention for internal, non-commercial uses. *Id.* ¶¶ 62-63. The Federal Circuit has held that this is not a substantial right: "A patentee that merely retains the right to practice the patent does not risk *losing* a substantial right if the claims are invalidated or the patent held unenforceable." *Luminara*, 814 F.3d at 1351. Indeed, here, Roche would gain *more* rights to exercise the claimed invention if the patent claims were held invalid or unenforceable because it would gain the right to commercialize the patented product, which it currently lacks. FOF ¶ 63.

Second, Roche retained a right to sue only if Immunex does not. *Id.* ¶¶ 62, 64-65. This, under Federal Circuit law, is an illusory right "because [Immunex] could 'render that right nugatory by granting the alleged infringer a royalty-free sublicense.'" *AsymmetRx, Inc. v. Biocare Med., LLC*, 582 F.3d 1314, 1320 (Fed. Cir. 2009); *accord Speedplay*, 211 F.3d at 1251; *EMC Corp.*, 165 F. Supp. 3d at 174-75.

As such, it is not a substantial right.

Even Immunex's Vice President, Law and Intellectual Property Officer, Mr. Watt, agreed that Immunex acquired "control" of the patent applications through his negotiation of the 2004 Agreement. FOF ¶ 61. Mr. Watt, an experienced patent practitioner, was fully aware of the doctrine of double patenting and that common ownership (or common inventors) was a requirement in order for the double patenting doctrine to apply. *Id*. ¶¶ 55-56. Mr. Watt knew Immunex would be required to report any formal assignment to the PTO. *Id*. ¶ 71. Not surprisingly, Immunex rejected Roche's offer to provide a formal assignment of the patent applications, insisting instead that the transfer be called a "license." *Id*. ¶¶ 66-67. Thus, the 2004 Agreement was never disclosed to the PTO and the PTO never considered the issue before this Court, namely, whether the claims sought in the patent in suit are invalid for double patenting over Immunex's patent applications. *Id*. ¶ 71. Notably, the transfer of the same basic rights from Roche to Wyeth outside of the U.S.—where there is no double patenting doctrine—was straightforwardly labeled an "assignment." *Id*. ¶ 70.

Mr. Watt's self-serving testimony to the contrary is belied by the facts. First, Mr. Watt testified that Roche in fact never offered to grant an assignment of the patents-in-suit. But Mr. Parise, who negotiated the 2004 Agreement on behalf of Roche, which unlike Immunex has no further interest in the patents in suit or in the

outcome of this litigation, unambiguously testified that Roche had made the offer. *Id*. ¶¶ 66-67. And email communications between the two companies during the negotiations of the 2004 Agreement make express reference to Roche's expectation that it would receive "an offer from Amgen to purchase" the applications. *Id*. ¶ 66.

Second, while Mr. Watt testified that the purpose of the 2004 Agreement was simply to buy out the royalty obligations of the 1998 License Agreement, he also conceded that Immunex acquired much more. Under the 1998 Agreement, Immunex was a non-exclusive licensee, with the ability to market Enbrel free from potential infringement claims; after the 2004 Agreement, Immunex completely controlled the patent applications. *Id*. ¶¶ 52-54, 57, 61. Immunex easily could have bought out its royalty obligations without assuming control of the patents as it did. Its purpose in assuming control was specifically to use those patents to extend its monopoly over Enbrel for an additional 15 years. *Id*. ¶¶ 82-83.

Third, Mr. Watt's assertion that maintaining Roche as the patent owner was necessary to ensure Roche's cooperation in patent prosecution and litigation is nonsensical and contradicted by Immunex's actions. *Id*. ¶ 69. Immunex dealt with its need for cooperation from Roche by negotiating an enforceable contractual agreement to cooperate in any prosecution or litigation. *Id*. The provision was necessary because maintaining Roche as the patent owner would have imposed no such obligation; indeed, as a true owner, Roche would have been free to do whatever

it wished with these patents. *EMC Corp.*, 165 F. Supp. 3d at 178. In addition, Mr. Watt admitted that he had no contemporaneous documentation that reflected his purported rationale for maintaining Roche's ownership interest. FOF ¶ 69.

Simply put, Roche did not retain any substantial rights in the patents-in-suit, instead transferring all of them to Immunex under the 2004 Agreement. Accordingly, Immunex is the owner of the patents-in-suit and the doctrine of obviousness-type double patenting applies.

2. Immunex's Arguments To Avoid A Finding Of Ownership Are Without Merit.

The Federal Circuit has never adopted Immunex's argument that the Court should not apply the Federal Circuit's ownership rules in the context of double patenting. On the contrary, the "all substantial rights" test is the one test that the Federal Circuit applies to determine patent ownership. Immunex offers no legitimate reason why that should not be the case here. Immunex also fails to provide its own definition of patent ownership, nor has it pointed to any alternative Federal Circuit law defining ownership. That is because the issue is the same in both standing and double patenting cases: which party owns the right to exclude.

Specifically, the purpose of the "all substantial rights" test is to determine who is the "patentee" under 35 U.S.C. § 281: "A patentee shall have remedy by civil action for infringement of his patent." Section 281 is the statutory basis for the right to enforce a patent. *Diamond Coating*, 823 F.3d at 618. And "[a] patent provides its

owner with the right to exclude others from making, using, and selling the claimed invention." *Vaupel*, 944 F.2d at 875 (emphasis added). Thus, the Federal Circuit's "all substantial rights" test provides the definitive test for determining who is the statutory owner of the patent. Nowhere has the Federal Circuit or Congress limited this statutory definition of ownership to standing cases, nor is there a logical basis to have a different meaning of "ownership" for ownership in the standing context than in the double patenting context. Indeed, the "all substantial rights test" fits exactly with the purpose of the double patenting doctrine "to prevent unjustified timewise extension of the *right to exclude*." *Lilly*, 251 F.3d at 968 (emphasis added).

In an effort to avoid the "all substantial rights" test, Immunex argues that the MPEP has limited common ownership under double patenting solely to cases in which the patents-in-suit and reference patents are commonly owned "at the time the claimed invention [of the patents-in-suit] was made." Neither the Federal Circuit nor any District Court has ever imposed this timing requirement in any double patenting case. On the contrary, the Federal Circuit has held a patent invalid for obviousness-type double patenting, even when the patents only became commonly owned later, *e.g.*, via merger, *see Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1377, 1382-86 (Fed. Cir. 2003) (holding patents invalid for obviousness-type double patenting where the patentee "own[ed] the [reference] patents because [it] has merged with the original assignees of those patents"), and where a later-filed

reference patent did not exist at the time the invention claimed in the target patent was made and therefore could not have been commonly owned at that time. *Lilly*, 251 F.3d at 955; *see also Ex parte Pfizer, Inc.*, Appeal No. 2009-004106, 2010 WL 532133, at *21 (B.P.A.I. Feb. 12, 2010). In any event, the MPEP is not binding on this Court. *Regents Of Univ. Of New Mexico v. Knight*, 321 F.3d 1111, 1121 (Fed. Cir. 2003).

Immunex's gamesmanship in refusing to take the formal title offered by Roche while taking all of the substantial rights should not be rewarded with an additional 15 years of market exclusivity for Enbrel. As the Federal Circuit has held, if a licensee to a patent has received "all substantial rights" in the patent, it becomes the patent owner or assignee "regardless of how the parties characterize the transaction that conveyed those rights." *Speedplay*, 211 F.3d at 1250.

B. The Asserted Claims Are Invalid In View Of The Psoriasis Patent Claims.

There is no dispute that the asserted claims of the patents-in-suit are obvious in view of the psoriasis patent claims. Sandoz presented abundant evidence at trial and Immunex did not even attempt to offer an expert opinion otherwise. FOF ¶¶ 90-96. Because the psoriasis patent claims are species of the asserted claims of the patents-in-suit, under black letter law, the asserted claims are invalid for obviousness-type double patenting. *See, e.g.*, *Geneva*, 349 F.3d at 1383 (holding that the earlier expiring claim was "basically a species" of the later expiring claims).

C. The Asserted Claims Are Invalid In View of Immunex's Jacobs '690 Patent Claim 3.

The clear and convincing evidence at trial proved that the asserted claims are also invalid for double patenting in view of claim 3 of the Jacobs '690 patent. FOF ¶¶ 97-117. The parties agree that claim 3 covers a protein consisting of the extracellular region of the p75 TNF receptor fused to a portion of a human IgG1, but dispute the construction of "fused to the constant domain." *Id.* ¶¶ 98-99, 117, 208. The intrinsic evidence to the Jacobs '690 patent—which was overlooked by Amgen's expert (*id.* ¶¶ 101, 105)—resolves this dispute.

The patent and file history show that claim 3 covers etanercept, wherein the extracellular region of the TNF receptor is fused to the hinge-CH2-CH3 region of IgG1. *Id.* ¶¶ 100-109. But even if claim 3 were construed to require fusing the extracellular region of the TNF receptor to the entire heavy and light chain IgG1 constant regions, as Immunex asserts, the prior art would have led a person of ordinary skill in the art to modify the claimed protein to create etanercept. *Id.* ¶¶ 117; *see also id.* ¶¶ 215-24. Thus, under either proposed construction, the asserted claims are not patentably distinct over claim 3 of the Jacobs '690 patent.

1. As Properly Construed, Claim 3 of the Jacobs '690 Patent Claims a Method of Administering Etanercept.

In construing claim language, "[t]he intrinsic evidence, '*i.e.*, the patent itself, including the claims, the specification and, if in evidence, the prosecution history …

is the most significant source of the legally operative meaning of disputed claim language.'" *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1338 (Fed. Cir. 2005). All the intrinsic evidence here points to claim 3 covering etanercept.

Etanercept is a chimeric antibody consisting of the extracellular domain of the p75 TNF receptor (amino acids 1-234 of SEQ ID NO: 1) fused to the hinge, CH2, and CH3 constant domains of a human IgG1. FOF ¶ 100. Etanercept, which is referred to as "TNFR/Fc" in the '690 patent specification, is featured prominently. *Id.* ¶¶ 102-104. Each of the figures describe etanercept, including its structure (Fig. 1), how to construct it (Fig. 2), and the effects of administering it (Figs. 3-7). *Id.* ¶ 102. The examples describe constructing and expressing etanercept and using etanercept to suppress the effects of arthritic conditions. *Id.* ¶ 104. The sole paragraph discussing a chimeric antibody references etanercept specifically as an example of the described chimeric antibody (the TNFR/Fc protein of SEQ ID NOS: 3 and 4). *Id.* ¶ 103. Construing the claims to exclude a preferred embodiment, as Immunex suggests, "is rarely, if ever, correct." *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996).

The prosecution history of the Jacobs '690 patent further affirms that the claimed chimeric antibody refers to etanercept. FOF ¶¶ 105-109. Importantly, Immunex drafted claims directed specifically to etanercept that were dependent on independent claims with the "chimeric antibody" language that Immunex now

argues does not include etanercept. *Id.* ¶ 106; *see Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012). (noting that "if [dependent] claim 2 covers the range from 0.0001% w/v–5% w/v, [independent] claim 1 must cover at least that range"). The applicants further relied upon the Moreland declaration reporting clinical data from administering etanercept to demonstrate the utility of the claimed chimeric antibody. FOF ¶ 108. At no point during prosecution did the applicants assert that the chimeric antibody would exclude etanercept or otherwise disavow any claim scope directed to it. *Id.* ¶ 107-109.

Immunex's litigation inspired argument that a person of skill in the art would have understood that the claimed "chimeric antibody" excludes etanercept has no support. Unlike Dr. Blobel, Dr. Wall improperly ignored the file history in forming his opinion. *Id.* ¶ 105. Nevertheless, based on his review of just the patent, Dr. Wall could not credibly disavow his original deposition testimony that he did not know whether the claimed chimeric antibody having the TNF receptor "fused to the constant domain of an immunoglobulin molecule" would "preclude it from being fused to the hinge-CH2-CH3." *Id.* ¶ 101. As he admitted, a person of skill in the art would have understood that the specification's discussion of the claimed chimeric antibody reflects that a human IgG1 has multiple constant region domains. *Id.* ¶ 103. In etanercept, the TNF receptor is fused to three constant domains of an immunoglobulin—namely, the hinge, CH2, and CH3. *Id.* That chimeric antibodies

in the '690 patent include etanercept is clear from the reference to the etanercept sequence as an example of a chimeric antibody. *Id.* The evidence therefore shows that, as properly construed, claim 3 of the '690 patent covers etanercept.

2. The Jacobs '690 Patent's Claimed Method of Administering Etanercept Renders Obvious the Asserted Claims.

The asserted claims are not patentably distinct over properly construed claim 3 of the Jacobs '690 patent. *Id.* ¶¶ 111-16. As Dr. Blobel explained, in constructing a species of the claimed chimeric antibody, a person of skill in the art would have been motivated to fuse the entire p75 extracellular region to the hinge-CH2-CH3 portion of a human IgG1, with the expectation that it would specifically bind human TNF. *Id.* ¶¶ 112-14. Thus, each of the asserted claims directed to etanercept, methods to produce etanercept, and pharmaceutical compositions comprising etanercept would have been obvious. *Id.* ¶¶ 115-16. None of Immunex's experts have disputed obviousness of the asserted claims under Sandoz's proposed construction.

3. In the Alternative, Under Dr. Wall's Construction, Jacobs '690 Patent Claim 3 Renders Obvious the Asserted Claims.

Under Dr. Wall's construction, the p75 extracellular region is fused to "a completely unchanged and unmodified constant region domain for the light chain and for the heavy chains." *Id.* ¶¶ 117, 208. When compared to Dr. Wall's construction of the claimed chimeric antibody, etanercept only differs in the removal of the light chain and the CH1 domain from IgG1. *Id.* ¶ 214. As the prior art taught,

receptor-IgG fusion proteins lacking the light chain and CH1 domains were preferred. *Id.* ¶¶ 215-20. Thus, this difference would have been the most obvious construct to a person of skill in the art.

Specifically, a person of skill seeking to improve upon the "chimeric antibody" of claim 3 of the Jacobs '690 patent would have been aware of and looked to the prior art describing other receptor-IgG fusion proteins. *Id.* ¶ 215. Based on the prior art, a person of skill in the art would have known that the receptor-IgG fusion proteins lacking the light chain were much easier to synthesize and were preferred. *Id.* ¶¶ 216-17. As Dr. Wall admitted, "there was a good reason for removing the light chain" from the receptor-IgG fusion proteins, because the light chain "didn't add anything." *Id.* Having removed the light chain, a person of skill in the art would have also been motivated also to remove the CH1 domain, which—as reluctantly admitted by Dr. Wall—was expected to improve the production and secretion of the receptor-IgG fusion proteins. *Id.* ¶¶ 218-19.

Indeed, as trial record confirmed, by August 1990, the receptor-IgG fusion protein art had evolved such that the preferred fusion proteins included those that lacked both the light chain and CH1 domain. *Id.* ¶ 219. Contrary to Immunex's contention, the alternative receptor-IgG fusion protein constructs in the Seed '262 publication and the Capon '964 patent, which retained the CH1 domain or removed the hinge domain, do not change the clear motivation in the prior art for removal of

CH1 domains. *Id.* ¶ 220. In each of these references, the only receptor-IgG fusion protein constructs that were selected for further testing lacked the light chain and CH1 domain. *Id.* Thus, a person of skill in the art would have been motivated to select receptor-IgG fusion proteins lacking the light chain and CH1 domain. *Id.*

Therefore, even under Dr. Wall's proposed construction of the claimed chimeric antibody, a person of skill in the art, following the clear evolution in the receptor IgG fusion protein prior art, would have been motivated to remove the light chain and CH1 domain from the claimed "chimeric antibody," and would have arrived at etanercept. *Id.* ¶¶ 117, 208-24. As such, each of the asserted claims would not have been patently distinct over claim 3 of the Jacobs '690 patent.

II. The Asserted Claims Of The Patents-In-Suit Are Invalid For Lack Of Written Description And Enablement.

The patents-in-suit are also invalid for lack of written description and enablement. To comply with the written description requirement, a patentee must describe "the invention, with all its claimed limitations" as of the filing date. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). It is the specification that must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter" based on "an objective inquiry into the four corners of the specification." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). Similarly, it "is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an

invention in order to constitute adequate enablement." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

Consistent with its clinical development efforts, Roche oriented its priority application to the p55 fusion protein. FOF ¶¶ 20, 138, 156-157, 174. Fourteen years after Roche filed the priority application, Immunex took over prosecution and amended the original specification and claims to cover etanercept. *Id*. ¶¶ 54, 72-81. Before then, etanercept was *nowhere* described in the original specification and was *never* even made by the Roche inventors. *Id*. ¶¶ 33-44. Roche's original specification does not demonstrate that Roche possessed etanercept, and it does not guide or direct a person of ordinary skill in the art to the specific embodiment Immunex pursued over a decade later. *Id*. ¶¶ 122. The specification unequivocally confirms that the Roche inventors *did not* possess etanercept in August 1990. *Id*. ¶¶ 122-179.

A. The Specification As Filed Does Not Describe Or Enable Etanercept.

1. The Specification's Focus Is On The Figure 1 p55 TNF Receptor.

The art, as of the filing date of the patents-in-suit, had definitively identified two TNF receptors: the p55 and the p75 (which was at that time known as the p80). *Id*. ¶¶ 4, 314. However, a person of skill in the art could not have said with certainty that there were only two TNF receptors. *Id*. ¶¶ 314.

Roche was the first to clone the full-length p55 TNF receptor using a cDNA

library "fishing" method by the summer of 1989, and focused the majority of its characterization and development efforts thereafter on that receptor. *Id*. ¶¶ 14-17. By April 1990, Roche had identified and filed a patent directed to its full-length p55 TNF receptor disclosed in Figure 1 of the patents-in-suit. *Id*. ¶¶ 27.

Around that time, Roche began making a p55-IgG3 fusion protein using its full-length p55 clone and the pcd4Hγ3 (IgG3) vector from Drs. Karjalainan and Traunecker. *Id*. ¶¶ 18-19. Roche's p55 TNF receptor fusion protein research led to its testing of a p55-IgG1 fusion protein in clinical trials starting in 1993 and preparation of a New Drug Application for its clinical candidate. *Id*. ¶¶ 20.

In contrast, Roche made no similar efforts to construct a p75 TNF receptor fusion protein in 1990. Indeed, Roche *never* made the claimed p75-IgG1 fusion protein or etanercept or pursued a p75 fusion protein as a clinical candidate. *Id*. ¶ 33. In fact, Roche borrowed a p75-IgG1 fusion protein from Immunex in 1994—four years after the priority date—for a clinical trial comparing its preferred p55 fusion protein to the p75-IgG1. *Id*. ¶ 34.

The primary focus of the specification is description of the p55 TNF receptor.[1]

[1] To the extent that Immunex argues that it satisfies the written description requirement because the p75 TNF receptor is an obvious substitution for the p55, the '182 patent is invalid for obviousness-type double patenting over the '279 patent. The sole difference between the asserted claims of the '182 patent and '279 patent claim 5 is the use of the extracellular region of the p75 receptor in place of a soluble fragment of the p55 TNF receptor. FOF ¶¶ 118-21.

That is not surprising given that Roche's development and clinical efforts focused *primarily* on the p55 TNF receptor and fusion proteins comprised thereof. *Id*. ¶¶ 14-20, 33-34. Starting with the Summary of the Invention, the Roche inventors clearly defined the "present invention" as Figure 1 first, with its variants. *Id*. ¶¶ 136-138. The Detailed Description of the Invention likewise focuses "first of all" on the p55 TNF receptor. *Id*. ¶¶ 140-141, 143-153, 156-157, 174-175. The entire disclosure plainly tells a person of skill in the art in 1990 that the invention is primarily about the p55 TNF receptor. *Id*.

2. Roche's Figure 4 Protein Is Not The Smith Protein Used In Etanercept.

After discovering in December 1989 that Immunex was working on a second TNF receptor, Roche devoted limited resources to cloning that TNF receptor using its fishing method. *Id*. ¶¶ 21-32. Roche never successfully sequenced the full-length p75 TNF receptor using this method. *Id*. ¶¶ 28-32. As a result of its various attempts to clone p75, in July 1990, Roche scientists published an article reporting a partial p75 sequence with a portion of the extracellular region that was more complete than what eventually became Figure 4 of the patents-in-suit ("Dembic 1990"). *Id*. ¶¶ 29-30. Meanwhile, Immunex published the sequence of a different p80 TNF receptor in May 1990 ("Smith 1990")—this protein is referred to today as the p75 TNF receptor ("Smith protein"). *Id*. ¶ 34. Roche learned about Immunex's TNF receptor protein around May 1990. *Id*. ¶ 29.

Despite having the information in Smith 1990 and Dembic 1990 available when it filed the priority application in August 1990, Roche did not include that information in its specification. *Id*. ¶¶ 35-37. Nor did Roche include plasmid N227 (later known as PTA 7942), despite representing in 2006 that the plasmid existed at the time that the priority application was filed. *Id*. ¶¶ 181-185; *see Ariad*, 598 F.3d at 1352 (stating that possession "outside of the specification" is insufficient to satisfy written description because "it is the specification itself that must demonstrate possession"). Rather, Roche made the deliberate decision to rely on, as a second alternative, the protein it discovered and claimed before Immunex: Roche's Figure 4 protein, a truncated, mutated p75 TNF receptor. FOF ¶ 124. Roche's Figure 4 protein reflects five significant amino acid differences compared to the Smith protein. *Id*. ¶ 126.

Compared to the Smith protein, Roche's Figure 4 protein deleted the first 70 amino acids at the beginning of the sequence, including the first 48 amino acids of what is now known as the extracellular region. *Id*. ¶¶ 126-127. The deleted 48 amino acids are now known (discovered after the priority date) to be important to TNF binding. *Id*. ¶ 128. In addition to the deleted amino acids, Roche's Figure 4 protein has four drastic, non-conservative differences—three mutations and one extra amino acid. *Id*. ¶¶ 129-134. A person of skill in the art in August 1990 would have understood that these mutations and extra amino acid would likely have a profound

effect on the shape or function (or both) of the molecule and thus would have considered Roche's Figure 4 and the Smith proteins to be distinct. *Id*. ¶ 135, 143-144.

At trial, Immunex contended that a person of skill in the art would have understood that the inventors meant to include the Smith protein despite the differences with the actually disclosed Figure 4 protein. *Id*. ¶¶ 72-81. This was squarely contradicted by Immunex's own expert's (Dr. Naismith's) testimony at trial where he openly admitted that the reference to Smith in the specification was "confusing" and "on its face ridiculous." *Id*. ¶¶ 145-146.

Moreover, Immunex's argument does not square with Roche's specification and its later admissions regarding its Figure 4 protein. *Id*. ¶¶ 42-44. During prosecution of related applications, Roche considered its Figure 4 truncated, mutated p75 protein to be a distinct, patent-worthy protein in its own right. *Id*. From one of the divisional applications filed off of the '279 patent application, Roche obtained U.S. Patent No. 5,808,029 covering a polynucleotide encoding Roche's Figure 4 protein. *Id*. ¶ 42. During prosecution, the examiner issued a rejection asserting that the Figure 4 protein and the Smith protein were exactly the same, such that the Smith protein anticipated the Figure 4 protein. *Id*. ¶ 43. To overcome that anticipation rejection, Roche explained that Roche's Figure 4 protein and the Smith protein are very different proteins. *Id*. ¶ 44. To prove that Roche's Figure 4 protein and the

Smith protein are distinct proteins, Roche relied on the very same differences cited by Dr. Capon: the mutations, the extra amino acid, and that Smith teaches a protein of about *80 kD*, whereas Roche's Figure 4 protein has an apparent molecular weight of about *75 kD*. *Id*. Roche's 1997 admission comports with a person of skill in the art's understanding of the specification, in light of the art, as directed to a different TNF receptor protein: Roche's Figure 4. *Id*. And now, before this Court, Roche cannot undo its representations to the PTO to retain its unwarranted patent monopoly.

3. The Examples Are Not Directed To The p75 TNF Receptor Or Etanercept.

The 11 examples in the specification are likewise directed primarily to the p55 TNF receptor. *Id*. ¶ 156. None of the examples describe a full-length p75 TNF receptor, a method for obtaining a full-length p75 TNF receptor, a p75 fusion protein, or any p75-IgG1 fusion protein, much less etanercept.

Example 8 of the specification, the sole example related to any p75 TNF receptor, references a method for identifying the Figure 4 sequence. *Id*. ¶ 157. The method in Example 8 cannot be used to obtain the full-length p75 TNF receptor. *Id*. ¶¶ 25-32, 157, 307. Indeed, the Roche inventors tried for months to obtain that full-length sequence and failed. *Id*. ¶¶ 25-32.

Example 11 of the specification, the sole fusion protein example, is directed to the DNA for a p55-IgG3 fusion protein, which is a different molecule than a p75-

IgG1 fusion protein. *Id*. ¶¶ 173-179. Indeed, there is no evidence in either the specification or Roche's notebooks or other internal documents that the inventors even conceived of a p75-IgG1 fusion protein, let alone made it. *Id*. ¶¶ 11, 33-34.

Nor is there any information in the specification that would direct a person of skill in the art to construct such a protein. *Id*. ¶¶ 174-177. Neither the full-length p75 TNF receptor, nor the extracellular region, nor the "exon-encoded hinge-CH2-CH3" region[2] were described. *Id*. ¶ 173. The specification does not provide an encoding polynucleotide for the molecule, an expression vector, an expressing host cell, an actual fusion protein, or any demonstration that the protein specifically binds TNF. *Id*. ¶¶ 173-178. Nor does the specification describe any example or method that can be used to make a p75-IgG1. *Id*. ¶¶ 175-177.

For these reasons, a person of ordinary skill in the art reading the examples would not believe that the inventors possessed a p75 fusion protein. *Id*. ¶ 179.

[2] The specification fails to describe the very specific "exon-encoded hinge" of an IgG1. *Id*. ¶¶ 162-172. The words "hinge," "exon," and "exon-encoded hinge" do not appear anywhere in the specification. *Id*. ¶ 162. A person of skill in the art would have understood that the specification described a pantheon of potential hinges, including a universe of variants, but not specifically the exon-encoded hinge. *Id*. ¶¶ 163-164. A person of skill further would have considered using a different hinge (the Edelman hinge) based on its wide usage and the use of the term domain in the specification. In fact, Immunex and Roche understood the specification to describe the Edelman hinge, not the exon-encoded hinge. *Id*. ¶ 172.

B. Immunex's Arguments Cannot Cure the Deficient Disclosure in the Specification.

Immunex cannot cure the written description deficiency based on an analysis that attempts to piece together the disclosure for the p75 TNF receptor extracellular region from ambiguous hints in the specification and prior art disclosures.

1. The Reference To Smith 1990 In The Specification Is Not Sufficient To Describe Etanercept.

Immunex seeks to remedy its written description problem by pointing to the sole passing reference to Smith 1990 in the original specification. But deriving support "from an amalgam of disclosures plucked selectively" from the application does not satisfy the written description requirement. *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013). The original disclosure must provide adequate direction which reasonably would lead persons skilled in the art to "single out" the invention from the various alternatives discussed in the disclosure. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326 (Fed. Cir. 2000).

Here, the specification teaches a person of ordinary skill in the art in 1990 *not* to use the Smith protein. *Id*. ¶¶ 123, 136-159. The Roche inventors knew about the Smith 1990 publication and could have described the Smith protein and incorporated it by reference. *Id*. ¶¶ 143-147, 159. They did not. *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (to incorporate material by

reference, the "document must identify with detailed particularity what specific material it incorporates"). Instead, the Roche inventors purposefully identified Smith 1990 in the specification only as an example of how a person of ordinary skill in the art could modify Roche's Figure 4 protein by deleting one amino acid at position 369. FOF ¶ 143. The Roche inventors make no other mention of Smith 1990 in the specification. *Id*. ¶ 144. Nowhere do the Roche inventors identify in the specification Smith 1990 or the Smith protein as a reference to find the claimed insoluble human TNF receptor extracellular region having "an apparent molecular weight of about 75 kilodaltons on a non-reducing SDS-polyacrylamide gel." *Id*. ¶¶ 143-144. In fact, as Roche admitted in 1997, the Smith protein is different from Figure 4 because it weighs about 80 kD on a non-reducing SDS-polyacrylamide gel, not 75 kD like Figure 4. *Id*. ¶¶ 43-44.

There is no dispute that a person of skill in the art in 1990 would have understood from this description that the Smith protein is *not* incorporated by reference into the specification. *Id*. ¶¶ 144-146. Dr. Naismith candidly conceded this point on cross examination. *Id*. ¶¶ 145-146. And despite submitting a declaration on behalf of Immunex to the PTO during prosecution of the '522 patent representing that Smith 1990 was incorporated by reference, Dr. Lyman—a former Roche employee hired by Immunex to file declarations to overcome written description rejections—also conceded at his deposition that the reference to Smith 1990 in the

specification does not direct a POSA to "[u]se Smith to complete the sequence of Figure 4." *Id*. ¶¶ 148-152.

2. Immunex's Reliance On Prior Art And The Infinite Number Of Sequences Disclosed In The Specification Is Wrong As A Matter Of Law And Fact.

At trial, Immunex argued that the "inventive concept" of the patents was fusing a TNF receptor with a human immunoglobulin, and a person of skill in the art could have looked outside the four corners of the specification and selected the Smith protein and the exon-encoded hinge of an IgG1 to make a fusion protein using no more than routine skill. Putting aside the contradiction with Immunex's arguments against obviousness, Immunex's reliance on the prior art to satisfy written description is wrong under the law: "[A] description that merely renders the invention obvious does not satisfy the [written description] requirement." *Ariad*, 598 F.3d at 1352. But even if the law allowed Immunex to pull all of the elements and methods from the prior art to construct the purported invention, there is no direction in the specification to select *etanercept* in particular from the millions of other possible fusion proteins potentially described under Immunex's theory.

The specification defines the relevant TNF receptor portions as any "soluble fragment" of (1) Roche's full-length p55 TNF receptor disclosed in Figure 1, or (2) Roche's Figure 4 protein, a *truncated, mutated variation* of the p75 TNF receptor. FOF ¶¶ 123-125, 160-161. Potential soluble fragments of Figures 1 and 4

include an enormous number of amino acid sequences encompassing the entire or a portion of the extracellular domain. *Id.* ¶ 161. The specification also identifies the immunoglobulin portion as any of 11 human immunoglobulin isotypes and subtypes and does not specify the particular junction between the TNF receptor-immunoglobulin, further broadening the number of possible prophetic proteins. *Id.* ¶¶ 163-164.

The only fusion protein DNA disclosed in the specification is *not* that of a p75-IgG1 fusion protein, but a p55-IgG3 fusion protein—a different molecule. *Id.* ¶ 329. But the asserted claims require a very different fusion protein that includes amino acids 1-235 comprising the *entire* extracellular region of the Smith protein. *Id.* ¶ 174. Nowhere does the specification describe such a fusion protein, much less using the 462-amino acid p75 TNF receptor, and certainly much less using the specific stretch of amino acids 1-235 of that sequence. *Id.* ¶¶ 123-161; *see Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011) (holding patent invalid for lack of written description where the "overwhelming majority" of the specification described mouse antibodies and "the mere fact that 'the words [human antibodies] appear' does not reasonably suggest to one of skill in the art that Centocor was in possession of such claimed human antibodies"). The Federal Circuit prohibits the addition of later claims to specific embodiments—such as Immunex's asserted claims to etanercept—where "the myriads of possibilities encompassed by

the broad disclosure [provide] no guide indicating or directing that this particular selection should be made rather than any of the many others which could also be made." *In re Ruschig*, 379 F.2d 990, 995 (C.C.P.A. 1967); *see also Ariad*, 598 F.3d at 1351.

C. Immunex's Actions After Taking Over Prosecution Confirm that the Original Specification Was Deficient.

1. Immunex's 2006 And 2007 Amendments Confirm That Etanercept Was Not Covered By The Original Specification.

Immunex's amendments to the specification 16 years after the original filing date constitute a clear admission that etanercept was not covered by the initial specification. Obviously, had the original specification disclosed etanercept, there would have been no need to amend. But, on taking control of the patent applications, Immunex sought claims to etanercept and recognized that it needed to amend the specification to support those claims.

First, in 2006, Immunex amended the specification of the '790 application to include a reference to Immunex's October 17, 2006 deposit of a plasmid PTA 7942.[3,4] FOF ¶¶ 181-182. The DNA for the PTA 7942 plasmid contains the full-

[3] Immunex added the same reference to the same plasmid PTA 7942 in the specification of the '791 application in 2007. *Id*. ¶ 186. That reference is deficient for the same reasons set forth herein.

[4] Immunex supported this amendment with a declaration from Dr. Lesslauer indicating that plasmid N227 from Roche is the same as PTA 7942. *Id*. ¶ 184. But Dr. Lesslauer did not supervise the deposit and relied on Amgen's representation that it made the deposit. *Id*.

length, non-mutated p75 TNF receptor. *Id*. ¶ 183. Notably, Immunex failed to inform the Appeal Board that the PTA 7942 plasmid was a completely different protein than the shorter, mutated p75 TNF receptor described in Figure 4. *Id*. ¶¶ 184-185.

Second, in 2007, Immunex amended the specification of the '791 application to insert the Smith protein. *Id*. ¶¶ 186-189. As explained above, the original specification taught using Smith 1990 in a specific, singular way: as an example of a deletion of one amino acid at position 369 that could be made to Roche's Figure 4 protein. *Id*. ¶¶ 144-152. The original specification did not incorporate Smith 1990 by reference. *Id*. ¶¶ 144-146. Instead, Immunex expressly "incorporated by reference" Smith 1990 in 2007, as is made clear by Drs. Naismith's and Lyman's testimonies. *Id*. ¶¶ 188. Further, Immunex felt compelled to insert its own prior art to fix the specification: Figure 5 and its figure legend are copied jot-for-jot directly from Immunex's Smith 1990 publication. *Id*. ¶¶ 187-188. Thus, the specification, as filed, pointed to Roche's Figure 4 protein, not to the Smith protein. *Id*. ¶ 189.

Taken together, Immunex's amendments to the specification to add the p75 TNF receptor missing from the specification as filed constitute clear admissions that etanercept was not covered by the initial specification.

2. Immunex's Misrepresentations to the PTO Improperly Concealed the Written Description Problem of the Specification.

Immunex's argument that the PTO already considered and rejected Sandoz's

112 defenses is misleading. During prosecution, Immunex misrepresented to the PTO and Appeals Board that "the amino acid sequence of Figure 4 is almost identical (almost 99% identical)" to Immunex's Smith 1990 publication and is "the same protein…Attached as Exhibit D is an alignment of the Figure 4 sequence with the complete sequence of p75 TNF receptor to illustrate this point" and "[d]espite differences between the sequences disclosed in the application and those in the Smith (1990) article, the amino acid sequences are nearly 99% identical overall." *Id*. ¶¶ 148-152. The amino acid sequence of Roche's Figure 4 protein is not almost 99 percent identical to the Smith protein. *Id*. ¶¶ 150-151. The extracellular region of Roche's Figure 4 protein is over 20 percent different from the Smith protein. *Id*. Overall, the proteins differ by 15 percent. *Id*.

Further, Exhibit D only compares the portions of the Smith protein and Roche's Figure 4 protein that overlap, not the "complete sequences." *Id*. ¶ 152. A person of skill in the art would understand that the primary amino acid sequence is the "backbone" of the protein. *Id*. Because a change in even one amino acid can drastically change the structure and function of a protein, a person of skill in the art in 1990, and today, would compare the entire length of the protein, not just the portion that overlaps. *Id*.

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In sum, the hallmark of written description is possession as of the time of

filing. The Roche inventors never, in fact, possessed the claimed invention and the specification makes that clear. None of Immunex's attempts to repurpose the specification to describe etanercept, either by pointing exclusively to prior art or by amending the specification,[5] save the patents-in-suit from invalidity for lack of written description and enablement. Therefore, the Court should hold the asserted claims of the patents-in-suit invalid for lack of written description. And because Immunex relies entirely on the prior art for the novel aspects of the invention (i.e., the methods and materials), the claims are not adequately enabled. *Novo Nordisk*, 108 F.3d at 1366.

III. The Patents-in-Suit Are Invalid For Obviousness.

At the end of trial, the only real dispute as to obviousness of the asserted claims concerned motivation. Both parties' experts agreed that the prior art as of August 1990 taught each element of the claimed invention. FOF ¶ 229. The DNA sequences of the p75 TNF receptor and the hinge-CH2-CH3 of IgG1 were known. *Id.* Fusion proteins consisting of a receptor extracellular region fused to the hinge-

[5] Each of these amendments impermissibly added new subject matter because as described above, the full-length p75 TNF receptor was not described in the specification. For this reason, the Patent Office should not have permitted the amendments or, in the alternative, Immunex should not be entitled to a priority date that pre-dates the amendments. In particular, asserted claims 35-36 of the '182 patent, which specifically claim the 2006 plasmid deposit, are invalid for anticipation because, as of 2006, Enbrel® had been on sale and publicly available for eight years. FOF ¶ 183.

CH2-CH3 of a human IgG1 were also known, including the deposit of a vector for constructing such a fusion protein. *Id.*; *see also id.* ¶¶ 216-20. Both parties' experts further agreed that, if a person of ordinary skill in the art had been motivated to construct etanercept, it would have been within his or her level of skill to produce etanercept by culturing a host cell and purifying it with a reasonable expectation that etanercept would specifically bind human TNF. *Id.* ¶¶ 229-30.

The only remaining dispute is motivation. Would a person of ordinary skill in the art in August 1990 have been motivated to construct a fusion protein of the p75 extracellular region fused to the hinge-CH2-CH3 of a human IgG1—*i.e.*, etanercept? The clear and convincing evidence at trial proved that they would have. The best evidence of such motivation is the undisputed evidence that Immunex actually did create etanercept. FOF ¶ 10-11. Not only that, but at least two other research groups also created TNF receptor-IgG fusion proteins with similar structures during this time period. *Id.* ¶¶ 233-36. Such evidence of simultaneous invention conclusively demonstrates that there was motivation to create the claimed fusion protein. Moreover, the only difference between the prior art and etanercept is the removal of the light chain and CH1 domain from the '760 patent's chimeric antibody. *Id.* ¶ 214. And the prior art expressly taught to make these modifications to improve fusion proteins. *Id.* ¶¶ 215-20.

In response, Dr. Wall presents a narrative that the Roche inventors were

mavericks in the face of prior art that would have discouraged a person of ordinary skill in the art. From Dr. Wall's perspective, no one would have ever considered targeting TNF with any immunoglobulin protein due to his fabricated concerns regarding effector functions in a patient with an autoimmune disease. *Id.* ¶ 225. Although this narrative was presented without challenge at the PTO and was key to issuance of the patents-in-suit, it was shown to be fundamentally flawed under the scrutiny of trial. *Id.* ¶¶ 77, 253. For one, Dr. Wall relied on no prior art (or any other evidence for that matter) supporting this hypothetical teaching away argument. To the contrary, the trial record showed that the prior art *encouraged* constructing a TNF receptor-IgG1 fusion protein and suggested using such proteins to treat an autoimmune disease, as further supported by the real-world evidence of simultaneous invention by at least three other groups. *Id.* ¶¶ 225-28, 231-36.

A. A Person of Ordinary Skill in the Art Would Have Been Motivated to Produce Etanercept From the '760 Patent's Chimeric Antibody.

1. The '760 Patent's Chimeric Antibody is a p75 TNF Receptor-IgG1 Fusion Protein.

By August 1990, there was significant interest in studying TNF and proteins capable of targeting TNF, and a significant amount of work had already been done in that area. FOF ¶¶ 196-203. Several major biotech institutions had published their research characterizing and cloning the TNF receptors. *Id.* ¶¶ 199-202. The availability of their DNA sequences allowed for the production of soluble forms of

the TNF receptors and soluble proteins derived from the TNF receptors, particularly for use in "explor[ing] the clinical value of TNF inhibition in pathological settings." *Id.* ¶ 203 (quoting JTX-24 at 4). The prior art expressly combined an IgG1 fusion protein with the p75 TNF receptor for this purpose. *Id.* ¶¶ 208-209.

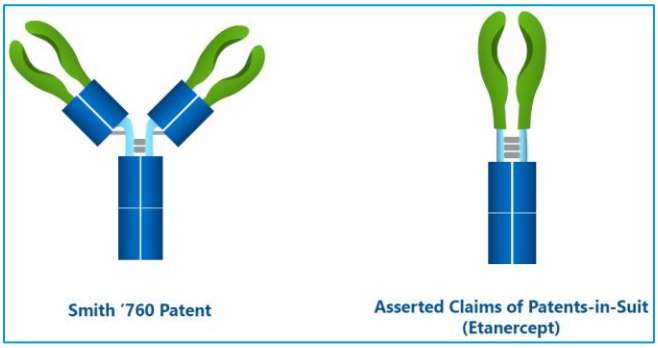
The '760 patent's chimeric antibody is a fusion protein, whereby the p75 extracellular region is attached to a human IgG1 light chain and/or heavy chain constant region. *Id.* ¶ 208. The parties' experts agree that the chimeric antibody was expected to provide for extended *in vivo* half-life, ease of purification, and enhanced TNF binding relative to a soluble TNF receptor (*e.g.*, the p75 extracellular region). *Id.* ¶¶ 210-14; *see also id.* ¶¶ 204-207. As Dr. Wall admits, this "chimeric antibody would have addressed all three" of these properties. *Id.* ¶ 210. The '760 patent teaches that it may be used in drug therapy "to bind or scavenge TNF, thereby providing a means for regulating the immune activities" of TNF. *Id.* ¶ 209.

2. A Person of Ordinary Skill in the Art Would Have Removed the Light Chain and CH1 Domain from the '760 Patent's Chimeric Antibody.

The obviousness inquiry evaluates whether "the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103. This inquiry requires "an expansive and flexible approach." *KSR Int'l*

Co. v. Teleflex, Inc., 550 U.S. 398, 415 (2007). A person of ordinary skill in the art is presumed to know all of the relevant prior art. *Id.* at 417, 420. The person of ordinary skill in the art need not rely solely on "precise teachings directed to the specific subject matter of the challenged claim," but may also make inferences and take creative steps in combining the prior art. *Id.* at 418. Thus, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416.

Etanercept is an obvious variant of the '760 patent's chimeric antibody in view of the fusion protein prior art. The only differences between etanercept and the chimeric antibody of the '760 patent are the removal of the light chain and the CH1 domain. FOF ¶ 214. It would have been obvious for a person of ordinary skill in the art to modify the '760 patent's chimeric antibody to remove the light chain and the CH1 region. *Id.* ¶ 215. In fact, at the priority date, the art recommended that fusion proteins should be made without the light chain or the CH1 region. *Id.* ¶¶ 216-20. By then, removal of the light chain and CH1 domain was known to improve the production and secretion of the fusion protein. *Id.* A person of ordinary skill in the art would have been motivated to make the same modifications to the '760 patent's chimeric antibody. FOF ¶ 215; *KSR*, 550 U.S. at



417 ("[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."). There is no dispute that this was within ordinary skill. FOF ¶¶ 229-30. The prior art provided a clear path to modifying the '760 patent's chimeric antibody to construct etanercept. *Id.* ¶¶ 215-20.

Against this backdrop, Dr. Wall attempts to distract from the clear guidance of the prior art by asserting that, since some used a linker and others used the partial hinge to connect a receptor to the hinge of the human IgG1, this somehow changes the obviousness conclusion. Dr. Wall is wrong. There were only a finite number of ways to construct the fusion site of a soluble receptor to the hinge-CH2-CH3 of a human IgG1. *Id.* ¶ 221. The prior art presented only two choices, each with two options: choice of hinge domain (full or partial) and choice of linker (absent or present). *Id.* ¶¶ 222-23. Any of these four options would have been obvious. *Id.*; *see KSR*, 550 U.S. at 402 ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp."). The experts agreed that all such combinations worked in fusion proteins. FOF ¶ 224. And both parties' experts agreed that a person of ordinary skill in the art would have understood that specifically fusing the p75

extracellular region to the full exon-encoded hinge-CH2-CH3 portion of a human IgG1 without a linker—*i.e.*, etanercept—would result in a fusion protein with the predicted activity of specifically binding human TNF. *Id.* ¶ 230. Dr. Wall presented no evidence that the choice reflected in etanercept (using no linker and the full hinge region) was disfavored or discouraged in the art. Instead, this combination would have been among the obvious choices that a person of ordinary skill in the art in August 1990 would have preferred to fuse the p75 extracellular region to the hinge-CH2-CH3 of a human IgG1. *Id.* ¶¶ 221-24.

3. Effector Functions Would Not Have Discouraged A Person of Ordinary Skill in the Art.

The essence of Dr. Wall's nonobviousness opinion is that a person of ordinary skill in the art would not have been motivated to combine an IgG1 fusion protein with a TNF receptor "because . . . the effector function of the Ig portion" would have made it unsuitable for use in treating TNF-mediated autoimmune diseases. FOF ¶ 225. Not so. Effector functions were not believed to be a problem in the development of a fusion protein to reduce TNF levels in August 1990. *Id.* ¶¶ 226-28.

Dr. Wall points to no prior art discouraging construction of a TNF receptor-IgG1 fusion protein due to effector functions, or for any other reason, in August 1990. In contrast, at trial, Sandoz provided evidence showing that scientists did not shy away from using fusion proteins due to Dr. Wall's hypothetical concerns about effector functions. Multiple prior art references reflected that anti-TNF antibodies

(which contain the effector portion of the IgG) had been tested in animals successfully to protect against the negative effects of TNF and further recommended their development into drug therapies to treat human inflammatory diseases. *Id.* ¶ 226. The prior art also expressly recommended administering a homing receptor-IgG fusion protein "for the treatment of patients with inflammations, such as for example due to rheumatoid arthritis or other autoimmune diseases." *Id.* ¶ 227. Thus, even if a person of ordinary skill in the art had considered effector functions as a potential concern (and there is no evidence that they would have), each of these references would have assuaged their concern. Dr. Wall does not come close to meeting the standard for teaching away. Dr. Wall's only response is that these several prior art authors were merely "speculating," when they contradicted his opinion. But, in fact, it is Dr. Wall's opinion that is speculative and without support in the prior art, which does not come close to meeting the standard for teaching away. *See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009).

Moreover, real-world evidence of simultaneous invention reflects "how those skilled in the art approached and solved problems" and greatly minimizes "the problem of hindsight" influencing whether there was a motivation to combine. *Int'l Glass Co. v. U.S.*, 408 F.2d 395, 405 (Ct. Cl. 1969). Simultaneous invention by Behringwerke, Immunex, Genentech, and UT Southwestern show that they were not

discouraged by effector functions from combining a TNF receptor with a portion of an immunoglobulin. FOF ¶¶ 5-11, 231-36. Instead, their research reflects their inspiration to create TNF receptor-IgG fusion proteins for the reasons of increased half-life, ease of purification, and enhanced binding to TNF—key motivations that Dr. Wall dismisses as insignificant. *Id.* ¶¶ 6, 234, 236.

Concern about effector functions is a nonexistent problem manufactured years later by Immunex. Dr. Wall relies on testing of etanercept's potential to elicit effector functions that was published more than a decade after August 1990 and several years after FDA approval of etanercept and the anti-TNF antibodies. *Id.* ¶ 228. Even then, effector functions were beneficial attributes. The anti-TNF antibodies like infliximab and adalimumab were found to be effective in treating a wider range of TNF-mediated diseases (*e.g.*, Crohn's disease) than etanercept due to their more potent effector functions. *Id.* ¶¶ 255-57.

While the drumbeat of Immunex's nonobviousness theory is that there is no motivation to combine due to concern about effector functions (which was unrebutted at the PTO and was pivotal to issuance of the patents-in-suit), the prior art and contemporaneous evidence showing how real-world scientists viewed the prior art prove otherwise.

B. The Objective Indicia Support Obviousness.

In the face of clear and convincing evidence that a person of ordinary skill in

the art would have been motivated to create the claimed invention with a reasonable expectation of success, Immunex has asserted a litany of objective indicia that it alleges show nonobviousness. And, at the PTO, Immunex's unchallenged evidence of unexpected results was successful in rebutting obviousness. FOF ¶¶ 77, 253. But trial proved why the patents-in-suit cannot be salvaged. The objective indicia actually support obviousness. Simultaneous invention demonstrates obviousness, and Immunex's objective evidence is not persuasive evidence of non-obviousness, because it either fails to distinguish etanercept from the prior art and/or lacks the required nexus to support the nonobviousness of the claimed invention.

1. Simultaneous Invention Provides Strong Evidence Rebutting Dr. Wall's Lack of a Motivation to Combine.

"[I]ndependently made, simultaneous invention, made 'within a comparatively short space of time,' are persuasive evidence that the claimed apparatus 'was the product only of ordinary mechanical or engineering skill.'" *Geo M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010). Especially here, where the obviousness dispute centers on the motivation, the evidence of simultaneous invention is dispositive of obviousness. COL ¶ 334.

The real-world evidence shows that three other research groups had, within a short time frame around August 1990, independently conceived of and were motivated to develop fusion proteins comprising the TNF receptor extracellular region and the hinge-CH2-CH3 of an immunoglobulin. FOF ¶¶ 5-11, 231-36. These

scientists were, in fact, inspired by the CD4-IgG1 fusion protein prior art to create IgG fusion proteins with a TNF receptor. *Id.* ¶¶ 5-6, 234, 236. Despite Dr. Wall's dismissal of the advantages of extended *in vivo* half-life, ease of purification, and enhanced TNF binding as insignificant, the real-world evidence shows that these factors, in fact, motivated—contrary to Dr. Wall's characterization—scientists to create their TNF receptor-IgG1 fusion proteins. *Id.* The scientists at the time viewed the prior art as inspiring—not discouraging, as Dr. Wall contends—the construction of TNF receptor-IgG1 fusion proteins, and they constructed them.

2. Immunex's Purported Unexpected Results Were Not Surprising

As it did in the PTO, Immunex relies heavily on alleged unexpected results as establishing the non-obviousness of the claimed invention. But, unlike the *ex parte* proceedings of the PTO, where the evidence was uncontested, the evidence at trial established that neither etanercept's enhanced binding to TNF nor its lack of aggregation and CDC/ADCC activity were unexpected.

a. Etanercept's Enhanced Binding to TNF Was Not Unexpected.

Etanercept's ability to bind TNF more strongly than a soluble p75 TNF receptor is not surprising. FOF ¶¶ 237-41. Since etanercept is a dimeric protein having two TNF receptors, due to the avidity effect, a person of ordinary skill in the art would have expected etanercept to bind TNF more strongly than a single TNF

receptor. *Id.* ¶ 238-39. The avidity effect was known to provide on average a 1,000-fold increase in the binding strength compared to monovalent binding. *Id.* The observed 50-times stronger binding and 1,000-time higher neutralization activity of etanercept compared to the soluble p75 TNF receptor was within the realm of expectations. *Id.* ¶ 241. Any difference in binding strength is merely a difference in degree that is not probative of nonobviousness. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) ("Unexpected results that are probative of nonobviousness are those that are different in kind and not merely in degree from the results of the prior art.").

b. Etanercept's Lack of Aggregation and Minimal CDC/ADCC Activity Was Not An Unexpected Property.

Etanercept's lack of aggregation and minimal CDC and ADCC activity directly result from its expected propensity to favor bivalent over monovalent binding. FOF ¶¶ 242, 247-50. A person of ordinary skill in the art would have expected that, due to the avidity effect providing significantly stronger binding, etanercept would have strongly preferred bivalent binding ("Mode 2" binding to the same TNF trimer) over monovalent binding ("Mode 1" binding to two different TNF trimers). *Id.* ¶¶ 237-39. When bivalent binding predominates, a person of ordinary skill in the art would not have expected aggregates to form and, thus, would not have expected etanercept to trigger CDC and ADCC activity. *Id.* ¶¶ 242, 247-50.

Immunex did not properly evaluate unexpected results. The Federal Circuit requires that "[w]hen an article is said to achieve unexpected (i.e. superior) results, those results must logically be shown as superior *compared* to the results achieved with other articles." *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). "Moreover, an applicant relying on comparative tests to rebut a prima facie case of obviousness must compare his claimed invention to the closest prior art." *Id.* Immunex did not compare etanercept to the prior art. As it did before the PTO, Immunex relies on comparisons of the properties of etanercept to those of the anti-TNF antibodies infliximab and adalimumab. FOF ¶¶ 244-45, 252-54. These anti-TNF antibodies, however, were not available in the prior art, and Immunex relies on no prior art testing of any anti-TNF antibodies. *Id.* By itself, Immunex's failure to compare etanercept to the prior art is fatal to its claim of unexpected results.

Even if this comparison were proper, Immunex's own evidence rebuts its claim of unexpected results. Immunex's study, Kohno 2007, reflects the expectation that aggregates would not form in the presence of TNF. *Id.* ¶ 245. It explains that the anti-TNF antibodies—not etanercept—deviated from expectations, as the antibodies "typically do not form precipitable complexes in these types of assays." *Id.* (quoting PTX-140 at 3). Similarly, Immunex's second study by Dr. Taruna Arora does not support its claims of unexpected effector functions. Arora 2009 reflects that, even as of 2009, there was no clear expectation in the field, as the role of IgG1's "Fc" region

in mediating effector functions "had not been thoroughly investigated." *Id.* ¶ 228. And, despite repeated attempts to elicit the testimony by Immunex's counsel, Dr. Arora would not agree that etanercept's results were surprising or unexpected. *Id.* ¶ 253. Instead, Dr. Arora testified that it would have been unexpected if etanercept had shown higher effector functions than the anti-TNF antibodies—which is not the case here. *Id.*

Further, Immunex has not shown that etanercept's lack of aggregation and little CDC and ADCC activity is a superior property. Immunex's entire evidence of CDC and ADCC activity is based on *in vitro* studies using mutated membrane-bound TNF under artificial experimental settings that are not representative of human conditions. *Id.* ¶ 252. Instead, due to their ability to elicit effector functions, the anti-TNF antibodies are therapeutically effective to treat more conditions in humans, like Crohn's disease, than etanercept. *Id.* ¶ 255-57. Etanercept is not even uniquely suited for treating rheumatoid arthritis, as all three drugs are effective and have been FDA-approved to treat rheumatoid arthritis. *Id.* ¶ 255.

3. Immunex's Evidence of Copying, Clinical Success, Praise, Long-Felt Need, and Failure by Others Lacks Nexus.

Immunex's remaining secondary consideration evidence—copying, clinical success, praise, long-felt need, and failure by others—does not cure its obviousness problem as such evidence lacks "the requisite 'nexus between the merits of the claimed invention' and the 'evidence of secondary considerations.'" *See Stamps.com*

Inc. v. Endicia, Inc., 437 F. App'x 897, 905 (Fed. Cir. 2011).

First, Immunex's evidence of clinical success, praise, and long-felt need are not "commensurate in scope with the claims which the evidence is offered to support." *See Therasense, Inc. v. Becton, Dickinson and Co.*, 593 F.3d 1325, 1336 (Fed Cir. 2010). Immunex artificially restricted the evidence its experts reviewed to include only those treatments for which etanercept had been approved and only those years of commercial sales that were best for etanercept. FOF ¶¶ 261-62. This selective review of evidence is improper. *Crowley v. Chait*, 322 F. Supp. 2d 530, 542 (D.N.J. 2004) ("selective furnishing of information by counsel to an expert runs afoul of" FRE 703).

The asserted claims do not recite use of etanercept for treatment of any particular disease. FOF ¶ 261. By artificially limiting the scope of objective evidence, Immunex failed to consider other treatments targeting TNF (*e.g.*, infliximab) that were approved prior to etanercept, and other TNF-mediated conditions (*e.g.*, Crohn's diseases and ulcerative colitis) for which etanercept did not receive FDA approval. *Id.* Similarly, in its economic analysis, Immunex failed to consider earlier patents claiming etanercept and to define what was novel about the patents-in-suit compared to those earlier patents. *Id.* ¶ 262; *see In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). In addition, Immunex's economic expert only analyzed the first 10 years that Enbrel was on the market, rather than its full 20 years

of market exclusivity. FOF ¶ 262.

Second, "evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." *Bayer Healthcare Pharm., Inc. v. Watson Pharm. Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013). The same should apply here. Sandoz selected the amino acid sequence for its biosimilar product years prior to the issuance of the patents-in-suit, and based on the commercial product, Enbrel®. FOF ¶¶ 84-88, 258-59. At the time, Sandoz believed that FDA approval would have required an identical amino acid sequence—a position that Plaintiff Amgen shared. *Id.* Any copying by Sandoz reflects its efforts to meet the FDA standards for approval of biosimilar products.

Finally, Immunex is plainly incorrect about the failure of others. Immunex succeeded in developing etanercept as an FDA-approved product, with no contribution from the named inventors at Roche. FOF ¶¶ 10-13, 260. Instead, Roche's attempt to commercialize its own TNF receptor-IgG1 fusion protein failed in clinical trials. *Id.* ¶ 20, 260.

Thus, the clear and convincing evidence at trial proved that development of etanercept was an obvious idea.

Dated: October 26, 2018

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CERTIFICATION OF SERVICE

The undersigned attorney certifies that copies of the foregoing **DEFENDANTS' SECOND CORRECTED POST-TRIAL BRIEF** and supporting documents were served by electronic mail on October 26, 2018, upon all counsel of record.

Dated: October 26, 2018

/s/ Christina Lynn Saveriano
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