Liza M. Walsh
WALSH PIZZI O'REILLY FALANGA LLP
One Riverfront Plaza
1037 Raymond Boulevard, 6th Floor
Newark, New Jersey 07102
(973) 757-1100

OF COUNSEL:

David T. Pritikin (*pro hac vice*)
SIDLEY AUSTIN LLP
One South Dearborn
Chicago, Illinois 60603
(312) 853-7000

Vernon M. Winters (*pro hac vice*)
SIDLEY AUSTIN LLP
555 California Street
San Francisco, CA 94104
(415) 772-1200

ADDITIONAL COUNSEL LISTED
ON SIGNATURE PAGE

Attorneys for Immunex Corporation and Amgen Manufacturing, Limited

David E. De Lorenzi
Charles H. Chevalier
Christine A. Gaddis
GIBBONS P.C.
One Gateway Center
Newark, New Jersey 07102-5310
(973) 596-4500

OF COUNSEL:

David I. Berl (*pro hac vice*)
Aaron Maurer (*pro hac vice*)
Thomas S. Fletcher (*pro hac vice*)
Seth R. Bowers (*pro hac vice*)
WILLIAMS & CONNOLLY LLP
725 Twelfth St. NW
Washington, D.C. 20005
(202) 434-5000

Attorneys for Hoffmann-La Roche Inc.

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

IMMUNEX CORPORATION; AMGEN MANUFACTURING, LIMITED; and HOFFMANN-LA ROCHE INC.;	)	Civil Action No.: 2:16-cv-01118-CCC-MF
Plaintiffs,	)	
v.	)	**PLAINTIFFS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW**
SANDOZ INC.; SANDOZ INTERNATIONAL GMBH; and SANDOZ GMBH;	)	
Defendants.	)	

TABLE OF CONTENTS

PLAINTIFFS' PROPOSED FINDINGS OF FACT

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Other Authorities

TABLE OF ABBREVIATIONS

Parties	
Immunex	Plaintiff Immunex Corporation
AML	Plaintiff Amgen Manufacturing, Limited
Roche	Plaintiff Hoffmann-La Roche Inc.
Plaintiffs	Plaintiffs Immunex, AML and Roche
Sandoz or Defendants	Defendants Sandoz Inc., Sandoz International GmbH, and Sandoz GmbH
Patents/Patent Publications	
’182 Patent	U.S. Patent No. 8,063,182
’522 Patent	U.S. Patent No. 8,163,522
Patents-in-Suit or Roche Patents	’182 Patent and ’522 Patent
’013 Application	U.S. Patent Application No. 07/580,013
EP707 Application	European Patent Application No. 90116707
the Patent Disclosure	’182 Patent, ’522 Patent, ’013 Application, EP707 Application
’640 Application	U.S. Patent Application No. 08/095,640
’790 Application	U.S. Patent Application No. 08/444,790
’791 Application	U.S. Patent Application No. 08/444,791
EP121 Patent	European Patent No. 0 939 121
Defined Terms	
aBLA	Abbreviated BLA
ADCC	antibody-dependent cell-mediated cytotoxicity
A&S	2004 Accord and Satisfaction
BPCIA	Biologics Price Competition and Innovation Act
BLA	Biologics License Application
CDC	complement-dependent cytotoxicity
Claims	Claims 11-12 and 35-36 of the ’182 Patent and Claims 3, 8, 10 of the ’522 Patent
COL	Conclusion of Law
Enbrel	ENBREL® (etanercept)
Erelzi	ERELZI® (etanercept)
FDA	U.S. Food and Drug Administration
FH	Patent File History
FOF	Findings of Fact
Inventors	The named inventors on the ’182 and ’522 Patents
Ig	Immunoglobulin or antibody

kD or kDa	Kilodalton
p55	p55 TNFR
p75	p75 TNFR
PHSA	Public Health Service Act
POSA	Person of Ordinary Skill in the Art on August 31, 1990
PTO Board	U.S. Patent Office Patent Trial and Appeal Board (formerly the Board of Patent Appeals and Interferences)
RA	Rheumatoid Arthritis
TNFR	Tumor necrosis factor receptor
USPTO	U.S. Patent and Trademark Office
Sandoz's Obviousness-Type Double Patenting References	
Finck Patents	U.S. Patent Nos. 7,915,225, 8,119,605, and 8,722,631
Jacobs '690 Patent	U.S. Patent No. 5,605,690
'279 Patent	U.S. Patent No. 5,610,279
Sandoz's Obviousness References	
Smith 1990	Smith CA *et al.*, A receptor for tumor necrosis factor defines an unusual family of cellular and viral proteins, *Science* 248:1019-23 (1990)
Smith '760	U.S. Patent No. 5,395,760
Bryn 1990	Byrn R *et al.*, Biological properties of a CD4 immunoadhesin, *Nature* 344: 667-670 (1990)
Capon '964	U.S. Patent No. 5,116,964
Seed '262	European Patent Application Publication No. 0 325 262
Karjalainen	European Patent Application Publication No. 0 394 827
Traunecker	Traunecker A *et al.*, Highly efficient neutralization of HIV with recombinant CD4-immunoglobulin molecules, *Nature* 339:68-70 (1989)
Watson	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)
General References	
Capon 1989	Capon D *et al.*, Designing CD4 immunoadhesins for AIDS therapy, *Nature* 337:525-31 (1989)
Dembic	Dembic Z *et al.*, Two Human TNF Receptors have similar extracellular, but distinct intracellular, domain sequences, *Cytokine* 2:231-237 (1990)
Feldmann	Feldmann M *et al.*, Anti-TNFα Therapy of Rheumatoid Arthritis: What Have We Learned?, *Annu. Rev. Immunol.*, 19:163-96 (2001)

Brennan 1989	Brennan FM *et al.*, "Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis," *Lancet*, 2:244-47 (1989)
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)
Citations	
JFPTO	Final Pre-Trial Order, D.I. 620
9/18A (Naismith) 53:5-10	Exemplary trial transcript cite; "A" denotes the morning session, "P," the afternoon, of the referenced date
PTX	Plaintiffs' Trial Exhibit (cites to exhibit page number)
PDX	Plaintiffs' Demonstrative
DTX	Sandoz's Trial Exhibit
DDX	Sandoz's Demonstrative

Plaintiffs submit these Proposed Findings of Fact and Conclusions of Law pursuant to Federal Rule of Civil Procedure 52 and the Court's Order. D.I. 635. Plaintiffs ask that where a finding of fact is appropriately deemed a conclusion of law, or vice-versa, or where a finding or conclusion under one heading is more appropriately placed under another heading, the Court do so.

PLAINTIFFS' PROPOSED FINDINGS OF FACT

I. THE PATENTS-IN-SUIT AND THE ASSERTED CLAIMS

1. The trial addressed the validity of claims 11-12 and 35-36 of U.S. Patent No. 8,063,182 ("the '182 Patent") and claims 3, 8, 10 of U.S. Patent No. 8,163,522 ("the '522 Patent") (the "Claims" of the "Patents-in-Suit").

2. Paragraphs 7-35 from the Final Joint Pretrial Order, D.I. 620 (JFPTO ¶¶ 7-35), addressing the Patents-in-Suit, are incorporated herein.

II. THE PARTIES

3. Plaintiff Hoffmann-La Roche Inc. ("Roche") owns the Patents-in-Suit, having received right and title to the underlying patent applications via assignment from F. Hoffmann-La Roche AG, JTX-3 at 879, which received all right and title to the patent applications via assignments from the inventors. JTX-3 at 876-878.

4. In 2004, Roche granted an exclusive license to the Patents-in-Suit to Amgen Inc. and its affiliates, including Immunex Corporation ("Immunex"). JTX-12. Those rights were consolidated in Immunex by a separate agreement. JTX-14; 9/24P (Watt) 28:20-29:8.

5. Immunex sublicensed exclusive rights related to ENBREL®'s commercialization to Amgen Manufacturing, Limited ("AML"). JTX-15 at 3.

6. Defendants Sandoz Inc., Sandoz International GmbH, and Sandoz GmbH (Defendants) develop biosimilars. 9/14 (McCamish) 12:25-13:8. Sandoz will import, market and sell its FDA-approved etanercept biosimilar in the United States

absent injunction. JFPTO ¶ 43; D.I. 28 ¶ 8.

7. JFPTO ¶¶ 1-6 are incorporated herein.

III. THE PRODUCTS AT ISSUE

8. Immunex is the reference product sponsor of the FDA-approved drug Enbrel; its active ingredient is etanercept. JFPTO ¶¶ 36, 38.

9. Etanercept is a dimeric fusion protein consisting of the extracellular region of the p75 TNF receptor ("p75") fused to the exon-encoded "hinge-CH2-CH3" of the constant region of a human IgG1 antibody heavy chain. JFPTO ¶ 37.

10. Enbrel is the first FDA-approved fusion protein. 9/20A (Wall) 54:13-16. Approved in November 1998 to treat RA, JFPTO ¶ 39, it targeted the pathway by which RA worked. *Id.* at 151:3-152:5. It was later approved to treat other indications. JFPTO ¶ 38.

11. The FDA approved Sandoz's biosimilar, trade named Erelzi™ ("Erelzi" or "GP2015"), for treating RA. JFPTO ¶ 43. Etanercept is its active ingredient. JFPTO ¶ 46 & Joint Exhibit 1.

12. JFPTO ¶¶ 36-40 and 41-46, and Sequence A in JFPTO Joint Exhibit 1 (referenced in JFPTO ¶ 46), are incorporated herein.

IV. JURISDICTION

13. This Court has personal jurisdiction over Defendants, D.I. 28 ¶ 19; D.I. 105 ¶ 30; D.I. 121 ¶ 38, and subject matter jurisdiction. 28 U.S.C. §§ 1331 and

1338(a). D.I. 28 ¶ 18; D.I. 105 ¶ 18; D.I. 121 ¶ 18.

V. STANDING

14. Defendants do not contest standing. JFPTO ¶¶ 39-40.

VI. ISSUES RESOLVED AND ISSUES REMAINING

15. JFPTO ¶¶ 47-50 are incorporated herein.

16. Defendants stipulated to infringing the Claims based on Erelzi, its production, and Sandoz, Inc.'s submission of its aBLA. D.I. 619 ¶¶ 1-4.

17. Defendants withdrew all invalidity defenses except for §§ 103 and 112, obviousness-type double patenting, JFPTO ¶¶ 52, 58; D.I. 597; 9/11P (Blobel) 93:2-94:4, and, for '182 Patent claims 35 and 36, anticipation. D.I. 597 at 3.

18. An ordinary artisan on August 31, 1990 ("POSA") was a research scientist with an M.D. or Ph.D. and one or two years of post-doctoral experience in immunology, molecular biology, cellular biology, and/or biochemistry, and experience with DNA cloning, expressing and purifying proteins, cell culturing, and basic immunology. 9/20A (Wall) 18:6-25; 9/11P (Blobel) 30:24-31:12, 32:2-5.

VII. SCIENTIFIC BACKGROUND

A. DNA and Fusion Proteins

19. A fusion protein is made by combining DNA sequences encoding parts of different proteins into one sequence, introducing that sequence into host cells, growing them, and using their natural internal machinery to produce the desired fusion protein. 9/11P (Blobel) 20:4-21:24; D.I. 595 at 6.

20. A protein is 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. 9/11P (Blobel) 16:24-18:8; D.I. 595 at 6.

21. DNA contains the genetic instructions for a cell to make proteins. 9/11P (Blobel) 18:22-20:3. The sequence of nucleotides in the DNA encoding a protein determines the order of amino acids in that protein. *Id*.; D.I. 595 at 6.

22. A protein sequence's beginning is the "N-terminus" and its end is the "C-terminus." 9/13A (Capon) 105:10-14. Cells synthesize proteins from the N-terminus to the C-terminus. *Id*. Scientists read DNA and protein sequences by moving left to right and top to bottom. *Id*. at 104:10-105:24.

B. The Immune System, Antibodies, and Effector Function

23. The immune system is made up of various cells and proteins that protect the body from foreign invaders. 9/20A (Wall) 46:23-48:9. One such protein is the antibody, also "immunoglobulin" or "Ig." Antibodies have two main functions: (1) binding foreign substances ("antigens"), and (2) recruiting other immune system components to attack antigens. 9/11P (Blobel) 27:8-18; 9/18P (Greene) 65:3-70:13.

24. An IgG consists of two heavy chains and two light chains. 9/11P (Blobel) 28:4-7. Each chain contains variable and constant regions; the latter includes the CH1, hinge, CH2, CH3 domains in the heavy chain and the CL in the light chain. *Id*. at 28:12-29:5. The variable region binds to an antigen. *Id*. at 28:14-

20. The constant region interacts with other components of the immune system to elicit a response. 9/12A (Blobel) 12:7-22.

25. When antibodies bind antigens, whether membrane-bound or soluble, they can form aggregates that trigger various inflammatory processes. *Id.*; 9/20A (Wall) 44:12-46:17, 46:18-50:1. Scientists call these processes "effector functions," and the constant region portions responsible for such functions "effector domains or regions." 9/12A (Blobel) 12:23-13:1.

26. Effector functions include CDC and ADCC, which are complex, separate, pro-inflammatory pathways by which the immune system kills other cells. 9/18P (Greene) 76:24-77:2; 9/11P (Blobel) 118:22-119:4; 9/20A (Wall) 45:2-46-9. CDC is triggered when an antibody's CH2 domain binds the C1q protein, which is the first component of the "complement cascade." 9/12A (Blobel) 12:7-10; 9/18P (Greene) 66:4-17, 125:16-22. ADCC is triggered when the region spanning the hinge and CH2 domain binds to Fc receptors on cell-killing immune cells. *Id*. at 69:13-16; 9/20A (Wall) 44:12-46:13, 46:18-50:1.

C. Cytokines, TNF, and TNF Receptors

27. Cytokines are messenger proteins with a wide variety of functions in the body, including initiating an immune response. 9/20A (Wall) 20:11-18. The body makes dozens of distinct cytokines, which often have redundant and overlapping functions. *Id*. at 20:21-22:24; PTX-10 at 4-5 (Table 1); PTX-34 at 5 (Table 1).

28. TNF plays a significant role in diseases such as RA. 9/11P (Blobel) 64:4-16; 9/20P (Wall) 47:7-12. TNF, one of dozens of cytokines known in 1990, can be insoluble (membrane-bound) or soluble (not membrane-bound). JTX-21 at 1; 9/20A (Wall) 41:20-43:20; 9/12A (Blobel) 90:17-91:1.

29. Like many cytokines, TNF is pleiotropic: it has many different functions. JTX-1 at 15 (col. 1:16-31); JTX-64 at 1; PTX-10 at 3; 9/12P (Blobel) 11:15-12:8. First found to kill tumor cells, 9/17 (Loetscher) 16:2-4, by August 1990, scientists associated it with inflammatory diseases, but did not understand its role. 9/20A (Wall) 21:23-27:15, 36:18-38:4. TNF is involved in diverse biological processes, including normal, beneficial ones such as anti-viral defense. JTX-64 at 1.

30. TNF binds cell-surface TNF receptors ("TNFRs"), having three regions: intracellular, transmembrane, and extracellular (the latter of which binds to TNF). 9/11P (Blobel) 24:10-25:5. In the body, that region can be cleaved off to yield a "soluble" fragment that binds to TNF. *Id*. at 26:6-15. These TNF-binding proteins were first isolated from human urine. 9/20A (Wall) 27:18-28:4.

31. By August 1990, the physiological role of soluble TNFR had not been established. *Id*. at 30:22-31:16. Based on *in vitro* studies, some researchers speculated that they acted as TNF inhibitors. *Id*. at 31:17-32:2; JTX-46 at 6. Researchers also postulated that they might have a "converse" role, acting as reservoirs to "prolong the [body's] exposure" to TNF, thereby aggravating disease.

9/20A (Wall) 32:15-33:5.

D. Rheumatoid Arthritis

32. RA is a chronic, systemic, inflammatory disease that affects joints and organs in the body. 9/20P (Fleischmann) 109:14-25. RA is an auto-immune disease, *i.e.*, it arises when an overactive immune system attacks an individual's own body. 9/12A (Blobel) 39:24-40:2. An estimated 1.3 million people suffer from RA in the US. 9/20P (Fleischmann) at 110:1-2.

33. Bone erosions and narrowing of the joint space in RA cause permanent damage and cannot be rectified absent surgery. *Id*. at 111:15-112:12, 113:4-6. Joint damage affects the ability to walk or go down steps; a cane, crutch, walker, or wheelchair is often required to aid the mobility of a patient with knee joint damage. *Id.* at 112:24-113:6; PTX-228.

34. Chronic inflammation from RA also destroys tendons and ligaments in the hand, causing fingers to bend outward and making hygiene, dressing, holding a cup, or writing very difficult. 9/20P (Fleischmann) 114:5-10; PTX226.

35. The combined impact of pain, stiffness, and infection associated with RA leads to depression and lesser cognitive function. 9/20P (Fleischmann) 115:19-116:14. Untreated, RA reduces life expectancy by 3 to 18 years. *Id*. at 110:10-13.

VIII. BACKGROUND: INVENTION, PATENT FILING AND LICENSURE

A. Roche's Scientists Identify Two TNF Receptors (p55 and p75)

36. The Inventors were the first to confirm there are two distinct TNFRs

that specifically bind TNF, one having a molecular weight of ~55 kD and the other ~75 kD. 9/17 (Loetscher) 20:1-18, 26:8-28:8; JTX-22 at 1. After the Inventors published that work, scientific articles typically adopted that nomenclature. 9/11P (Blobel) 25:6-26:5; JTX-22 at 4; JTX-21 at Summary; JTX-23 at 1.

37. As of August 31, 1990, the scientific evidence strongly indicated these were the only two TNFRs. 9/18A (Naismith) 75:1-17; 9/13P (Capon) 47:13-18; 9/11P (Blobel) at 25:6-9. The Inventors made monoclonal antibodies that recognized each TNFR and used them to isolate and characterize each, publishing that work in April 1990. JTX-22 at 1, 4; 9/13A (Capon) 83:13-19; 9/11P (Blobel) 67:13-22.

38. The Inventors determined partial amino acid sequences of the p55 and p75 they had purified. 9/17 (Loetscher) 30:9-25. They also made DNA probes using those partial amino acid sequences and "fished" cDNAs encoding each receptor out of cDNA libraries. *Id.* at 30:16-25, 35:14-18; 36:16-37:6, 41:11-42:6; JTX-85 (Dembic) at 56:5-11, 56:13-17, 57:1-16, 57:18-23, 58:1-2; JTX-23 at 1-3.

39. In April 1990, the Inventors published the complete cDNA and amino acid sequences of p55. JTX-21 at 1; 9/17A (Loetscher) 31:22-32:25. In July 1990, they published the complete amino acid sequence of p75 and a cDNA sequence encoding part of it. 9/17 (Loetscher) 33:1-33:23; JTX-23 (Dembic) at 2, Fig. 1.

40. Two months earlier, in May 1990, Immunex scientists published in Smith 1990 the p75's complete amino acid sequence. JTX-24 (Smith 1990) at 3, Fig.

3B; 9/17 (Loetscher) 38:6-24. This paper reported that a cDNA sequence encoding the p75 had been deposited with GenBank under accession number M32315 and that the authors would provide this sequence upon request. JTX-24 (Smith) at 3, Fig. 3B.

41. Dembic cites Smith 1990 and indicates that it describes the same p75. JTX-23 at 1, 4; 9/17 (Loetscher) 41:11-42:6. Dembic and Smith 1990 both report the same amino acid sequence for p75's extracellular region and the same extracellular and transmembrane region boundaries. 9/17 (Loetscher) 42:7-14; JTX-23 at 2, Fig. 1; JTX-24 at 3, Fig. 3B.

42. The Inventors prepared a cDNA encoding the full p75 before August 31, 1990, inserted it into a plasmid designated N227 and stored the plasmid in a freezer per standard Roche practices. 9/17 (Loetscher) 55:17-56:4; JTX-81 (Lesslauer I) 164:4-25; PTX-6.367 ¶¶ 3-6. Roche maintained the cDNA clone at least until a sample of it was deposited with a public depository, the American Type Tissue Culture (ATCC), in 2006. JTX-81 (Lesslauer I) 164:4-9, 164:10-165:25; JTX-82 (Lesslauer II) 322:23-323:5, 323:8-11, 323:13-324:4; PTX-6.367 ¶¶ 3-6.

43. A POSA understood that the approximate molecular weight reported for p75 determined by the SDS-PAGE technique could vary based on experimental conditions or other factors, such as the degree of glycosylation, that is, sugars attached to certain amino acids. 9/18A (Naismith) 80:9-81:5; PTX-35 at 4.

44. Dembic reported a 65 kD band co-purified with a 75 kD band from

HL60 cells. JTX-23 at 1; 9/17 (Loetscher) 34:12-20. It also reported that: (i) each band specifically bound TNF-α and TNF-β and was bound by p75-specific antibodies; (ii) the 65 kD band's N-terminal sequence of the 65 kD band overlapped with the partial cDNA clone obtained for p75; and (iii) the HL60 cells used to isolate the receptor contained only one messenger RNA coding for p75 and therefore produced only one TNFR. JTX-23 (Dembic) at 1-2, 4-5, Figs. 1 & 4; 9/17 (Loetscher) 34:21-35:13, 37:7-21; 9/18A (Naismith) 77:12-79:9.

45. It "assume[s] the 65-kD protein to be derivative or fragment of the 75 kD receptor and refer[s] to the two proteins as the 75-kD receptor." JTX-23 at 1.

B. Roche Invents the p75-IgG1 Fusion Protein

46. The Inventors formed the core of Roche's TNF research project in the late 1980s and early 1990s. 9/17 (Loetscher) 16:16-23. Led by Dr. Werner Lesslauer, they sought to develop a molecule to block TNF. *Id.* at 16:12-14, 16:24-17:5. Toward 1989's end, Dr. Lesslauer conceived the idea of TNFR-Ig fusion proteins (fusing the extracellular region of a TNFR to the hinge-CH2-CH3 of an Ig heavy chain) and brought the idea to a group meeting. *Id.* at 24:21-25; JTX-81 (Lesslauer I) 76:21-77:6, 77:21-78:1; JTX-82 (Lesslauer II) 219:3-7, 219:24-25, 220:4. Before August of 1990, the Inventors were aware of CD4-IgG fusion proteins that had been developed to "stimulate the immune system and activate immune cells" against HIV-infected cells. 9/17 (Loetscher) 25:1-16. Dr. Lesslauer likewise was aware that CD4-

IgG fusion proteins were made to specifically induce effector functions via the Ig part of the protein. JTX-81 (Lesslauer I) 82:11-83:3.

47. The Inventors did not want to have, in an anti-inflammtory molecule, components that trigger immune response mechanisms. *Id.* They intended to develop a TNFR-Ig fusion protein to accomplish "exactly the opposite"— they sought to "dampen the immune system" and to "inhibit inflammatory reactions associated with TNF activity." 9/17 (Loetscher) 25:17-23.

48. The Inventors' colleagues outside the project were skeptical about the idea of a TNFR-Ig fusion protein. JTX-82 (Lesslauer II) 318:5-318:13, 318:18-318:20, 318:23-319:21. One suggested using something "immunologically innocent," such as albumen, instead of an Ig constant region. JTX-81 (Lesslauer I) 78:22-79:15. Colleagues from the immunology side were concerned that inclusion of an Ig constant region component might trigger more inflammation. JTX-82 (Lesslauer II) 318:5-13, 318:18-20, 318:23-319:21. Dr. Lesslauer believed, however, that his fusion protein would not elicit effector functions because it would not cause aggregation, and later studies confirmed that belief. JTX-81 (Lesslauer I) at 84:14-84:17, 84:19-85:17.

49. The Inventors contemplated fusion proteins based on both TNFRs. 9/17 (Loetscher) 20:24-21:1; JTX-82 (Lesslauer II) 219:3-219:7. They documented this in a Roche laboratory notebook showing fusion proteins based on both TNFRs.

PTX-745 at 65; JTX-81 (Lesslauer I) 133:12-134:3, 135:8-136:5. The Inventors made a p55 fusion protein first because they had a cDNA clone of the entire p55 first. 9/17 (Loetscher) 24:2-9, 56:16-20; JTX-81 (Lesslauer I) 86:3-86:12; JTX-1 at 24 & JTX-2 at 34 (Examples 11). They later made a p75 fusion protein using the same techniques. 9/17 (Loetscher) 24:10-14; PTX-745 at 183, 207.

50. Although the Inventors made TNFR-based fusion proteins containing the hinge-CH2-CH3 of IgG3, they had in mind using both IgG1 and IgG3 in fusion proteins. 9/17 (Loetscher) 23:4-24:14; 9/18A (Naismith) 91:15-92:18; JTX-1 at 17 (col. 5:54-61, 8:56-9:8); JTX-2 at 28 (col. 6:9-16, 9:14-32).

C. Roche Files Patent Applications on TNFR-Ig Fusion Proteins

51. On August 31, 1990, the Inventors filed a patent application in Europe designated EP Application No. 90116707 (the "EP707 Application"). On September 13, 1990, the Inventors filed a U.S. application designated Application No. 07/580,013 ("the '013 Application"). The Patents-in-Suit claim the benefit of the '013 Application and priority to the EP707 Application. JTX-1 at 3; JTX-2 at 3.

52. The '013 Application's disclosure is the same as the EP707's. 9/18A (Naismith) 41:9-22; 9/18P (Naismith) 6:5-20. The disclosures of the Patents-in-Suit convey essentially the same information as those of the EP707 and '013 Applications. 9/18A (Naismith) 40:19-41:22; 9/18P (Naismith) 6:5-20, 8:7-25.

53. The '522 Patent disclosure contains an additional figure (Figure 5), an

additional sequence listing (SEQ ID NO: 27) and slight modifications in a passage referring to Smith 1990. None of those changes add new matter to the '522 Patent's disclosure relative to the '182 Patent's, as the Patent Office approved each while examining the '522 Patent. 9/21 (Kunin) 94:19-96:20; JTX-2 at 26-27 (col. 3:1-3, 5:34-40); PTX-7.351 at 2; PTX-7.416 at 16. Although there are wording differences in the Patents-in-Suit's disclosure, each conveys essentially the same information to a POSA. 9/18A (Naismith) at 41:9-25; 9/18P (Naismith) 6:5-20, 8:7-25.

54. As used herein, the phrase "the Patent Disclosure" refers collectively to the '182 Patent (JTX-1), the '522 Patent (JTX-2), the '013 Application (JTX-10) and the EP707 Application (JTX-7).

55. A fusion protein consisting of the extracellular domain of p75 and all domains of a human IgG1 heavy chain constant region except for the first was one of the molecules that the Inventors had in mind when they filed their August 1990 patent application. 9/17 (Loetscher) 23:7-19. Although the Inventors did not make a p75 TNFR-IgG1 fusion protein, their Patent Disclosure describes that fusion protein. *Id.* at 58:1-59:5; 9/18A (Naismith) 49:2-52:17.

56. European Patent No. 0 939 121 ("the EP121 Patent") claims priority to the EP707 Application filed on August 31, 1990, was granted in April 2003 and claims a p75-IgG fusion protein and a DNA encoding it. PTX-1536 (EP121 Patent) at 19; 9/24P (Watt) 43:5-11, 43:19-22.

57. Roche filed U.S. Application No. 08/095,640 ("the '640 Application") on July 21, 1993, and later filed two divisionals of it (*i.e.*, Nos. 08/444,790 ("the '790 Application") and 08/444,791 ("the '791 Application")) on May 19, 1995. JTX-5 ('279 Patent) at 1; JTX-1 at 3; JTX-2 at 3. On March 11, 1997, the '640 Application issued as U.S. Patent No. 5,610,279 ("the '279 Patent"), claiming a genus of p55-IgG fusion proteins. JTX-5 at 1, 20. The '279 Patent's file history, available to the public on that date, revealed divisional applications of the '279 Patent with claims to a p75-IgG fusion protein. JTX-9 at 389-390; 37 C.F.R. § 1.11 (May 1985).

D. The Inventors Described Their Work in the Roche Patents-in-Suit

58. The Patent Disclosure describes the Inventors' work with TNFRs; it, conveys, as a whole, a "pathway of experimental work leading to a TNFR fusion protein." JTX-82 (Lesslauer II) 256:18-24; 9/17 (Loetscher) 20:21-23, 25:24-26:7, 31:16-21, 44:16-23. The Examples describe this pathway, starting in Example 1, a test to detect TNF-binding proteins, and ending, in Example 11, illustrating how to make a TNFR-IgG fusion protein. 9/17 (Loetscher) 44:16-45:19, 56:5-57:13; JTX-82 (Lesslauer II) 259:14-260:5, 260:8-13, 297:21-298:1, 298:6-7; 9/18A (Naismith) at 54:16-21. In between, they describe isolating p55 and p75 from HL-60 cells, which express both TNFRs (Example 2); isolating, purifying, and cloning both (Examples 3-8), and recombinant expression of p55 (Examples 9 and 10). 9/17 (Loetscher) 45:20-48:7, 49:20-51:2; JTX-82 (Lesslauer II) 264:3-4, 264:7-265:6,

270:19-20, 270:23-24, 275:7-8, 275:12-19; 9/18A (Naismith) 54:13-15, 55:1-11, 82:3-83:6; JTX-1 at 23-24 (Examples 9, 10); JTX-2 at 33-34 (Examples 9, 10).

59. The Patent Disclosure shows that the Inventors contemplated using the procedures described in Example 11 to make a p75 fusion protein. JTX-82 (Lesslauer II) 298:11-14, 298:17; 9/17 (Loetscher) 58:1-59:5; 9/18A (Naismith) 93:3-8. It also repeatedly identified p75 as one of two choices of TNF binding proteins to use in a fusion. 9/17 (Loetscher) 21:14-23:3; 9/18A (Naismith) 91:15-92:2; *see also* JTX-1 at 3 & JTX-2 at 3 & JTX-10 at 58 & JTX-7 at 2 (Abstracts).

60. The "soluble TNF-binding fragment" that Example 11 illustrates to be fused directly to the exon-encoded hinge-CH2-CH3 region of an IgG heavy chain is the entire extracellular region. 9/17 (Loetscher) 56:10-57:13; 9/18A (Naismith) 54:16-21. Examle 11 illustrates using a cDNA encoding the extracellular region, made using PCR primers that match that region's starting and ending sequences. 9/18A (Naismith) 94:10-14, 94:20-95:6; 9/13A (Capon) 90:9-17; *see also* JTX-1 at 24 & JTX-2 at 34 & JTX-10 at 46 & JTX-7 at 38 (Example 11).

61. The Patent Disclosure identifies a vector, pCD4-Hγ1 (DSM 5314), deposited with the DSMZ in April of 1989, that contains the human IgG1 heavy chain gene's hinge, CH2 and CH3 exons. 9/18A (Naismith) 90:10-91:7; 9/17 (Loetscher) 58:18-59:5; *see also* JTX-1 at 18 (col. 8:56-65); JTX-2 at 29 (col. 9:14-22); JTX-7 at 14-15 (pp. 14:29-15:4); JTX-10 at 22 (p. 17:18-27); JTX-16

(Kittendorf Decl.) at 32-34. When expressed in a host cell, the plasmid yields a fusion containing the exon-encoded-hinge-CH2-CH3 portion of a human IgG1 heavy chain. 9/17 (Loetscher) 58:18-59:5; 9/18A (Naismith) 91:15-92:18.

62. Example 6's reported results established that the 65 and 75 kD bands contained the same p75. 9/17 (Loetscher) 47:21-48:7, 49:20-25; JTX-1 at 22 (col. 15:27-36); JTX-2 at 32 (col. 15:49-61); JTX-7 at 28 (p. 28:10-21); JTX-10 at 35 (p. 31:9-22). The patent thus refers to p75 as the 75/65 kD TNF binding protein. JTX-1 at 15, 17, 22, 23 (col. 2:61-62, 5:35-38, 16:31-32, 17:30-31); JTX-2 at 25, 27, 32, 33 (col. 2:66-67, 5:56-59, 16:52-53, 17:53-54); JTX-7 at 8, 30, 32 (p. 8:9-11, 30:12-13, 32:10-11); JTX-10 at 9, 15, 37, 39 (p. 4:35-36, 10:23-26, 33:21-22, 35:33-32). Differences in glycosylation—the addition of sugars—explain the different molecular weights of the 65 and 75 kD bands. 9/18A (Naismith) at 80:9-81:5.

63. Example 7 in the EP707 and '013 Applications and the Patents-in-Suit describes amino acid sequencing of isolated p55 and p75. 9/17 (Loetscher) 50:1-53:25. It reports peptide "IID," or SEQ ID NO: 10, an 18-amino acid sequence determined from N-terminal sequencing of the full p75 that the Inventors isolated and purified from HL-60 cells. 9/18A (Naismith) 56:10-57:18, 59:9-62:6; 9/13P (Capon) 11:14-13:2; JTX-1 at 16, 22 (col. 4:24-25, 16:27-28); JTX-2 at 26, 32 (col. 4:36-37, 16:48-49); JTX-7 at 30 (p. 39:8-9); JTX-10 at 37 (p. 33:16-17). It also reports that the Inventors chopped the isolated p75 into smaller fragments and

performed N-terminal sequencing on each. 9/17 (Loetscher) 50:1-24; 9/18A (Naismith) 55:4-11; JTX-1 at 22 (col. 15:60-16:7); JTX-2 at 32 (col. 16:15-28); JTX-7 at 29 (p. 29:11-26); JTX-10 at 36 (p. 32:9-25). One of those peptides is also an 18-amino acid sequence, designated "IIA," or SEQ ID NO: 7. Example 7 also provides six other sequences of p75 internal peptides: IIB (SEQ ID NO: 8); IIC (SEQ ID NO: 9); IIE (SEQ ID NO: 11); IIF (SEQ ID NO: 12); IIG (SEQ ID NO: 13); and IIH (SEQ ID NO: 14). JTX-1 at 22 (col. 16:33-49); JTX-2 at 32-33 (col. 16:53-17:2); JTX-7 at 30 (p. 30:8-9); JTX-10 at 37-38 (pp. 33:16-32, 34:1-10).

64. In Example 8, the Inventors describe work to isolate and sequence cDNAs encoding p55 and p75. JTX-82 (Lesslauer II) 275:7-8, 275:12-276:10. The Roche inventors isolated cDNA clones of varying lengths from an HL60 cDNA library using a DNA probe based on the 18-amino acid long SEQ ID NO: 7 obtained from p75. JTX-82 (Lesslauer II) 276:11-277:22; 9/17 (Loetscher) 31:1-21, 44:6-23.

65. Figure 4 shows one such cDNA, which the Patents described as a partial cDNA, meaning that it is only a part of the DNA encoding the complete p75. 9/17 (Loetscher) 54:16-22; JTX-1 at 17 (col. 5:35-38); JTX-2 at 27 (col. 5:56-59); JTX-7 at 8 (p. 8:9-11); JTX-10 at 15 (p. 10:23-26). Relative to Smith 1990's p75 sequence, Figure 4's sequence omits the first 48 amino acids, has different amino acids in three positions of the extracellular region (*i.e.*, positions 141, 196 and 230 of Smith Figure 3B), and includes one more amino acid in the intracellular region.

9/13A (Capon) 28:5-13, 30:22-31:13, 32:18-22, 33:24-34:4, 34:19-35:3.

66. Before August 31, 1990, a p75 having the same amino acid variations shown in the Figure 4 sequence at positions 141 and 196 was tested and shown to bind TNF specifically. 9/18A (Naismith) 99:16-101:13; PTX-35 (Heller 1990) at 2.

67. The Patent Disclosure reflects the Inventors' awareness of p75 allelic variants, JTX-1 at 17 (col. 5:17-22), which differ in one or more amino acids but typically do not change function or identity. 9/18A (Naismith) 89:22-91:8, 100:20-101:13; 9/17 (Loetscher) 43:22-44:5. The Inventors expected p75 allelic variants to specifically bind TNF. 9/17 (Loetscher) 43:22-44:5; 9/18A (Naismith) 89:22-91:8.

68. The Patents-in-Suit identify a publicly available plasmid deposited with the ATCC and designated PTA 7942 that contains a cDNA encoding the complete p75. JTX-1 at 17 (col. 5:45-53); JTX-2 at 27 (col. 5:65-6:8); *see* FOF 42. PTA 7942's extracellular region is identical to that in Figure 3B of Smith 1990 and Figure 1 of Dembic. 9/18A (Naismith) 87:21-88:23; 9/13P (Capon) 79:17-80:9, 60:5-9.

E. Immunex Licenses Roche's TNFR-Ig Fusion Protein Applications

69. Dr. Goodwin, an Immunex scientist, testified that he did not make etanercept until November or December of 1990—two to three months after the August 31, 1990 filing of the EP707 Application. JTX-74 (Goodwin) 53:20-54:12.

70. With Roche having priority to the p75-IgG1 fusion invention, Immunex licensed the pending applications in 1999, effective to 1998, when Immunex

launched etanercept. 9/24P (Watt) 22:16-23:16; JTX-76 (Kirschner) at 145:1-11, 149:19-150:6, 151:19-21, 151:23; JTX-13 (1998 License) at 1, 6-8. Immunex paid tens of millions of dollars in royalties to Roche. 9/24P (Watt) 23:17-24:5; JTX-76 (Kirschner) at 168:24-169:4; JTX-13 (1998 License) at 12-18.

71. Amgen acquired Immunex in 2002. *Id.* at 21:18-20. Thereafter, the 1998 license was superseded by the 2004 A&S, through which Immunex fully paid-up its royalty obligations and received an exclusive license. 9/24P (Watt) 24:19-25:14. The 2004 A&S was executed June 7, 2004. JTX-12 at 17-21. Stuart Watt, Amgen's Vice President of Law and Intellectual Property Officer, was Amgen's and Immunex's primary negotiator for it. *Id.* at 25:15-18. Negotiations began because Amgen wanted to reduce the ongoing royalty burden on Enbrel by "buying out" or "buying down" future royalty obligations, in effect converting licenses requiring a running royalty into fully paid-up licenses. *Id.* at 25:1-14. Mr. Watt approached Roche. *Id.* at 22:18-24:5; JTX-13 (1998 License) at 12-18.

72. In April 2003, Roche obtained issuance of European Patent No. 0939121 ("the EP121 Patent"), stemming from the same priority application as the Patents-in-Suit. 9/24P (Watt) 43:5-11; PTX-1536 (EP121 Patent) at 1; *see also* JTX-12 (2004 A&S) at 22. It claimed p75-IgG fusion proteins and DNA coding for them. PTX-1536 (EP121 Patent) at 19 (claim 1 & 3). Because Roche had obtained claims to p75-IgG fusion proteins in Europe, Amgen expected that Roche would obtain

claims related to p75-IgG fusion proteins in the U.S. 9/24P (Watt) 43:19-44:10.

73. Immunex sought in the 2004 A&S to be able to guide prosecution to ensure that the patent applications on which it had been paying and would pay substantial royalties might issue as patents and thus provide Immunex valuable protection it had not yet received. 9/24P (Watt) 34:13-35:4, 56:16-25, 78:10-20.

IX. SCOPE OF THE ASSERTED CLAIMS OF THE PATENTS-IN-SUIT

74. The '790 application issued November 22, 2011 as the '182 Patent. The '791 application issued April 24, 2012 as the '522 Patent. Both are "Pre-GATT" patents (*i.e.*, issuing from applications filed before June 7, 1995) and expire 17 years from issuance. Pub. L. No. 103-465, 108 Stat. 4809, §§ 532, 534 (Dec. 8, 1994).

75. Claims 11 and 12 of the '182 Patent depend from claim 1, while Claims 35 and 36 depend from claim 30. JTX-1 at 34-35 (claims 1, 11-12, 30, 35-36). Claims 3 of the '522 Patent depends from claim 1, while Claims 8 and 10 depend from claim 7. JTX-2 at 47-48 (claims 1, 3, 7-8, 10). The '182 Patent's 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, while the '522 Patent's asserted claims define a method of producing this fusion protein. JTX-1 at 34-35 (claims 11-12, 35-36); JTX-2 at 47-48 (claims 3, 8, 10); 9/11P (Blobel) 14:19-15:14; 9/18A (Naismith) 45:23-46:2, 48:13-49:1; 9/13A (Capon) 18:3-16; 9/20A (Wall) 19:4-12.

76. The p75's "extracellular region" is that portion that protrudes outside the cell. D.I. 136. "[A]ll of the domains of the constant region of a human IgG1 immunoglobulin heavy chain other than the first domain of said constant region" is a portion of the human IgG1 heavy chain constant region containing only the exon-defined hinge, CH2 and CH3 domains of the human IgG1 heavy chain constant region. D.I. 518. The Claims cover etanercept and methods to make it. 9/11P (Blobel) 14:22-15:17; 9/13P (Capon) 82:22-83:3; JFPTO ¶ 64.

X. SANDOZ COPIED THE CLAIMED INVENTIONS

77. Defendants copied etanercept's amino acid sequence and its method of manufacture using Chinese Hamster Ovary (CHO) cells. 9/14 (McCamish) 16:12-25, 68:1-4, 79:8-9; JTX-83 (Alliger) 105:17-25, 141:23-142:12; JFPTO ¶ 46.

78. Sandoz studied Enbrel's patent protection. PTX-691 (Sandoz 03-2006 Meeting) at 2 ("US patent situation has to be evaluated"); 9/14 (McCamish) 70:3-11, 71:19-24, 74:17-75:5. While pre-GATT patent applications in the United States were typically kept confidential, European patents gave an indication of what patents were pending and might issue in the United States. 9/24P (Watt) 43:19-44:10.

79. When starting to develop their etanercept, Sandoz was aware of the EP121 Patent and the '279 Patent (the US parent of the Patents-in-Suit). PTX-622 at 4 ("first became aware" "on or before January 13, 2006"); JTX-83 (Alliger) 105:4-9, 147:3-5 (GP2015 project started April 10, 2006). The EP121 Patent issued in 2003

with claims related to p75 fusion proteins and DNA encoding them, and expired in 2015. 9/24P (Watt) 93:3-94:16; PTX-1536 (EP121 Patent) at 1, 19. This expiration date likely gave rise to the code name used for Sandoz's biosimilar: "GP2015."

80. The '279 Patent's file history was available for public inspection upon its issuance on May 11, 1997. 37 C.F.R. § 1.11(a) (1997). It identified, by serial number, the '790 and the '791 Applications, both filed as divisionals of it. JTX-9 ('013 Application FH) at 389-390. Identification of these two applications gave the public the right to then inquire as to their status. 37 C.F.R. § 1.14(a) (1997).

81. Sandoz called no witnesses and offered no evidence as to whether they had reviewed the '279 Patent file history, or, if not, why they had not done so, and offered no evidence that either that they were "surprised" by the issuance of the Patents-in-Suit from the two applications identified therein, or that they should not reasonably have seen the possibility of such issuance.

82. Sandoz's efforts to develop their etanercept biosimilar began in 2006, before a regulatory pathway existed in the United States for the approval of a biosimilar drug. 9/14 (McCamish) at 84:15-85:6; JTX-83 (Alliger) at 147:3-5. Sandoz initially chose to copy etanercept, and the host cell system used to make etanercept, independent of any FDA guidance. FOF 245-46.

83. To try to circumvent Enbrel's patent protection, Sandoz investigated "design around" variants of etanercept that they believed could have potentially

gained regulatory approval. FOF 248-49; JTX-83 (Alliger) 214:12-15, 214:18-24, 215:2-7, 215:10, 218:3-6, 218:9, 218:17-25; 225:15-18, 225:21; PTX-701 (Design Around Memo) at 5-6. Although Sandoz believed these variants could have avoided infringement, they instead deemed it commercially expedient to copy etanercept and the CHO host cell system used to make etanercept. FOF 249.

XI. SANDOZ FAILED TO PROVE THE PATENTS-IN-SUIT INVALID FOR LACK OF WRITTEN DESCRIPTION OR ENABLEMENT

84. Sandoz has failed to prove by clear and convincing evidence that either of the Patents-in-Suit is invalid for lack of written description or enablement.

A. The Patent Disclosure Demonstrates Possession of the p75/IgG1 Fusion Protein of the Claims

85. The Patent Disclosure establishes that, by August 31, 1990, the Inventors possessed the two component parts of the claimed fusion protein (*i.e,*, the extracellular region of p75 and the exon-encoded hinge-CH2-CH3 region of an IgG1 heavy chain), and the claimed p75-IgG1 fusion itself. 9/18A (Naismith) 105:20-106:3, 49:18-52:15, 95:7-14.

1. By August 31, 1990, p75 and Its Extracellular Region Were Well Known

86. A POSA knew there were two TNFRs: p55 and p75. FOF 36-37. A POSA understood the Patent Disclosure's references to TNF binding proteins weighing about 55 kD or about 75 kD to refer to p55 and p75, respectively. FOF 36.

87. A POSA knew that Dembic reported isolating the same p75 as Smith

1990, and that both reported the same extracellular region amino acid sequence for p75. FOF 41; 9/18P (Naismith) 20:15-17, 50:11-13; 9/13P (Capon) 60:5-9. A POSA knew p75's extracellular region starts at its N-terminus and ends one amino acid before the start of its transmembrane region, and that Smith 1990 shows its sequence in Figure 3B as residues 1 to 235 (positions 23 to 257), and Dembic's Figure 1 shows it as positions 1 to 235. JTX-24 at 3, Fig. 3B; JTX-23 at 2, Fig. 1; 9/18A (Naismith) 70:20-72:7; 9/13P (Capon) 60:5-16; 9/17 (Loetscher) 40:15-41:4, 42:7-14.

2. The Patent Disclosure Identifies the Extracellular Region of the Known p75 as a Soluble TNF-Binding Fragment to Use in the Described Fusion Proteins.

88. The Patent Disclosure indicates that a soluble fragment of a "TNF binding protein"/"TNF-BP" is a component of the Inventions. JTX-1 at 15, 18 (col. 2:33-39, 8:56-58); 9/18A (N aismith) 50:3-6, 51:2-4. "TNF-BP" are described as "non-soluble proteins, *i.e.* for example membrane proteins or so-called receptors, and soluble … fragments thereof, which bind TNF (TNF-BP), in homogeneous form," and "[p]referred proteins are those which according to SDS-PAGE under non-reducing conditions are characterized by apparent molecular weights … especially those about 55 kD and 75 kD" and "are characterized by containing at least one" of "(IIA) … (SEQ ID NO: 7)" and "(IID) … (SEQ ID NO: 10)." JTX-1 at 16 (col. 4:1-25), at 22, 16:22-48. A POSA would have recognized that sequences designated IIA/SEQ ID NO: 7 and IID/SEQ ID NO: 10 are found only in the p75

TNFR, and not the p55 TNFR. 9/18P (Naismith) 15:13-20, 29:16-30:2; *see* FOF 63.

89. A POSA knew p75, as described in Smith 1990 and Dembic: (i) is a membrane protein that binds TNF, (ii) has an apparent molecular weight of "about 75 kD," and (iii) contains SEQ ID NO: 10 and SEQ ID NO: 7 from the Patent Disclosure. JTX-24 at 3-4, Fig. 3B; JTX-23 at 1-2, Fig. 1; 9/18A (Naismith) 118:22-119:24; 9/18P (Naismith) 53:20-22, 56:5-8.

90. The odds of a human TNF-binding protein containing (i) the IID (SEQ ID NO: 10) sequence, (ii) the IIA (SEQ ID NO: 7) sequence, or (iii) both sequences, but not being the p75 described in Smith 1990 and in Dembic, are about 1 in a million, 1 in ten million, and zero, respectively. 9/18A (Naismith) 68:13-25. Sending either of SEQ ID NO: 10 or SEQ ID NO: 7 to GenBank on August 31, 1990, would have returned the deposited full p75 sequence from Smith. *Id.* at 67:14-68:25; 9/12P (Blobel) 9:14-10:7, 14:6-12; FOF 40. A POSA would have understood these extremely small odds, and thus would have understood that a TNFR containing the 18-amino acid sequences designated SEQ ID NO: 10 and SEQ ID NO: 7, either individually or together, unambiguously identifies (like fingerprints) the p75 reported in Smith 1990 or in Dembic. PTX-6.396 (Lyman Decl.) at 7-8, ¶ 16; 9/18A (Naismith) 67:14-68:25, 53:20-24; 9/12P (Blobel) 9:14-10:7, 14:6-12.

91. A POSA therefore knew from statements in the Patent Disclosure that "the proteins of the present invention are non-soluble proteins, *i.e.* for example

membrane proteins or so-called receptors, and soluble … fragments thereof, which bind TNF (TNF-BP), in homogeneous form," that "[p]referred proteins are those which according to SDS-PAGE under non-reducing conditions are characterized by apparent molecular weights … especially those about 55 kD and 75 kD" and that such proteins "are characterized by containing at least one" of "(IIA) … (SEQ ID NO: 7)" and "(IID) … (SEQ ID NO: 10)," identified the extracellular region of the p75 reported in Smith 1990 and Dembic. JTX-1 at 16 (col. 4:1-25); JTX-24 at 3, Fig. 3B; JTX-23 at 1-2, Fig. 1; 9/18P (Naismith) 20:23-21:2, 29:16-30:9, 53:20-56:8; *see* FOF 68.

92. Other passages in the Patent Disclosure conveyed to a POSA that the p75 reported in Smith 1990 and in Dembic is one source of a soluble TNF binding fragment to be used in the claimed fusion proteins: (i) the "present invention is concerned with non-soluble proteins and soluble … fragments thereof, which bind TNF, in homogeneous form, as well as their physiologically compatible salts, especially those proteins having a molecular weight of about … 75 kD (non-reducing SDS-PAGE conditions)…." (JTX-1 at 3 (Abstract); 9/18A (Naismith) 49:24-50:14); (ii) "there are also preferred sequences which code for a protein of about 75/65 kD" (JTX-1 at 17 (col. 5:35-36); 9/17 (Loetscher) 54:24-55:6; 9/18A (Naismith) 85:25-86:9); (iii) "On the basis … of *the already known sequences for certain receptors*, those partial sequences which code for soluble TNF-BP fragments can be

determined and cut out of the complete sequence using known methods" (JTX-1 at 18 (col. 7:42-46) (emphasis supplied); 9/20A (Wall) 94:5-15).

93. A POSA knew from Examples 1-8 that the Inventors possessed p75. 9/18A (Naismith) 58:21-59:8. By August 31, 1990, the Inventors possessed a plasmid containing a cDNA encoding a complete p75 with the same extracellular region reported in Smith 1990 and Dembic. FOF 42, 68.

94. That plasmid was deposited with the ATCC and designated PTA 7942. FOF 42, 68. The Patent Disclosure states: "DNA sequences which code for insoluble (deposited on Oct. 17, 2006 with the American Type Culture Collection under Accession No. PTA 7942) as well as soluble fractions of TNF-binding proteins having an apparent molecular weight of 65 kD/75 kD are also preferred." JTX-1 at 17 (col. 5:45-50). That told the POSA that the inventors possessed p75, and that PTA 7942 is another source of a soluble TNF-binding fragment of p75 to be used in the claimed fusion protein. 9/18A (Naismith) 87:8-17.

95. The PTO Board concluded that the '182 Patent specification was properly amended to include reference to PTA 7942 because adding that deposited cDNA sequence did not add any "new matter" to the disclosure. PTX-6.456 at 9; 9/21 (Kunin) 92:2-94:7. The PTO Board found that the Patent Disclosure did not need to include the full sequence information for p75, because that sequence information was known in the prior art before August 31, 1990. PTX-6.456 at 6.

96. A POSA understood that one TNF-binding soluble fragment described in the Patent Disclosure is the extracellular region of p75. 9/18P (Naismith) 17:19-18:8, 48:6-19. A POSA understood that a TNF-binding soluble fragment of p75 could contain less than the complete extracellular region, as long as it included at least the cysteine-rich repeats region located at residues 17 to 179 of the sequence in Figure 3B of Smith 1990. JTX-24 at 3, Fig. 3B; 9/18P (Naismith) 19:9-23, 49:5-22.

97. A POSA understood the Patent Disclosure to refer to Smith 1990, JTX-1 at 17 (col. 5:22-24), as a source of soluble fragments of the known p75 to use in fusion proteins. JTX-79 (Lyman) 115:17-24, 116:24-117:05; 9/18P (Naismith) 52:10-53:7, 22:15-23:3.

98. The Patent Disclosure's following statements are also consistent with the extracellular region of the p75 reported in Smith 1990 and in Dembic being a TNF-binding soluble fragment to use in the described fusion proteins:

(i) "[t]his invention also comprises TNF-binding proteins … analogous to the sequence[s] of … FIG.4 or to fragments thereof" (JTX-1 at 15 (col. 2:26-30));

(ii) "[t]he TNF-binding proteins of the present invention include … proteins containing amino acid sequences analogous to the amino acid sequence[s] of … FIG.4 (SEQ ID NO: 4) or to fragments thereof" (*id.* at 16 (col. 3:4-11));

(iii) "there are also preferred DNA sequences which code for a protein of about 75/65 kD" and "which contain the partial cDNA sequences shown in

Figure 4 are preferred" especially since the "present invention embraces not only allelic variants, but also those which result from deletions, substitutions and additions from one or more nucleotides, whereby in the case of the proteins coded thereby there come into consideration, just as before, TNF-BP" (*id.* at 17 (col. 5:17-22, 5:35-38); FOF 65, 67); and (iv) Smith 1990 is "[o]ne sequence which results from … a deletion" of an "allelic variant[]" of a TNFR or "DNA sequence[] which result[s] from deletions, substitutions and additions from one or more nucleotides of the sequence[] given in … FIG.4, whereby in the case of the proteins coded thereby there come into consideration, just as before, TNF-BP" (*id.* at 17 (col. 5:17-24); FOF 65).

3. The Patent Disclosure Identifies the Known Exon-Encoded Hinge-CH2-CH3 Portion of Human IgG1 to Use in the Described Fusion Proteins

99. The claimed fusion protein's Ig component is described as a partial DNA sequence "coding for all domains other than the first domain of the constant region of the heavy chain of human immunoglobulins such as IgG, . . . , in particular IgG1 or IgG3 subtypes." JTX-1 at 17 (col. 5:54-61). A POSA knew there are four subtypes of human IgG: IgG1, IgG2, IgG3 and IgG4. JTX-19 at 1; 9/18A (Naismith) 51:11-13; 9/12A (Blobel) 67:3-6. A POSA knew the amino acid and nucleotide sequences of the human IgG1 heavy chain constant region and its allelic variants, such as those reported in Ellison 1982. JTX-19 at 3-4, Fig. 2; 9/18A (Naismith)

89:13-90:8; 9/12P (Blobel) 53:15-19, 54:5-12.

100. A POSA knew the human IgG1 heavy chain constant region consisted of the CH1, hinge, CH2 and CH3 domains, the amino acid sequences for which are encoded by a corresponding exon in the human IgG1 gene. JTX-19 at 2-4, Fig. 2; 9/20 (Wall) 14:24-15:5; 9/13 (Capon) 58:24-60:17; FOF 24. A POSA knew the nucleotide sequences of those exons, the amino acid sequences encoded by those exons, and the boundary between the CH1 and hinge domains of the human IgG1 heavy chain constant region. JTX-19 at 2-4, Figs. 2, 4; 9/20A (Wall) 92:22-93:1; 9/13P (Capon) 68:23-69:14; FOF 99.

101. As suitable sources of DNA sequences encoding all of the domains of a human IgG1 or IgG3 in a TNFR-based fusion protein, the Patent Disclosure identifies vectors containing exons encoding the hinge, CH2, CH3 sequences of human IgG3 and IgG1 heavy chains. JTX-1 at 18, 24-25 (col. 8:58-65, Example 11); 9/18A (Naismith) 90:10-91:14; 9/17 (Loetscher) 57:4-25; FOF 61. A host cell transfected with the pCD4-Hγ1 vector yields a fusion protein with the exon-encoded hinge-CH2-CH3 region of a human IgG1 heavy chain. FOF 61.

102. A POSA therefore understood from the Patent Disclosure that the Inventors possessed the IgG component of the claimed fusion proteins—a portion of the known human IgG1 heavy chain containing the exon-defined hinge, CH2 and CH3 domains. 9/18A (Naismith) 89:2-12, 91:8-14.

4. The Patent Disclosure Demonstrates Possession of the Claimed p75-IgG1 Fusion Protein

103. The Patent Disclosure consistently describes the inventions to include fusion proteins that combine a TNF-binding soluble fragment of one of the two known TNF-binding proteins (*i.e.*, p55 or p75) and all of the domains of a human Ig constant region except the first domain. JTX-1 at 3 (Abstract), 15 (col. 2:33-39) (Summary), 17 (col. 5:54-61) (Detailed Description).

104. The Patent Disclosure states (i) "[f]or the expression of proteins which consist of a soluble fragment of non-soluble TNF-BP and an immunoglobulin fragment, *i.e.* all domains except the first of the constant region of the heavy chain, there are especially suitable pSV2-derived vectors" and (ii) that the "pCD4-Hγ1 (DSM 5314 deposited on 21 Apr. 1989)" and "pCD4-Hγ3 (DSM 5523, deposited on 14 Sep. 1989)" are "especially preferred vectors." JTX-1 at 18-19 (col. 8:56-9:8; 9/17 (Loetscher) 58:6-59:5; FOF 101). A POSA would have understood from these statements together that a soluble fragment of either p55 or p75 is to be combined with the hinge-CH2-CH3 portion of a human IgG1 or IgG3 heavy chain constant region. 9/18A (Naismith) 90:10-92:18.

105. A POSA understood the phrase "data with respect to the further use of these vectors for the expression of chimeric proteins (see also Example 11) and for the construction of vectors for the expression of such chimeric proteins with other immunoglobulin fragments" to mean that the extracellular region of either p55 or

p75 may be used in the described fusion proteins. JTX-1 at 19 (col. 9:4-8); 9/18A (Naismith) 92:21-93:2. The statement's reference to Example 11 would have conveyed to a POSA to follow the recipe provided there. 9/18A (Naismith) 93:3-8.

106. A POSA understood from the Patent Disclosure that the approach in Example 11 should be followed, and that it would yield fusion proteins consisting of (i) the extracellular region of either "TNF-BP" (*i.e.*, p55 or p75) and (ii) an Ig fragment made up of the exon-defined hinge, CH2 and CH3 of a human IgG1 or IgG3 heavy chain. 9/18A (Naismith) 91:15-93:8; 9/17 (Loetscher) 58:6-59:5, 75:1-7; JTX-82 (Lesslauer II) 298:11-14, 298:17.

107. The Patent Disclosure conveys to a POSA that the Inventors possessed four possible fusion proteins, one being the claimed fusion consisting of the extracellular region of p75 fused to all domains of the human IgG1 heavy chain constant region except the first. FOF 85; 9/18A (Naismith) 91:15-92:18, 93:12-22.

B. The Patent Disclosure Demonstrates Possession of Methods of Producing the Claimed Fusion Proteins in CHO Host Cells

108. A POSA understood that the Inventors possessed the method of producing the fusion protein defined in Claims 3, 8, and 10 of the '522 Patent because the Patent Disclosure identifies CHO cells as one option for a host cell to be used in producing TNFR-based fusion proteins. JTX-2 at 28, 47-48 (col. 8:59, claims 3, 8, 10); 9/18A (Naismith) 96:23-97:22.

C. The Patent Disclosure Demonstrates Possession of Pharmaceutical Compositions

109. The Patent Disclosure describes pharmaceutical compositions of TNF binding protein inventions described elsewhere in the disclosure, thus establishing that the Inventors possessed the pharmaceutical compositions defined in claims 12 and 36 of the '182 Patent by August 31, 1990. JTX-1 at 17, 19, 34-35 (col. 6:26-30, 10:11-23, claims 12, 36); 9/18A (Naismith) 95:21-96:10.

D. The Patent Disclosure Enables the Claimed Fusion Proteins and Their Methods of Production.

110. Sandoz's enablement challenge is based in large part on their written description defense. 9/13A (Capon) 73:12-21. As explained above, the claimed fusion protein and its claimed method of production are adequately described in the Patent Disclosure. *See* FOF 85-109.

111. Both of Sandoz's experts agree that a POSA would have been able to successfully express and purify a fusion protein like etanercept (one consisting of the extracellular region of p75 fused to all of the domains of the human IgG1 heavy chain) using no more than ordinary skill and routine methods known in the art.[1]

[1] The Court credits Dr. Blobel's "strong disagree[ment]" with Dr. Capon's opinion that it would take undue experimentation to "identify, make, and use the TNF-binding soluble fragments of the p75 TNF receptor and the claimed fusion proteins." *See* 9/12P (Blobel) 60:4-12. His disagreement was more credible than his attempt to distinguish it from Dr. Capon's opinion on the basis of "identifying" the receptor, as Dr. Blobel admitted that both TNFR had been identified, sequenced, and available by the time of the invention. *Id.* at 60:12-61:13.

9/12P (Blobel) at 55:20-56:5; 9/13P (Capon) 73:5-14. There is no dispute on this point. *See also* JFPTO ¶ 255 (D.I. 620 at 67); 9/20A (Wall) 92:10-15.

112. The factual inquiries specified in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), separately confirm that the Claims are fully enabled. 9/20A (Wall) 97:5-22, 110:14-23; 9/12P (Blobel) 59:12-15, 54:15-56:13.

113. The **nature of the invention** is the combination of two known partial sequences—the p75 extracellular region and the exon-encoded hinge-CH2-CH3 portion of human IgG1. 9/11P (Blobel) 14:19-15:5; 9/20A (Wall) 19:4-12.

114. The **scope of the Claims** is limited and covers etanercept. 9/13P (Capon) 82:22-83:3; 9/11P (Blobel) 14:19-15:14.

115. The **state of the art** of recombinant DNA technology was well-developed and allowed for the construction and production of fusion proteins. JFPTO at 65, ¶ 247; 9/12P (Blobel) 54:13-56:13.

116. The Patent Disclosure provides ample **direction and guidance**. The Patent Disclosure identifies the p75 TNF receptor as one of two preferred embodiments for making fusion proteins. FOF 59, 103. It provides information that a POSA could use to prepare a cDNA encoding the extracellular region of the known p75. JTX-1 at 22, 17, 18 (col. 16:22-48, 5:22-24, 7:42-46); 9/18A (Naismith) 60:13-62:6; 9/18P (Naismith) 53:12-54:6; 9/20A (Wall) 93:13-94:15. It provides information a POSA could use to prepare a DNA encoding all of the domains of a

human IgG1 constant region except the first, including identifying a publicly accessible exemplary vector pCD4-Hγ1. JTX-1 at 18 (col. 8:55-66); 9/20A (Wall) 94:16-95:15; FOF 61, 101, 104. And directs a POSA to follow the recipe in Example 11 to make the claimed TNFR fusion proteins. FOF 58, 105-106; 9/18A (Naismith) 53:22-54:2; 9/17 (Loetscher) 56:5-9.

117. Example 11 illustrates one way of generating a cDNA encoding an extracellular region of TNFR using peptide sequences from the Patent Disclosure. FOF 60. A POSA could have adapted this technique to p75 using peptide sequences from the Patent Disclosure and publicly available sequence information. FOF 89, 105-106; 9/20A (Wall) 93:22-94:4; 9/12P (Blobel) 8:6-10:2, 14:6-12; 9/18A (Naismith) 67:14-68:25, 72:15-73:1, 73:17-74:8.

118. Example 11 illustrates making a plasmid encoding a fusion combining the extracellular region of a TNFR (p55) with all domains except the first of a human IgG (IgG3) heavy chain constant region using one of the deposited vectors (pCD4-Hγ3) identified in the Patent Disclosure. JTX-1 at 18-19, 24-25 (col. 8:56-9:8, 20:46-21:3); 9/18A (Naismith) 54:18-19, 93:3-94:14; 9/17 (Loetscher) 56:5-9, 57:4-13; 9/13A (Capon) 87:1-22. Isolation and purification of the expression product of a host cell transfected with this plasmid can be carried out by conventional procedures described in the Patent Disclosure and known in the field. JTX-1 at 25 (col. 21:3-10); 9/18A (Naismith) 53:12-13; 9/13A (Capon) 97:6-98:13.

119. A POSA could have readily adapted Example 11 to make the claimed fusion protein combining the extracellular region of p75 with the exon-encoded hinge, CH2, CH3 region of human IgG1 using only routine experimentation. 9/20A (Wall) 95:16-18; 9/18A (Naismith) 93:19-22; 9/17 (Loetscher) 58:13-59:5.

120. CHO cells are identified in the Patent Disclosure, and a POSA could have expressed and purified the claimed fusion proteins from them with only routine experimentation. 9/20A (Wall) 96:16-97:22; 9/18A (Naismith) 97:10-11; 9/11P (Blobel) 45:6-9, 60:1-2; 9/12P (Blobel) 55:2-19; JTX-1 at 18 (col. 8:25-44).

121. A POSA's **relative skill in the art** is high. 9/11P (Blobel) 30:24-32:5; 9/20A (Wall) 18:6-25.

122. A POSA would have been able to make the claimed fusion protein with only **routine experimentation**. FOF 111, 119; JFPTO at 65, ¶ 247.

123. Although the biological arts are generally unpredictable, there was no dispute at trial that a POSA would have reasonably expected that the claimed fusion protein could be produced and that it would specifically bind human TNF. 9/12P (Blobel) 56:6-13; 9/20A (Wall) 95:19-96:13; JFPTO ¶ 254 (D.I. 620 at 67).

E. Sandoz Did Not Prove its Written Description and Enablement Defenses

124. Dr. Capon's testimony that the Patent Disclosure fails to describe and enable the Claims was not consistent with the evidence.

1. Dr. Capon Incorrectly Reads the Patent Disclosure as Describing Only One p75 Having the Figure 4 Sequence

125. Dr. Capon testified that the only p75 described in the Patent Disclosure is a "truncated, mutated" TNFR consisting of the Figure 4 sequence or smaller portions of it, and that it is a different protein than the known p75. 9/13A (Capon) 22:4-7, 46:12-15; 9/13P (Capon) 98:9-22. That opinion conflicts with numerous Patent Disclosure passages and with scientific evidence existing before August of 1990. The PTO Board rejected a similar argument during prosecution. PTX-6.456 at 9; PTX-6.332 at 21-22, 74. 9/13P (Capon) 85:5-88:16, 96:10-97:24.

126. The Patent Disclosure describes Figure 4 as a "partial" cDNA. JTX-1 at 17 (col. 5:35-38). A POSA understood that a "partial" cDNA does not encode the complete amino acid sequence of a protein, and that, contrary to Dr. Capon's testimony, Figure 4 is not describing a "truncated and mutated" TNF receptor distinct from the known p75. 9/18A (Naismith) 85:25-86:22, 98:11-104:10.

127. The Patent Disclosure states that fusion proteins contain soluble fragments of one of two "preferred" TNF binding proteins, and that one of them (the "75/65 kD" TNF binding protein) contains the 18-amino acid N-terminal sequence designated "IID" and "SEQ ID NO: 10." FOF 63, 92. That sequence is contained in the known p75 reported in Smith 1990 and Dembic, but is not in the partial sequence in Figure 4. JTX-1 at 22, 13-14 (col. 16:27-28, Fig. 4); JTX-24 at 3, Fig. 3B, JTX-23 at 2, Fig. 1; 9/18A (Naismith) 105:18-19; 9/18P (Naismith) 54:10-56:8. A POSA

familiar with these facts understood that the Patent Disclosure describes fusion proteins that may incorporate a soluble fragment of the known p75 which contains the "IID"/"SEQ ID NO: 10" sequence *or* a p75 containing the Figure 4 partial sequence, and not that *only* the partial sequence of Figure 4 should be used. 9/18A (Naismith) 105:11-19, 86:10-22; 9/18P (Naismith) 48:20-49:22.

128. The Patent Disclosure also indicates that "preferred DNA sequences" include those "which code for a protein of about 75/65 kD" as well as "those which contain the partial cDNA sequences shown in FIG. 4." JTX-1 at 17 (col. 5:35-38). This conveys to a POSA that a soluble fragment of a TNF-binding protein in a fusion protein may, not must, contain Figure 4's sequence. 9/18A (Naismith) 85:25-86:9.

129. The Patent Disclosure also explains that the TNF-BP used in fusion proteins may contain sequences that vary from the ones depicted in Figures 1 or 4. It states that the 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, whereby in the case of the proteins coded thereby there come into consideration, just as before, TNF-BP." JTX-1 at 17 (col. 5:17-22); FOF 67. A POSA would recognize the known p75 sequence reported in Smith 1990 and Dembic is a "TNF binding protein" within the meaning of the Patent Disclosure that constitutes substitutions and additions to Figure 4, as it (i) substitutes amino acids at positions 141, 196 and 230 of the sequence in Smith

Figure 3B; and (ii) it adds 48 amino acids to the N-terminus. FOF 65, 98.

130. The Examples are "intended to illustrate details of the invention" and "not intended to limit its scope in any manner." JTX-1 at 19 (col. 10:24-27).

131. Dr. Capon's testimony necessarily implies that HL60 cells express two different-sized p75 proteins: (1) the known, full-length p75 and (2) a truncated p75 missing 48 amino acids. Contrary to his testimony, however, experimental evidence published by the Inventors before August 1990 shows that HL60 cells make *only one* p75 protein because they generate only one mRNA "message" when they express p75. FOF 44; 9/17 (Loetscher) 34:12-35:13; 9/18A (Naismith) 77:12-79:8, 83:3-5. If HL60 cells made two different-sized p75 proteins, two different sized mRNA "messages" would have been observed. 9/18A (Naismith) 105:6-10.

132. Dr. Capon theorized that a POSA would have believed the proteins the Inventors observed in the 65 and 75 kD bands on the SDS-PAGE gel in Example 6 were two different TNFR proteins. 9/13P (Capon) 10:24-11:9; 9/18A (Naismith) 104:11-20. That theory is foreclosed by Dembic's experimental evidence that HL60 cells make one mRNA message and thus only one p75 protein. FOF 44, 131. It is also inconsistent with the Patent Disclosure's statement that the same p75 was in both bands, and the evidence therein showing that the protein in both bands bound TNF-α and was bound by an antibody that only binds to p75. JTX-1 at 22 (col. 15:27-39); 9/18A (Naismith) 79:19-80:8, 82:3-83:6; 9/17 (Loetscher) 34:24-35:11,

47:11-48:7, 49:22-25, 95:10-17.

2. Dr. Capon's Theories About the Potential Effects of Amino Acid Differences in Figure 4 Are Ruled Out by Experimental Evidence

133. Dr. Capon argued a POSA would have expected each of the differences between the partial sequence of Figure 4 and the p75 reported in Smith 1990 and Dembic to cause the two proteins to exhibit different biological properties. 9/13A (Capon) 30:20-34:18.

134. Dr. Capon testified that the Figure 4 sequence "is missing some 70 amino acids from" the p75 disclosed in Smith 1990.[2] He theorized that a fusion protein made with Figure 4 might not bind TNF. 9/13A (Capon) 72:15-18, 28:14-30:18. What Dr. Capon's theoretical Fig. 4-based fusion protein might do is irrelevant—the Claims do not encompass such a protein because they require the fusion protein component to contain SEQ ID NO: 10. 9/18A (Naismith) 105:11-19.

135. A POSA would not have read the Patent Disclosure to mean that Figure 4's sequence *must* be used as the TNF binding component of the claimed fusion proteins. Nor would a POSA have made a fusion protein using a soluble fragment of the p75 TNFR protein missing its first amino acids 1 to 48; such a fragment

[2] Dr. Capon included the 22 amino acids in the signal sequence in his 70-amino acid difference. A POSA would not have done that, as the signal sequence is not part of the p75 protein. 9/18A (Naismith) 127:13-14, 71:15-22.

lacked a portion of the cysteine-rich repeats region where the TNF binding site was believed to be located. 9/18P (Naismith) 48:20-49:22; JTX-24 at 1, 3, Fig. 3.

136. Dr. Capon identified an extra amino acid in the intracellular region of the Figure 4 sequence. 9/18A (Capon) 34:19-35:8. That difference is irrelevant because the claims require use of the extracellular region of p75. JTX-1 at 34, 35 (claims 11-12, 35-36); JTX-2 at 47, 48 (claims 3, 8, 10).

137. Dr. Capon testified that the two amino acid differences he notes in the extracellular region of the Figure 4 sequence relative to p75 (*i.e.*, at positions 141 and 196 of the Smith 1990 sequence) were "non-conservative" and would introduce "a very drastic change" (141) or be a "drastic mutation" (196). 9/13A (Capon) 31:16-19, 32:19-20. He testified a POSA would "definitely know" that p75 and the Figure 4 protein "were two different proteins with two very different structures likely to have different biological properties" (*id*. at 32:6-9) or would be "expected to have differences in biological function" (*id*. at 33:8-11).

138. Dr. Capon's theories are directly refuted by experimental evidence known before August 31, 1990 that he failed to address. By that date, published data showed that allelic variants of p75 TNFR with amino acid changes at positions 141 and/or 196—the same changes that Dr. Capon identified in Figure 4—did not differ in the relevant biological function: they retained the ability to specifically bind TNF. FOF 66; 9/18A (Naismith) 103:5-104:10.

139. Dr. Capon admitted that a third amino acid difference at position 230 was a "conservative" change (threonine to serine), but suggested it could affect glycosylation and biological activity of p75. 9/13A (Capon) 35:15-18. Evidence in the Patent Disclosure contradicts his theory.

140. In Example 6, the Patent Disclosure reports that p75 isolated from HL60 cells migrated to two positions in the SDS-PAGE gel. JTX-1 at 22 (col. 15:31-34). The protein in both bands bound specifically to TNF-α, and was bound specifically by an antibody that reacts only with p75 TNFR. FOF 44. A POSA would have understood that glycosylation patterns of p75 explained the two positions. JTX-23 at 1, 5, Fig. 4; 9/18A (Naismith) 80:12-81:5; 9/18P (Naismith) 51:8-52:9. Both forms of p75, however, bound specifically to TNF-α. JTX-1 at 22 (col. 15:31-34). As Dr. Naismith explained, a POSA would not have expected glycosylation differences to affect TNF binding by p75. 9/18A (Naismith) 122:17-22.

141. Dr. Capon's written description testimony was not consistent with the Patents-in-Suit or the state of the art. Although he admitted that the Patents-in-Suit disclosed a fusion protein, 9/13P (Capon) 72:16-73:1, Dr. Capon refused to admit known facts that even Sandoz's Dr. Blobel acknowledged, including that: (i) Smith 1990 disclosed the extracellular region of p75 and (ii) a POSA sending SEQ ID NO: 10 to GenBank would have received the p75 sequence of Smith 1990 in return. *Compare* 9/13P (Capon) 36:16-37:3, 28:15-20, *with* 9/12P (Blobel) 8:5-9, 14:6-12.

142. The partial sequence of Figure 4 is nearly identical to the Smith 1990 sequence. Dr. Lyman found a sequence alignment of 98.977% identity when comparing Figure 4 to the disclosure in Smith (1990) where the sequences are overlapping. PTX-6.396 (Lyman Decl.) ¶ 16, Ex. D; 9/18A (Naismith) 118:4-121:21. While Dr. Capon contends that Dr. Lyman's calculation of 98.977% sequence identity is "garbage …, untrue and misleading" (9/13P (Capon) 108:9-109:17), Dr. Capon is incorrect, as Dr. Lyman's methodology was standard in the art. 9/18A (Naismith) 118:18-21, 120:1-121:21.

XII. SANDOZ HAS FAILED TO PROVE CLAIMS 35 AND 36 OF THE '182 PATENT INVALID FOR ANTICIPATION

143. Claims 35 and 36 of the '182 Patent, as well as its specification, each identify a publicly available plasmid deposited with the ATCC and designated PTA 7942. JTX-1 at 17, 35 (col. 5:45-50, claims 35, 36).

144. As explained above, the Inventors made the plasmid by August 31, 1990, deposited it with the ATCC in 2006, and the '182 Patent specification was amended in compliance with applicable PTO rules and practices to refer to the ATCC deposit. FOF 42, 94.

145. The PTO Appeal Board allowed the amendment, concluding that reference to the deposit did not add new matter, and that the Patent Disclosure did not need to include the full sequence information for p75, because that information was known in the prior art before August 31, 1990. FOF 95.

146. Because the amendment of the '182 Patent specification to reference the deposited PTA 7492 plasmid did not add any new matter not described in the priority EP707 Application (FOF 51), Claims 35 and 36 of the '182 Patent are entitled to the August 31, 1990 priority date of the EP707 Application. As such, they are not anticipated or otherwise rendered obvious by any post-August 31, 1990 art.

XIII. NONE OF THE CLAIMS WOULD HAVE BEEN OBVIOUS

A. Sandoz's Contentions

147. Sandoz asserted six obviousness combinations.[3] They contended that: (1) certain references (Smith '760 and Smith 1990) disclosed the protein sequence of, and the DNA sequence that encodes, the p75's extracellular region; (2) the other references disclosed Ig fusion proteins that combined a receptor protein with various fragments of an Ig heavy chain; and (3) to make a reagent or a potential therapeutic to address excess inflammation, a POSA would have had three motivations to combine various references to make a fusion protein within the Claims.

148. Sandoz asserted three motivations to combine: (1) to purify using

[3] The first five combinations were: Smith '760 in view of: (1) Seed '262; (2) Byrn; (3) Watson; (4) Karjalainen '827; and (5) Capon '964 in further view of Traunecker. The sixth combination was Smith 1990 in view of Watson. All of the prior art references relied upon by Sandoz and Dr. Blobel were previously considered by the Patent Office during prosecution. 9/12A (Blobel) 33:25-36:4. Combinations of prior art including the Smith '760 and Capon '964 were also considered by the Patent Office Board in an obviousness challenge in an *inter partes* review proceeding, but were rejected for failing to show a "reasonable likelihood" of success on the merits. *Id.* at 36:5-39:4; PTX-1089 at 19.

Protein A; (2) to extend the soluble p75's half-life (the amount of time it would normally take the body to clear half of the soluble receptors from circulation); and (3) to increase the soluble p75's avidity (the overall strength of binding between the receptor and TNF). None of these asserted motivations would lead a POSA to make the claimed fusion protein.

B. The State of the Art Generally

149. As of August 31, 1990, the art reflected a prevailing view that many cytokines were thought to be involved in excess inflammation, that blocking a single cytokine likely would not work, and that cytokines were probably a poor choice in any event. As a later review article by leading researchers in the field summarized:

> It is a misconception to think that TNFα was an obvious therapeutic target in the early 1990s since it is pro-inflammatory and present in synovium. The same could be said for IL-1, IL-6, GM-CSF, IL-8, and so on. The plethora of possible cytokine therapeutic targets and the concern about cytokine redundancy led some workers in the field to consider cytokines to be poor therapeutic targets. The prevailing view in the early 1990s was that blocking any one pro-inflammatory mediator in isolation would not be beneficial as those remaining would drive the biological processes.

PTX-34 (Feldmann) at 6; 9/20A (Wall) 36:18-37:25.

150. Feldmann reflects a POSA's understanding that cytokines, like TNF, were difficult to study due to the pleiotropic and redundant nature of their activity, which meant that a POSA would not have regarded any single cytokine as the best starting point. 9/20A (Wall) 21:7-22:24; 36:18-37:25. The art had identified many

cytokines, but their "relative importance" in diseases remained "unclear." DTX-75 at 1; 9/20A (Wall) 26:17-27:15; *see also id.* at 23:17-24:9.

151. Even within the context of a single starting point, the art did not reflect a consensus view that TNF would have been the best one. Rheumatic diseases had many potentially important mediators, and some believed that IL-1, rather than TNF, had the strongest link with RA. PTX-10 at 8; 9/20A (Wall) 23:17-24:14.

152. TNF would have been an unlikely cytokine target due to concern in the art that TNF receptors could aggravate disease by binding TNF and then later re-releasing it into the body in active form. JTX-46 at 6; 9/20A (Wall) 28:24-33:15. Dr. Blobel's testimony that a POSA would have focused on TNF reflects hindsight bias.

153. A POSA deciding to use a TNFR would have likely used the p55, in light of published experimental evidence showing that the p55 bound TNF with five times greater strength, and was superior in neutralizing TNF, than the p75. JTX-47 at 3; 9/18P (Greene) at 108:21-109:24. Dr. Blobel's testimony that a POSA would have chosen the p75 reflects hindsight bias.

154. A POSA deciding to use the p75 would have faced an array of choices. 9/12P (Blobel) 15:21-17:6. She could have used a soluble receptor, of (contrary to the Claims) varying lengths, as Smith 1990 suggested by encouraging production of "soluble, recombinant *forms* of this receptor," JTX-24 at 4 (emphasis supplied); JTX-65 at 10, 13 (col. 4:12-21, 9:17-60).

155. A POSA could have used any of the non-Ig options that Smith '760 discussed, JTX-65 at 13 (col. 10:35-53), including monovalent forms, *id.* (col. 10:33-35). Smith '760 suggested many polyvalent forms, *id.* (col. 10:35-53), including to combine it with polyethylene glycol, or PEG, using what that patent called "conventional coupling techniques," *id*. (col. 10:39-44), which would have increased its half-life without raising immunogenicity concerns while also adding an extra binding site, 9/20A (Wall) 68:3-18; 71:4-8. By August 1990, PEG had a long history of prior use and numerous PEG-modified proteins were in clinical trials. *Id.* 68:22-70:24; PTX-116 at 3. By the August 1990, the FDA had approved at least one PEGylated compound. 9/20A (Wall) 68:22-69:18; PTX-116 at 3.

156. A POSA would not have been motivated to select Ig as a fusion partner. Prior experience, confirmed by experiments with both antibodies and with CD4-Ig fusions, reflected that such constructs elicited the pro-inflammatory effector functions of CDC (because they contained the CH2) or ADCC (because they contained the hinge/CH2 junction). 9/18P (Greene) 80:15-81:9; 9/20A (Wall) 56:24-59:11. Such concerns made selecting an Ig that contained CH2 and the hinge/CH2 junction unlikely in a recombinant biologic designed to reduce excess inflammation. 9/20A (Wall) 39:14-40:9. Dr. Blobel's testimony that a POSA would have selected Ig as a fusion partner reflects hindsight bias.

157. A POSA selecting an Ig would not have selected an exon-encoded-

hinge-CH2-CH3 of IgG1. Contrary to the Claims, Smith '760 teaches fusion proteins with "unmodified constant region domains," JTX-65 at 13 (col. 10:56-57); 9/12P (Blobel) 19:16-20:2, which means they retained CH1. Smith '760 also teaches that "TNFR sequences," JTX-65 at 13 (col. 10:53-54), which need not necessarily be the full-length extracellular region, *id.* at 10 (col. 3:57-63), be "substituted for the *variable* domains of either or both of the immunoglobulin molecule heavy and light chains," *id.* at 13 (col. 10:53-56) (emphasis supplied). Contrary to the Claims, Smith 760's construct retains the light chain constant regions. *Id.* (col. 10:53-61).

158. A POSA, even if selecting an Ig, would still need to decide which Ig, and which portion of an Ig, to use. There are many Ig classes and subclasses, and prior art constructs used other Igs, including IgM and IgG2a, used in Traunecker and Karjalainen '827, or IgG3, also used in the latter. 9/12A (Blobel) 66:22-67:14; JTX-25 at 1-2; JTX-60 at 5, 11. A POSA considering the Ig fusion art also would find it showed no consensus towards selecting the exon-encoded-hinge-CH2-CH3 of the Claims. There was no "evolution" towards Ig fusion proteins lacking the CH1 after Traunecker. *Cf.* 9/12A (Blobel) 19:17-25, 20:7-16. On direct, Dr. Blobel mis-ordered dates and omitted structures after Traunecker that disclosed a CH1. *Id.* at 21:2-7, 22:24-23:16. Capon '964, filed after Traunecker published, *id.* at 26:4-20, 63:7-12, JTX-25 at 1, disclosed a "particularly preferred" embodiment having a CH1, 9/12A (Blobel) at 23:12-16, 67:19-69:2, and the later-filed Smith '760

describes chimeric antibodies having a CH1 and light chains, *id.* at 26:4-20. Seed '262 published after Traunecker disclosed one construct having CH1 and one having no hinge. *Id.* at 54:14-17, 56:22-57:16; JTX-57 at 10-11.

159. A POSA selecting an Ig needed to make other choices, as well, including whether to use a full, exon-encoded hinge, a shorter, two-cysteine hinge, or no hinge, each of which the prior Ig fusion art embodies, 9/20A (Wall) 82:24-83:8. And Dr. Blobel admitted it was "not so obvious" to use a three-cysteine as opposed to a two-cysteine hinge. 9/12P (Blobel) 34:5-13, 39:24-40:11. A POSA selecting an Ig would also have had to have decided whether to use a linker, 9/20A (Wall) 82:1-4; 89:19-90:1, and, if so, of what length, as the art reflected varying lengths, *id.* 88:17-23; *see also* JTX-57 at 10; PTX-26 at 6. Beutler described his linker as functional. JTX-67 at 15 (col. 7:5-8, 8:19-22); 9/18P (Greene) 109:25-110:8. A POSA deciding to use a hinge-CH2-CH3 would have had to decide whether to use a full-length extracellular region rather than a truncated receptor, as in Dr. Lauffer's constructs, *id.* at 88:14-23, or in one of Dr. Capon's, 9/11P (Blobel) 80:19-81:6. There was no evolving consensus on which parts of an Ig to use in the prior art fusion proteins in August of 1990. 9/20A (Wall) 75:12-18. Dr. Blobel's testimony that a POSA would have resolved each of these choices to arrive at the Claims reflects hindsight bias.

C. Sandoz's Asserted Prior Art

1. The TNFR Art

a. Smith 1990

160. Smith 1990 was published in the peer-reviewed, highly regarded journal *Science* in May 1990. JTX-24 at 1. It was a landmark paper. 9/13P (Capon) 34:13-35:13; 9/18A (Naismith) 69:1-4, 69:12-18, 70:8-11.

161. In Smith 1990, Immunex researchers reported isolation of a p75 cDNA clone. JTX-24 at 1. In Figure 3 and associated text, they disclosed to the field the intracellular, transmembrane, and extracellular regions of p75, as well as the deduced amino acid sequence of each region. *Id.* at 3; *see* 9/20A (Wall) 33:19-25; 9/18A (Naismith) 69:1-4, 69:12-18, 70:19-71:6, 71:15-72:7.

162. Smith 1990 concluded that the p75's extracellular region presumably contained the TNF binding sites. JTX-24 at 3.

163. Smith 1990 taught the use of recombinant soluble p75 as a research tool, and suggested forms of the soluble receptor might also be used to "explore the clinical value of TNF inhibition in pathological settings." *Id.* at 4.

b. Smith '760

164. The Smith '760 patent issued in March 1995 from an application filed on May 10, 1990, to three of the co-authors on Smith 1990. JTX-65 at 1. They filed that application after the publication of many of the Ig fusion protein references upon which Sandoz rely. 9/12A (Blobel) 26:5-20. Entitled "DNA Encoding Tumor

Necrosis Factor-α and -β Receptors," the issued patent contains 20 claims, none of which specify a fusion protein.

165. Smith '760 states that "[b]oth monovalent forms and polyvalent forms of TNF-R are useful in the compositions and methods of this invention," JTX-65 at 13 (col. 10:33-35), but does not express a preference for either. The patent identifies a variety of potential uses for the TNF receptor, including studying the structural and biological characteristics of TNF receptor systems and to use TNFRs "effectively in therapy, diagnosis, or assay[.]" *Id.* at 9 (col. 2:15-22).

166. Smith '760 reports a wide variety of acceptable options or choices for polyvalent forms: "Polyvalent forms possess multiple TNF-R binding sites for TNF ligand. For example, a bivalent soluble TNF-R may consist of two tandem repeats of amino acids 1-235 of FIG. 2A, separated by a linker region. Alternate polyvalent forms may also be constructed, for example, by chemically coupling TNF-R to any clinically acceptable carrier molecule, a polymer selected from the group consisting of Ficoll, polyethylene glycol or dextran using conventional coupling techniques." *Id.* at 13 (col. 10:35-52); *see generally* 9/20A (Wall) 66:20-68:2.

167. As a non-preferred alternative to the myriad modifications just discussed, Smith '760 states that "[a] recombinant chimeric antibody molecule may also be produced," by creating an antibody which has "TNF-R sequences substituted for the variable domains of either or both of the immunoglobulin molecule heavy

and light chains[.]" JTX-65 at 13 (col. 10:53-56). Smith '760 teaches such chimeric antibody has "unmodified constant region domains," *Id.* (col. 10:53-57), thus making clear its chimeric antibody should retain the CH1 domain and the light chain structures of conventional antibodies. 9/20A (Wall) 75:2-6.

168. A POSA would have no reason to modify the Smith '760 chimeric antibody, as even Dr. Blobel described the chimeric antibody as "a great idea," alleging that it would have allowed a POSA to "instantly make a TNF-binding molecule and a drug." 9/11P (Blobel) 74:6-11.

169. Smith '760 contains a separate section on "Purification of Recombinant TNF-R," JTX-65 at 16 (col. 15:59-16:56), that describes a wide variety of different purification methods known in the art, but does not mention Protein A. The described methods include using an "affinity matrix" using TNF "bound to a suitable support" and takes advantage of the ability of the p75 TNF-R to selectively bind TNF with high affinity. *Id.* (col. 16:4-6); 9/20A (Wall) 72:3-21. The patent also discusses other purification matrixes of various types or reversed-phased high performance liquid chromatography steps. JTX-65 at 16 (16:4-6) The patent mentions Protein A purification only once, and then only as a non-preferential alternative to another technique. *Id.* at 22 (col. 27:3-7).

170. Smith '760 suggests using "an effective amount of soluble TNF-R proteins," but does not describe such a use for its chimeric antibody. *Id.* at 16 (col.

16:57-17:25); 9/20A (Wall) 34:24-35:12; 9/12P (Blobel) 15:7-16:1.

2. The Ig/Receptor Fusion Art

171. In the late 1980's/early 1990's, the HIV epidemic was at its peak. HIV is a virus that infects specific cells of the immune system, in particular, T-cells, causing AIDS. 9/18P (Greene) 72:10-74:13.

172. HIV enters T-cells when a protein on its surface, gp120, binds to CD4 receptor expressed on the surface of these cells, allowing it to microinject its genetic material into the cell to become integrated into the cell's DNA. *Id.* HIV can then hijack the cells' biological process so that they become virus-producing "factories" that make more copies of HIV. 9/18P (Greene) 75:4-76:7, 77:3-16.

173. In the late 1980s/early 1990s, researchers first designed and made CD4 fusion proteins ("CD4-Ig fusions") to trigger the immune system by stopping the virus and killing such HIV-infected cells. 9/20A (Wall) 38:14-39:6; 9/18P (Greene) 76:8-23. They did so by combining the extracellular region of the CD4 receptor with Ig fragments the art had shown could elicit the pro-inflammatory effector functions of CDC and ADCC. 9/18P (Greene) 76:8-77:2.

174. These CD4-Ig fusion proteins incorporated pro-inflammatory, cell-killing antibody effector regions, where the effector functions CDC and ADCC were understood to reside. Specifically, the C1q protein involved in eliciting CDC was known to bind to the CH2 domain. 9/18P (Greene) 78:3-6, 79:7-11. The Fc-γ

receptors on natural killer cells involved in eliciting ADCC were known to bind at the hinge/CH2 junction. *Id.* at 79:14-80:5.

175. A POSA expected these fusions to bind gp120 proteins expressed on the surface of HIV-infected T-cells and then to form aggregates, which would then activate these effector functions to kill the infected T-cells. 9/18P (Greene) 77:17-78:2; 9/12A (Blobel) 11:8-11; *see also id.* 11:22-25, 14:24-15:8.

a. Capon 1989 (JTX-58)

176. Capon 1989, the first fusion Ig reference, published in February 1989 to Sandoz's expert witness, Dr. Capon. 9/12A (Blobel) 11:4-7, 39:13-16; JTX-58 at 1. It reported experimental results of CD4-Ig fusions designed to trigger immune system responses in HIV-infected patients by eliciting the effector functions in the CH2 and CH2/hinge regions of human IgG. JTX-58 at 4 (effector function "found in the constant region of the heavy chain (the CH2 domain for C1q and the region linking the hinge to the CH2 for Fc cell receptors)"); 9/18P (Greene) 83:13-21.

177. As relevant here, Capon 1989 reports the making and testing of two constructs, each using a human *CH1*+hinge+CH2+CH3: one used CD4's first two soluble domains, the other used all four. JTX-58 at 2, Fig. 1; 9/12A (Blobel) 44:6-9; 9/24A (Skerra) 90:17-91:10.

178. Consistent with expectations, Capon 1989 reported that each CD4-IgG fusion bound Fc receptors, the first step in ADCC. JTX-58 at 4-5. But, a result the

authors deemed "perhaps surprising," they found that neither bound C1q, the first step in CDC. *Id.* at 5; 9/12A (Blobel) 46:8-11.

b. Traunecker (JTX-25)

179. Traunecker, published in *Nature* in May 1989, also described experimental results of CD4-Ig fusion proteins designed to mobilize the immune system of HIV-infected patients. JTX-25 at 1; 9/12A (Blobel) 51:11-16.

180. The Traunecker constructs used mouse IgG2a and mouse IgM sequences, JTX-25 at 1 Fig. 1, and were intended to retain the effector functions of an Ig molecule to attack HIV-infected cells. JTX-25 at 1; 9/12A (Blobel) 53:23-54:2; *see also id*. 51:17-22. These researchers reported removing the CH1 domain restored C1q binding, JTX-25 at 1; 9/18P (Greene) 84:12-19, their constructs retained "the effector functions of normal immunoglobulin molecules, such as binding to Fcγ receptors . . . ." JTX-25 at 2; 9/20A (Wall) 56:24-57:13.

181. The experimental results in Traunecker taught a POSA that a receptor-Ig fusion protein that retained the hinge-CH2-CH3 but deleted CH1 would retain the pro-inflammatory, cell-killing effector functions of ADCC and CDC. 9/18P (Greene) 84:12-19; 9/20A (Wall) 78:18-79:1.

c. Seed '262 (JTX-57)

182. Seed '262 published in July 1989. JTX-57 at 1. It also describes CD4-Ig fusion proteins specifically designed to trigger the immune systems of HIV-

infected patients. 9/12A (Blobel) 54:18-56:6. It emphasizes that "any amount of the N-terminus of the immunoglobulin heavy chain can be deleted as long as the remaining fragment has antibody effector function." JTX-57 at 5 (p. 5:44-45); 9/20A (Wall) 57:23-58:10. A POSA would have understood it to emphasize the importance of preserving effector functions. 9/12A (Blobel) 55:16-56:5.

183. Seed '262 exemplifies a variety of CD4-Ig constructs, including one that included the CH1 domain, one that deleted it, and one that had neither the CH1 nor hinge domain. JTX-57 at 10 (p. 10:47-49); 9/12A (Blobel) 56:22-57:5; 9/20A (Wall) 79:12-21.

184. Each CD4-Ig construct disclosed in Seed '262 included a linker for "technical purposes." 9/12A (Blobel) 57:17-22. Dr. Blobel was mistaken about the length of the linker: he testified it had three amino acids, 9/12A (Blobel) 31:10-22, but it had five, 9/20A (Wall) 79:12-21. The linkers were integral and were included to facilitate cloning. 9/20A (Wall) 79:25-80:6.

d. Capon '964 (JTX-61)

185. Capon '964, naming Dr. Capon as an inventor, issued from an application filed November 1989. JTX-61 at 1. Its constructs were also designed to trigger immune responses in HIV-infected patients. It explains that the constructs were intended to retain effector functions "such as complement binding, cell receptor binding, and the like." JTX-61 at 22 (col. 4:43-47); 9/12A (Blobel) 60:23-61:13.

186. Capon '964 contemplates many different fusion configurations. JTX-61 at 25-27 (cols. 10-14); 9/12A (Blobel) 64:17-21, 65:25-66:2. It also contemplates that Ig fusions from a range of different Ig types and classes, including IgG2, IgG3, IgG4, IgD, IgM, and IgG. JTX-61, (col. 14:65-67); 9/12A (Blobel) 67:10-14.

187. Capon '964 describes two "particularly preferred" embodiments, each of which "contain[s] the effector functions of immunoglobulin G_1 . . . ." JTX-61 at 28 (col. 15:4-8); 9/12A (Blobel) 67:19-68:7. Unlike the fusion proteins covered by the Claims, one of the two particularly preferred embodiments included a CH1 domain. 9/12A (Blobel) 68:8-18; 9/20A (Wall) 82:5-23. The other lacked a CH1 domain, but did not include an exon-encoded hinge, as required by the Claims; instead, the Capon '964 constructs included a truncated hinge having only two cysteine residues. 9/12A (Blobel) 69:7-11; 9/20A (Wall) 82:5-23.

e. Byrn (JTX-56)

188. Byrn, which published in April 1990, also names Dr. Capon as a coauthor. JTX-56 at 1. It describes CD4-Ig fusion proteins that attached the CD4 receptor to a partial hinge-CH2-CH3. These constructs were designed to leverage the effector functions of Igs as a potential means for treating patients with AIDS. JTX-56 at 1; 9/12A (Blobel) 70:4-19; 9/18P (Greene) 85:24-88:14. These constructs had only two cysteine residues in the hinge, rather than the full exon-encoded hinge required by the Claims. 9/12A (Blobel) 71:16-72:1.

189. Byrn provides experimental evidence showing that CD4-Ig fusion proteins lacking the CH1 domain could induce ADCC and kill HIV- infected cells. JTX-56 at 1-2; 9/12A (Blobel) 70:20-71:15; 9/18P (Greene) 87:5-19.

190. Byrn did not test for CDC, apparently because Traunecker had demonstrated that removing the CH1 domain restores the fusion's triggering of CDC. 9/18P (Greene) 87:5-88:20. As Dr. Capon had written in Capon 1989, the art understood that CDC was triggered by C1q binding to the CH2 domain, JTX-58 at 1, 4; the Byrn 1990 constructs retained that CH2 domain, and thus a POSA would have understood those constructs to have been intended to, and have been capable of, triggering CDC. 9/18P (Greene) 88:4-14; JTX-56 at 2, Fig. 1.

f. Karjalainen '827 (JTX-60)

191. Karjalainen '827, a European patent publication, was not published until October 31, 1990, two months after the priority date, JTX-60 at 1; the experts agreed it was not prior for purposes of their analysis. 9/12A (Blobel) 84:2-13; 9/20A (Wall) 84:11-16. Karjalainen '827 is not admitted prior art and is exempt as prior art under § 103(c)(1). 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. 9/17 (Loetscher) 21:11-13; JTX-3 at 875-79; JTX-4 at 706-10; JTX-60 at 1; 35 U.S.C. § 103(c)(1).

192. Karjalainen '827 also expressed the intention that its constructs

leverage effector function to treat AIDS. 9/20A (Wall) 60:21-25. It reported results with CD4-Ig fusion constructs that bound Fc receptors and complement C1q, JTX-60 at 2, 9 (pp. 2:32-35, 9:1-14), showing the ability of the fusion construct to elicit CDC and ADCC, 9/18P (Greene) 65:16-24., 67:15-68:25

g. Watson (JTX-59)

193. Watson does not describe CD4-Ig fusions directed to treating patients infected with the HIV virus. Instead, it reported experiment results involving a "probe" that used a receptor other than CD4—a lymphocyte homing receptor—for studies *in vitro*, not in the body. 9/20A (Wall) 59:23-60:13; JTX-59 at 1. The Ig fragment in the Watson fusion proteins utilized a partial hinge region that included only two cysteine residues. 9/12A (Blobel) 76:12-16; JTX-59 at 3, Fig. 1A.

194. As Dr. Wall testified at trial, Watson used the same Ig portion that Byrn showed, through experimental evidence, to have retained cell-killing effector functions. 9/20A (Wall) 59:12-22; JTX-59 at 3, 8. Watson, however, did not discuss those effector functions, because it concerned a probe for *in vitro* studies, for which cell-killing effector functions would not be relevant. 9/20A (Wall) 61:9-13.

195. Watson includes a speculative suggestion that its construct might be useful to address excess inflammation. *Id.* 61:1-8; JTX-59 at 8. But it neither provided nor referenced any experimental results to support that speculation, which was contrary to the prior Ig fusion art as a whole. 9/20A (Wall) 39:13-40:9. And Dr.

Wall explained why Watson's speculation would have made little sense: its construct would have had to have been administered before evidence of inflammation was present, which would not have been practical for therapeutic purposes. *Id.* 61:1-8.

h. Other Ig Fusion Protein References

196. In formulating his initial obviousness opinion, Dr. Blobel failed to consider Ig fusion protein art that reflected additional concerns that the effector regions of such fusion proteins might limit their potential for therapeutic use. *See, e.g.*, 9/12A (Blobel) 78:1-19.

197. Zettlmeissl describes CD4-Ig fusion proteins designed for treating AIDS. *See* PTX-26 at 1.

198. Zettlmeissl stated, "One of the most important issues confronting these [receptor-Ig fusion] agents is the extent of autoimmune damage arising from the interaction of the fusion protein with its native ligand [*i.e.*, binding partner]." PTX-26 at 10; 9/12A (Blobel) 81:15-82:3. A POSA would have understood the authors to be cautioning about damage to tissue caused by the effector functions of fusion proteins. 9/12A (Blobel) 81:15-83:9.

199. Zettlmeissl CD4-Ig fusion proteins included a five amino acid linker sequence between the CD4 receptor and the Ig component, the function of which was to facilitate joining of the two fusion components. PTX-26 at 6. Gregersen 1990, published June 1990, describes one of the same CD4-Ig fusion proteins disclosed in

Zettlmeissl. PTX-26 at 8; 9/18P (Greene) 89:5-9.

200. Gregersen showed that its CD4-Ig fusion proteins were capable of eliciting CDC cell-killing activity against HIV-infected cells. PTX-23 at 16; 9/18P (Greene) 89:10-15. The authors reported that their CD4-Ig fusion proteins "unequivocally" killed cells by a "complement-dependent event." PTX-23 at 17.

D. The Differences Between the Prior Art and the Claims

201. In two fundamental respects, Dr. Blobel's testimony reflected that he did not correctly understand the scope of any of the challenged claims. First, Sandoz agreed before trial that the "all domains other than . . ." limitation required the exon-encoded, three-cysteine hinge. D.I. 618. But Dr. Blobel testified that his analysis assumed, contrary to that construction, that a two-cysteine hinge was within the Claims' scope. 9/12A (Blobel) 30:19-24. Second, he initially testified that a fusion construct with a linker would be within the claims' scope, *id.* at 32:2-5, and then testified that he was not sure, *id.* at 33:17-24. Both positions were wrong; the Claims do not allow a linker. Dr. Blobel did not establish a *prima facie* obviousness case, because of these two critical mistakes about claim scope.

1. The Differences Between the Asserted TNFR Prior Art and the Claims

202. Smith 1990 concerned the disclosure of the human p75's sequence information—the deduced amino acid sequence that it published, and the cDNA sequence that encodes it. FOF 161.

203. Dr. Blobel testified that this passage in Smith 1990 concerned fusion proteins: "[s]oluble, recombinant forms of [the p75] may also be produced to explore the clinical value of TNF inhibition in pathological settings." JTX-24 at 3. The paper also reported that the recombinantly produced receptor retained the native receptor's ability to specifically bind TNF. JTX-24 at 1, 3; 9/11P (Blobel) 70:22-71:7; 9/12P (Blobel) 12:25-13:7. The quoted passage would have thus suggested that a POSA use molecular biology techniques to produce "recombinant forms" of the receptor, of various lengths, to study their use, without further modification, as potential therapeutics. 9/20A (Wall) 34:1-19. Nothing in this passage, or the paper itself, suggested enlarging the receptor. Dr. Smith's later patent, Smith '760, likewise discusses using soluble receptors as a therapeutic, 9/20A (Wall) 34:20-35:11, but none of its claims require that the soluble receptor be modified. JTX-65 at 22.

204. Smith '760 similarly did not disclose or suggest making the fusion protein of the Claims. Its only section about therapeutic administration concerns the soluble receptor by itself. 9/12P (Blobel) 15:7-20. Smith '760 discloses that many modifications to p75, including ways to modify a monovalent form or ways make the receptor polyvalent, are possible, JTX-65 10:33-52, but does not express a preference for any of them. Among these possibilities was combining p75 with polyethylene glycol, *id.* at 13 (col. 10:36-52), which did not create immunogenicity risks. 9/20A (Wall) 68:3-15. PEG-modified molecules had the further benefit of

having been "approved by the FDA for use in drugs (parenterals, topicals, suppositories, nasal sprays), foods, and cosmetics," PTX 116 (Fuertges 1990) at 2; it was "a widely used and very acceptable, convenient technology," 9/20A (Wall) 70:19-24. PEG would "shield portions of the protein and prevent it from being chewed up by—there are lots of proteinases in serum, so it would improve its stability in lifetime as well." *Id.* 70:15-18. A PEGylated p75 would have expressly satisfied two of Dr. Blobel's motivations (multivalency, and increasing size and half-life) and could easily have been purified using TNF affinity, as described in Smith '760. 9/20A (Wall) 67:16-24, 70:3-6, 72:16-21; JTX-65 at 13 (col. 10:33-52).

205. Smith '760 also disclosed a "recombinant chimeric antibody molecule," which included an "unmodified constant domain region"—*i.e.*, including CH1. JTX-65 at 13 (col. 10:53-57). Directly contrary to that teaching, the Claims require that CH1 be deleted. 9/20A (Wall) 74:15-75:6. The chimeric antibodies of Smith '760 also require that "TNF-R sequences," defined to include proteins "substantially similar" to the native receptor (col. 3:40-42), be "substituted for the variable domains of either or both of the immunoglobulin heavy and light chains." *Id.* at 13 (col. 10:53-57); 9/12A (Blobel) 26:15-20. By contrast, the Claims require the full extracellular region of the p75, not truncated versions of that region. The Claims do not allow light chains, as Smith '760 contemplates.

2. The Differences Between the Asserted Ig Fusion Prior Art and the Claims

206. Sandoz's asserted Ig fusion prior art and the Claims likewise are fundamentally different. Except for Watson, its asserted Ig fusion references concerned fusion proteins specifically designed to take advantage of effector functions triggered by the CH2 domain (which led to CDC) or the junction between the CH2 domain and the hinge (which led to ADCC). FOF 156, 174. Those constructs were designed to implement those cell-killing functionalities because those constructs were designed to kill cells—specifically, HIV-infected cells. FOF 173. Thus, these constructs were designed to elicit pro-inflammatory processes (CDC and ADCC) to restore immune response in AIDS patients. FOF 174-75.

207. That is the opposite problem that a POSA trying to address the problem of excess inflammation in an auto-immune disease would have faced. That POSA's challenge would have been to interrupt, not trigger, immune system responses by stopping, not causing, pro-inflammatory biological processes. FOF 156. That POSA would have been "dissuaded" by the ability of these fusion proteins to elicit such effector function. 9/20A (Wall) 113:1-6, 113:20-114:2.

208. All of the Ig fusion protein references describe IgG fusion protein fragments that had been shown to elicit ADCC/CDC based on their ability to bind Fc receptors on immune cells or C1q, or based on their ability to kill HIV-infected cells (*i.e.*, CD4) by ADCC and CDC pathways. 9/20A (Wall) 56:4-16. This art thus

led in the "opposite direction" and applying it in an autoimmune setting would have been counter-intuitive. *Id.* at 39:14-40:9, 43:13-44:6, 78:18-79:6.

209. Concerns about autoimmune damage elicited by the effector function of these fusion proteins were real would have discouraged a POSA from combining TNFR with the effector region of an IgG. As reported in Zettlmeissl 1990, which Dr. Blobel failed to consider when formulating his obviousness opinions, "one of the most important issues confronting" Ig fusion proteins was "the extent of autoimmune damage." PTX-26 at 10; 9/12A (Blobel) 81:15-82:3, 82:25-83:13.

210. Given this experience with prior art Ig fusion proteins, a POSA would have expected a fusion protein that combined a TNFR and an IgG could lead to autoimmune damage caused by effector functions, 9/20A (Wall) 39:14-40:9, 56:7-16; 9/18P (Greene) 90:25-91:16, particularly with a fusion protein that lacked the CH1 domain, as in the claimed fusion proteins. 9/20A (Wall) 39:14-40:9, 56:7-16; 9/18P (Greene) 90:25-91:16. Because the scientific evidence led in a different direction, a POSA looking to address an autoimmune condition would have been dissuaded from this counter-intuitive combination. FOF 207-209.

211. Dr. Blobel inappropriately discounted concerns regarding autoimmune damage caused by effector functions, asserting incorrectly that effector functions only resulted when the target protein was membrane bound, and were not a concern with soluble antigens like TNF. 9/12A (Blobel) 81:19-83:19. Dr. Blobel

acknowledged that IgG fusion proteins included all the elements necessary for effector functions and were specifically designed to have cell-killing activity. 9/12A (Blobel) 16:21-17:9; *see, e.g.*, *id.* at 41:8-25. Dr. Blobel acknowledged he was "not an immunologist." 9/12A (Blobel) 67:3-4, 88:13. Dr. Wall, an immunologist with over 30 years of experience teaching and publishing in the field, explained, that because the immune system is designed to respond to both cell-membrane-bound and soluble targets, its effector function would have been a concern with respect to both cell-membrane-bound and soluble targets. 9/20A (Wall) 46:18-50:12. Dr. Wall's testimony was supported by Paul 1989 (PTX-3), Cooke 1985 (PTX-31), and Debets 1988 (PTX-27) references; Dr. Blobel's was unsupported, and the Paul 1989 textbook refuted it. Paul 1989 states the "[d]eposition of immune complexes in local tissues with resultant inflammation is common in rheumatic disease"; It also "recognizes soluble complexes cause inflammation by "activat[ing] the complement cascade" and binding to cell-killing immune cells, PTX-3 at 724, which are involved in pro-inflammatory effector function pathways, as Dr. Wall explained. 9/20A (Wall) 49:6-53:8, 46:18-48:22; *see also* 9/12A (Blobel) 88:17-90:2. Plaintiffs' expert, Dr. Greene, also an immunologist, confirmed that immune complexes bound to soluble forms of TNF would have been expected to activate effector function pathways that result in inflammation. 9/18P (Greene) 125:20-126:11, 137:4-138:6.

212. Not only did Dr. Blobel erroneously opine that only membrane-bound

forms of a protein can lead to effector functions; he also overlooked that by August 1990, it was known that TNF exists in both soluble and membrane-bound forms. 9/12A (Blobel) 90:17-91:1; 9/20A (Wall) 40:10-19, 41:20-42:23; JTX-21 at 1. Both soluble and membrane bound TNF were believed to be biologically active. 9/20A (Wall) 42:24-43:14. Thus, a POSA would have understood that any therapy intended to target soluble forms of TNF would also impact the membrane bound forms of TNF. 9/20P (Wall) 101:22-102:4.

213. Dr. Blobel's reference to prior art disclosing anti-TNF antibodies to show a POSA would not have been concerned about the effector function of Ig fusion proteins reflects an incomplete analysis of the prior art. Dr. Wall testified that based on the art as a whole, including art that Dr. Capon authored, a POSA seeking to treat a pro-inflammatory disease would have been concerned with a fusion protein's pro-inflammatory effector function. 9/20A (Wall) 55:2-12.

214. Contemporaneous references Dr. Blobel did not consider in his initial analysis support Dr. Wall's testimony. 9/12A (Blobel) 78:10-19. Zettlmeissl 1990 reports "one of the most important issues confronting" Ig fusion proteins was "the extent of autoimmune damage." PTX-26 at 10; FOF 197-98. Dr. Blobel admitted Zettlmeissl 1990 "cautions" "when you start making these fusion proteins you need to think about autoimmune damage," 9/12A (Blobel) 81:24-82:3, 82:25-4, and it is something a POSA "can take into consideration for sure," 9/12A (Blobel) 82:4-13.

In August 1990, experimental evidence had shown that CD4 fusion proteins elicited CDC and ADCC. 9/18P (Greene) 88:21-89:1.

215. A POSA would not have ignored the fusion protein experimental evidence in view of references describing the scattered use of anti-TNF antibodies. Two of these references relate to acute conditions where effector function would not have been an issue. 9/20A (Wall) 65:10-13. Only one, Brennan 1989, mentions any potential use of these antibodies for RA, but this was based on preliminary (*in vitro*) studies based on limited data that did not account for effector functions and would not have alleviated the prior art's concerns regarding them. 9/20A (Wall) 25:14-19, 63:15-18. A POSA would have expected that, upon introducing a molecule like the fusion of the Claims (*i.e.*, etanercept) into a system with soluble TNF, it would form immune complexes and elicit a pro-inflammatory effector response. 9/20A (Wall) 50:2-12, 51:1-4; 9/18P (Greene) 90:25-91:16; 135:21-136:8, 137:4-138:6.

216. In addition, the IgG fusion art is different from the claims in a variety of ways, for which there generally were technical reasons. 9/20A (Wall) 84:17-85:3. None used TNFRs, either the p55 or the p75. 9/12A (Blobel) 14:21-23.

217. Capon 1989's constructs retained CH1. JTX-58 at 2; 9/12A (Blobel) 44:6-9. Etanercept does not contain CH1. 9/18P (Greene) 84:10-11. Traunecker used mouse Ig, not human; and did not use IgG1. JTX-25 at 1, Fig. 1. Rather, it used IgM in one construct, and IgG2a in another. *Id.*; *see* 9/18P (Greene) 85:18-20; 9/20A

(Wall) 56:17-23. The claims require human IgG1. 9/11P (Blobel) 29:17-24. Capon 1989 also found that that the affinity—that is, the strength of binding—of his constructs was "indistinguishable" from soluble CD4. JTX-58 at 2, 4. Etanercept, by contrast, binds its target with approximately 50-fold greater strength. 9/18A (Naismith) 116:17-117:6; PTX-140.

218. Traunecker's IgM construct did not have a hinge, in contrast to etanercept; and its IgG2a construct's hinge is different from IgG1's hinge, JTX-25 at 1, Fig. 1, also in contrast to etanercept.

219. Seed '262 embodied three constructs, each of which employed a five-amino acid linker, JTX-57 at 10-11; 9, in contrast to etanercept; and one of which had no hinge, *id.* at 10-11, also in contrast to etanercept. 9/20A (Wall) 79:7-24. Seed '262 emphasized that "[p]referably, any amount of the N-terminus of the immunoglobulin can be deleted as long as the remaining fragment has antibody effector function." JTX-57 5:44-45; 9/12A (Blobel) 55:16-56:13; 9/20A (Wall) 57:23-58:14. Etanercept, by contrast, tends not to exhibit effector functions. 9/18P (Greene) 91:17-92:15; PTX-130.

220. Capon '964 described a variety of fusion embodiments—monomers, dimers, or tetramers—as well as Ig portions of various lengths. JTX-61 at 25-27 (col. 10:60-14:53); 9/12A (Blobel) 64:7-11. Etanercept, by contrast, is only a dimer, with an Ig portion of a specific length. Capon '964 had two preferred embodiments; one

retained CH1, JTX-61 at 28 (col. 15:8-11); 9/12A (Blobel) 68:24-69:2, in contrast to etanercept, and the other had a partial (*i.e.*, two cysteine) hinge, JTX-61 at 28 (col. 15:11-17); 9/12A (Blobel) 69:7-11, also in contrast to etanercept. Capon '964's "particularly preferred" embodiment "contain[ed] the effector function of an immunoglobulin," JTX-61 at 28 (col. 15:4-8); etanercept, by contrast, tends not to exhibit effector functions. FOF 219.

221. Byrn 1990, on which Sandoz's expert Dr. Capon was also an author, had a partial (*i.e.*, two cysteine) hinge, 9/12A (Blobel) 71:16-22, in contrast to etanercept. Byrn 1990 also found that his IgG fusion construct mediated ADCC, JTX-56 at 1-2; 9/12A (Blobel) 70:20-71:15; 9/18P (Greene) 87:12-15, in contrast to etanercept, which tends not to.

222. Karjalainen '827, as noted above, is not prior art, as it was published after the priority date and as Sandoz's experts conceded on cross-examination. It had five examples of fusion proteins; two had no hinge; two had a hinge but did not use IgG1; and only one used IgG1 and a full hinge. 9/12A (Blobel) 84:6-14. Of the seven "[e]specially preferred" fusions, several used Ig other than human IgG1: mouse IgG2a; mouse IgM; human IgM; human IgG3; human IgA1; and human IgA2. JTX-60 at 3:5-8. Etanercept, by contrast, uses only IgG1. Karjalainen '827 also taught that the retained regions of both IgG and IgM "could fix complement—*i.e.*, trigger CDC—leading to "more efficient" killing of targeted cells. JTX-60 at 2:26-27.

Etanercept, by contrast, tends not to fix complement, and is not designed or intended to kill cells. It is designed to do the opposite: interrupt a process by which the body is killing its own cells. 9/17 (Loetscher) 25:17-23; 9/20A (Wall) 39:14-40:3.

223. Watson, which describes in detail one of the two "particularly preferred" fusion proteins identified in the Capon '964 patent, is likewise fundamentally different. As Dr. Wall testified, Watson used the same Ig portion that Byrn 1990 showed, through experimental evidence, to have retained cell-killing effector functions. 9/20A (Wall) 59:12-18. Watson, however, was not concerned with those functions, because it was a probe that used a different receptor (lymphocyte homing receptor) for *in vitro* studies, for which cell-killing effector functions would not be a concern. JTX-59 at 1, 5; 9/20A (Wall) 59:23-60:8. The paper speculated that its construct might be useful to address excess inflammation, JTX-59 at 8, but neither provided nor referenced any experimental results to support that speculation, which was contrary to the prior Ig fusion art as a whole, including the concerns raised in Zettlmeissl 1990. 9/20A (Wall) 61:9-13. Dr. Wall provided a compelling—and unrebutted—reason why Watson's speculation was incorrect: its construct would have had to have been administered before the evidence of inflammation was present, which would not have been practical. 9/20A (Wall) 61:1-8. The authors of Watson themselves recognized that the complexity of immune disorders "may limit the efficacy of any particular blocking reagent as an anti-

inflammatory drug." JTX-59 at 8; 9/20P (Wall) 38:22-39:7.

E. A POSA Would Not Have Been Motivated to Make Any of Sandoz's Six Asserted Combinations

224. To use as a therapeutic, Sandoz asserted three motivations to combine: (1) to make a protein that could be purified by using Protein A; (2) to increase the protein's half-life; and (3) to increase the p75's avidity. 9/12P (Blobel) 27:10-25.

225. During cross-examination, however, Dr. Blobel conceded that a POSA could have achieved each of these three goals by making the chimeric antibody disclosed in Smith '760:

> Q. And in fact, all of these benefits could have been achieved by making the chimeric antibody disclosed in Smith's '760 patent instead of etanercept. Right?
>
> A. In principle, yes.

9/12P (Blobel) 28:1-6. This concession resolves against Sandoz the issue of whether a POSA would have been motivated to combine Smith '760 with any of Dr. Blobel's asserted references to make the fusion proteins of the Claims.

226. That concession is consistent with other record evidence. Dr. Blobel conceded that Smith 760's section regarding "therapeutic administration" of TNF receptors concerned only the soluble receptors, 9/12A (Blobel) 15:7-16:8, suggesting soluble receptors alone would have sufficed for use as a therapeutic. Smith '760's "recombinant chimeric antibody molecule[s]" were different from the Claims in two fundamental respects. They had "unmodified constant region

domains." JTX-65 at 13:10-53-57. And they retained the constant region. *Id;* 9/20A (Wall) 73:20-74:8. Smith '760 expressly states that those constructs, different from the Claims, were appropriate "for use in . . . assay of TNF-R," *id.* at 9 (col. 2:62-66), as well as "directly in therapy to bind or scavenge TNF, thereby providing a means for regulating the immune activities of this cytokine." *Id.* at 10 (col. 3:2-6).

227. Dr. Blobel's testimony that the desire to use Protein A purification techniques would have motivated a POSA to combine Smith '760 with the Ig fusion protein references to make the fusion proteins of the Claims for therapeutic use does not make sense. Protein A purification works by binding to an Ig Fc region, and thus would have worked for Smith '760's unmodified proteins, making modification unnecessary, as Dr. Blobel conceded on cross. 9/12P (Blobel) 27:21-28:14.

228. Sandoz also contended that a POSA would have been motivated to combine the receptor with hinge-CH2-CH3 to enhance the receptor's half-life so it would last longer in the body as a therapeutic molecule for treating inflammatory disorders. As noted above, that ignores that PEG was a more likely partner, and that Smith '760's chimeric antibodies satisfied Dr. Blobel's asserted motivations. In short, Dr. Blobel's obviousness testimony on this alleged motivation assumes much of what Sandoz had the burden to prove, as FF 224-227, above, reflects.

229. Sandoz's argument, presented through both Drs. Blobel and Skerra, that a POSA would have been motivated to create etanercept in an effort to increase the

p75 TNF receptor soluble region's avidity is contrary to the record evidence. This testimony is premised on the proposition that a POSA would have expected a molecule with two binding arms to have higher avidity.

230. The evidence at trial was to the contrary, as Dr. Naismith explained. Based on experimental results with Igs, and with CD4-Ig fusions, a POSA would have expected etanercept to predominantly exhibit what he called "Mode 1" binding—that is, each "arm" of etanercept would, in the vast majority of cases, bind to a separate TNF trimer, rather than both arms binding to the same trimer (Mode 2). 9/18A (Naismith) 110:10-21, 111:14-112:11, 114:11-25. If it did what was expected, there would be no avidity contribution, which requires Mode 2 binding under the rationale of Drs. Blobel and Skerra. *See* 9/11P (Blobel) 100:4-11; 9/24A (Skerra) 45:18-21. In August 1990, a POSA did not have information that would have allowed that person to predict whether etanercept would have the precise arrangement of binding arms necessary to deviate from its expected Mode 1 binding to TNF trimers. *See* 9/18A (Naismith) 110:22-111:8, 111:17-112:5; 9/24A (Skerra) 99:6-10, 99:17-25, 102:3-16, 107:11-18.

231. The experimental evidence of record at the time was consistent with that testimony. Capon 1989 reported that the arms of those fusion constructs were flexible enough to bind with separate gp120 molecules without steric hindrance and "cross-link" different gp120 targets, which showed these bivalent IgG-based fusion

proteins exhibit Mode 1 binding. 9/18A (Naismith) 113:8-114:10; JTX-58 at 2. Capon 1989 reported that the binding strength of both of his CD4-Ig constructs was "indistinguishable" from that of the soluble CD4 receptors. JTX-58 at 2.

232. The testimony of Sandoz expert witness Dr. Skerra that a POSA would have expected etanercept to bind more strongly was based on a protein that had a TNF portion with 185 amino acids, as Sandoz's counsel told him. 9/24A (Skerra) 81:6-14. In fact, etanercept's TNF portion has 50 additional amino acids. *Id.* 81:2-5. On direct, Dr. Skerra suggested this 50-amino-acid difference was a "typographical" error, *id.* 38:13-39:9, but his cross-examination made clear that, in fact, Dr. Skerra's substantive analysis had been based on the wrong molecule, *id.* 81:6-10—and, when asked to consider the right molecule, he testified that that was more likely to bind to two separate TNF trimers, *id.* at 83:7-15, 103:1-25, 104:8-21; that is Mode 1 binding, as Dr. Naismith described it. *Id.* 104:1-10.

233. Dr. Blobel's testimony that Protein A purification techniques would have provided a POSA with a motivation to combine either Smith 1990 or Smith '760 with any of the asserted Ig fusion protein references is inconsistent with the knowledge in the art that such techniques could have equivalently been used with Smith '760's recombinant chimeric antibody molecules, 9/12P (Blobel) 27:21;28:7, as Protein A works by binding to the Fc region which also is present in those molecules, 9/12P (Blobel) 55:8-19.

234. Also, Smith '760 describes a number of conventional methods that could have been used to purify the receptor, including methods that took advantage of the fact that the receptor bound TNF with high affinity. One of the prior art references Sandoz relied on to characterize the state of the art describes the use of such an "affinity" method to purify TNFR "in a rather convenient way." JTX-47 at 1536 (6/7); 9/20A (Wall) 72:22-73:19. This method was actually used by the authors of the paper to purify p75 to homogeneity. 9/20A (Wall) 73:10-17.

235. Dr. Blobel's testimony that removal of CH1 was considered preferable to address "secretion" issues, 79:1-15, is not consistent with the record evidence, because fusion proteins retaining the CH1 domains had been made before and after Traunecker and were even labeled as "particularly preferred." *Id.* 79:20-80:4; JTX-25 (Traunecker) at 1; JTX-61 (Capon '964) at 28 ("particularly preferred" embodiment is a fusion to Fc portion of an antibody).

236. Dr. Blobel's testimony about Smith 1990 in view of Watson assumes much of what Sandoz had to prove.

237. As Dr. Wall explained, Watson used the same construct that Byrn 1990 demonstrated, with experimental results, to retain effector functions, *i.e.*, the tendency to kill targeted cells through both CDC and ADCC. 9/20A (Wall) 59:12-18. Because of that, a POSA would not have been motivated, against intuition, to fuse all (or even a truncated version) of the p75's extracellular region to hinge (full

or partial)-CH2-CH2, with or without a linker. 9/20P (Wall) 103:3-23. Although Watson speculated that its construct might be useful to address excess inflammation, it provided no experimental results or theoretical basis as to why, as the prior Ig fusion art demonstrated, such constructs would not have retained their effector functions, even though they retained the Ig domains known to trigger those functions. 9/20A (Wall) 61:1-13. In addition, as Dr. Wall explained without rebuttal by Sandoz, the Watson construct would not have been practical: it would have had to have been administered before the excess inflammation was apparent, which is effectively impossible. 9/20A (Wall) 61:1-8.

F. Objective Indicia

1. Praise, Unmet Need, Failure of Others, Copying, Licensing

238. The Claims cover etanercept and the parties' methods to make them. 09/11P (Blobel) 15:1-17.

239. Etanercept has been lavishly praised, including by Sandoz, which told the FDA's Arthritis Advisory Committee that etanercept was a drug that had "changed the practice of medicine." 9/14A (McCamish) 41:13-17.

240. At trial, Immunex's expert, Dr. Fleischmann, testified without rebuttal or contradiction by Sandoz that etanercept met a long-felt but unmet need for a safe and effective RA therapy. 9/20P (Fleischmann) 146:20-147:9. Prior art therapies in use since the late 1980s were of limited utility because they typically only treated

symptoms, could not halt disease progression, and had dose-limiting side effects, while methotrexate, approved in 1988 and the most common existing therapy, helped only ~30% of patients, many of whom could not tolerate it for extended periods. 9/20P (Fleischmann) 124:11-125:5, 136:8-137:17.

241. According to a 1991 review article, the long-term outlook for treating RA was "depressing" without "any specific targeted therapy." *Id.* 123:9-124:1; PTX-244 at 4. Enbrel's approval changed that; its efficacy in ~70% of patients, including halting or slowing disease progression (*i.e.*, joint destruction), was hailed as a true "breakthrough." 9/20P (Fleischmann) 139:8-24, 149:2-9, 146:20-147:9, 151:3-17. For example, in one Enbrel study as monotherapy, the improvements were so immediate and pronounced relative to placebo that the study could no longer be characterized as "blinded." *Id.* at 131:1-13. Similarly, the invention of Enbrel ushered in a "new era" for the treatment of juvenile arthritis. *Id.* at 155:7-156:14.

242. Others tried and failed to develop TNF-based RA therapeutics. For example, Dr. Blobel relied on publications from Yeda and the affiliated Weizmann Institute regarding the use of the p55 alone. 9/11P (Blobel) 65:24-67:6; 9/18P (Greene) 109:3-17; JTX-62 at 4; JTX-46; JTX-47. But there is no record evidence that any p55-based therapeutic has ever been approved or even submitted to the FDA, including by Yeda, as a biologic drug to treat RA or any other inflammation disease. Indeed, there is record evidence of failure in that regard, including by

Synergen. 9/20A (Wall) 71:4-14, 86:4-87:1; PTX-123.1 at 1.

243. Sandoz's opening statement conceded Enbrel's clinical/commercial success. 9/11A (Sandoz Opening) 49:20-25. Enbrel's success with the relevant populations—patients and the doctors who treat them—is beyond debate, as confirmed by the unrebutted facts explained by both Drs. Fleischmann and Dr. Vellturo. 9/20P (Fleischmann) 143:8-145:4; 9/21 (Vellturo) 17:10-28:6; PTX-317; 9/20P (Fleischmann) 145:17-146:7.

244. Enbrel was widely prescribed from approval in 1998 onwards, and the number of prescriptions rose rapidly through 2008, despite shortages in supply and the entry of two major competitors, HUMIRA and REMICADE. 9/21 (Vellturo) 14:22-15:19; PTX-317. These successes were driven by etanercept's ability to bind and neutralize TNF (from the p75 component), and its stability in the body (from the IgG component). 9/20P (Fleischmann) 148:16-149:20; 9/21 (Vellturo) 29:2-21.

245. Sandoz copied Enbrel; Sandoz's biosimilar has the exact same primary amino acid sequence and the same higher-order structures. 9/14 (McCamish) 48:10-25; PTX-68 at 35. Sandoz has told physicians and clinicians that they can consider its biosimilar to be just another batch of Enbrel. *Id.* 45:17-22, 46:5-8.

246. According to Sandoz's internal documents, Sandoz did not believe it had to copy Enbrel. Sandoz's efforts to develop its biosimilar version of etanercept began in 2006, before a regulatory pathway existed in the United States for the

approval of a biosimilar drug. 9/14 (McCamish) at 84:15-85:6; JTX-83 (Alliger) at 147:3-5. Sandoz therefore initially chose to copy etanercept, 9/14 (McCamish) 79:8-9; JTX-83 (Alliger) at 105:17-25, and the host cell system used to make etanercept, *Id.* at 141:23-142:12, independent of any guidance from the FDA.

247. Relevant FDA Guidance, proposed during Sandoz's development of its biosimilar, allowed for amino acid sequence differences "such as N or C terminal truncations" that the applicant could demonstrate "will not have an effect on safety, purity, or potency." DTX-931 at 12; *see* JTX-17 ¶ 51. Relatedly, the proposed Guidance allowed "differences between the chosen expression system" if "carefully considered." DTX-931 at 12; *see also* JTX-17 ¶ 52.

248. Sandoz considered the proposed Guidance and developed biologics in which the only difference were single-amino-acid substitutions in the TNFR's N-terminal. 9/14 (McCamish) 59:3-9, 60:9-14, 61:7-10; PTX-698 at 3. Sandoz believed at the relevant time that it could have sought market approval with that single substitution under the then-proposed and now-effective FDA Guidance. *See* JTX-17 ¶¶ 50-51, 58-59, 63-64.

249. Although Sandoz concluded that some of those variants specifically bound human TNF, 9/14 (McCamish) 61:11-13, 63:2-7, it did not pursue developing them because it gave other corporate projects higher priority, *i.e.*, Sandoz thought it would be too expensive, 9/14 (McCamish) 62:3-7; JTX-83 (Alliger) 230:22-231:1,

231:4-5. Sandoz believed that those variants would have been outside of the Roche Patents' scope. PTX-701 at 3-4. Likewise, Sandoz continued to develop, and ultimately sought approval for, a biologic produced using the same host cell expression system as Enbrel. JTX-83 (Alliger) 141:23-142:12.

250. In 1998, Immunex licensed the Roche Patents while they were pending as applications, and thereafter paid tens of millions of dollars in royalties on Enbrel sales. 9/24P (Watt) 23:17-24:5. That license, to an application, demonstrates the real-world strength of the disclosure of these patents and the claims that issued based on that disclosure. *Id.* 23:8-16, 44:4-10, 54:20-55:11.

251. The 1998 license was superseded by the 2004 A&S, which further demonstrates the real-world commercial value of the Roche Patents. In it, Amgen purchased from Roche a paid-up license on future North American sales of Enbrel for an effective price of $82.5 million, despite the risk of substantial competition from HUMIRA, a then-newly approved biologic. 9/24P (Watt) 24:16-27:20, 28:20-29:1, 103:13-104:2; JTX-12 at 7.

2. Unexpected Properties

252. Etanercept exhibits a number of properties that were unexpected based on prior experience with antibodies and CD4:Ig fusions, and in comparison to other antibody-based therapeutics. Etanercept exhibits little to no CDC or ADCC, despite retaining the portions of IgG1 that had been shown by experimental evidence,

including in the Ig/receptor fusion context, to trigger both of those cell-killing effector functions. PTX-130 at 6, 7; 9/18P (Greene) 70:17-71:17, 91:4-22. Etanercept also does not aggregate in the presence of TNF trimers. PTX-140 at 2, 3; 9/18A (Naismith) 114:11-115:23; 9/18P (Greene) 98:17-19. This was unexpected based on prior experimental experience with Igs and CD4:Ig receptor fusions, which not only cross-linked multimeric targets, JTX-58 at 2; 9/18A (Naismith) 113:8-114:10; 9/24A (Skerra) 103:10-23, but also caused CDC and ADCC, necessarily demonstrating they aggregated, which is a predicate to those effector functions, JTX-56; PTX-23; 9/18P (Greene) 86:12-90:1, 91:4-16, 97:23-98:8.

253. Dr. Naismith explained a POSA would not have expected etanercept to bind in "Mode 2"--with both of its p75 TNFR arms binding TNF molecules within one TNF trimer--as opposed to binding in "Mode 1" where each arm would bind a separate TNF trimer. 9/18A (Naismith) 110:10-111:19, 112:6-11. He pointed out that Mode 2 binding requires a precise arrangement between the bivalent molecule and its multivalent target, "really only one," whereas Mode 1 has fewer restrictions and many more binding possibilities. *Id.* at 111:12-112:11. The consequence of Mode 1 binding is aggregation, which was routinely observed for bivalent antibodies. *Id.* at 112:12-113:2. Etanercept unexpectedly does not cause aggregation. *Id.* at 114:11-115:23; 9/18P (Greene) 98:17-19; PTX-140 at 2, 3.

254. Etanercept also exhibited unexpectedly high binding strength and TNF

neutralization compared to soluble TNFR. 9/18A (Naismith) 106:17-25. This comparison is appropriate because a POSA would have expected Mode 1 binding from etanercept. *Id*. 110:13-114:22. A POSA would have not expected etanercept to bind fifty times more strongly to TNF than the soluble receptor, PTX-73 at 4; 9/18A (Naismith) 116:7-117:6, or to exhibit 1000-fold superior TNF-neutralizing properties, PTX-73 at 4; 9/18A (Naismith) 117:7-118:3. If, as the facts showed, a POSA would have expected etanercept to bind in Mode 1, a POSA would not have expected those increases. 9/18A (Naismith) 116:10-16. And prior art Ig fusions exhibit binding that Sandoz's expert Dr. Capon characterized, in his article, as "indistinguishable" from that of the soluble receptor component. JTX-58 at 2.

255. Etanercept's unexpectedly low levels of CDC and ADCC were shown by comparing it to two commercially available anti-TNF antibodies (adalimumab and infliximab) and two fusion protein variants, known as Delta 57 and Protein 3.5D. PTX-6.459; PTX-130 at 6, 7; 9/18P (Greene) 91:17-93:12, 94:13-96:23, 100:10-101:10. Consistent with the expectations of a POSA, the anti-TNF antibodies induced by CDC and ADCC. 9/18P (Greene) 64:19-70:16. Using the prior CD4:IgG fusions for CDC and ADCC comparisons would have yielded the same results: the prior art reported that the CD4:IgG fusion proteins also trigger CDC and ADCC—as expected, because they retained the CH2 and hinge/CH2 junction known to cause those effector functions. *See* FOF 156, 173-74. Thus, based on prior reported

experimental results with antibodies and the prior CD4:Ig fusions, a POSA would have expected etanercept to tend to cause CDC and ADCC, 9/18P (Greene) 70:17-71:2, which it does not, *id.* at 91:17-96:25; PTX 130 at 6-7.

256. Other work shows that the unexpected results associated with etanercept are linked to its specific structure. Molecules having structures similar to etanercept, but incorporating modifications to the p75 component, the hinge domain, and the addition of linker sequences exhibit significant ADCC and CDC activity *in vitro*. 9/18P (Greene) 100:22-101:16; PTX-6.459 at 1-2. These results demonstrate that the unique structure of etanercept is critical to its biological activity and clinical success. 9/18P (Greene) 101:13-16.

257. Colleagues of the Inventors' were concerned that the Ig portion may be pro-inflammatory and harmful in a molecule intended to be anti-inflammatory. JTX-82 (Lesslauer vol. 2) at 14-15 (318:5-13, 318:18-20, 318:23-319:21). During Enbrel's clinical development, rheumatologists also initially expressed hesitancy in using a drug that acted by a novel mechanism of action, and in particular, a drug that targeted TNF, a cytokine which first gained attention as a molecule that could kill tumor cells. 9/20P (Fleischmann) at 144:17-145:20.

258. The testimony from Drs. Blobel and Skerra that a POSA would have expected these properties was not consistent with the contemporaneous evidence. *See* FOF 156, 211-15, 260.

259. Dr. Skerra testified that Dr. Arora's experimental work regarding etanercept was "artificial" and did not reflect how etanercept works in the body. 9/24A (Skerra) 65:10-24. But he admitted on cross-examination that the FDA cited that work in explaining how etanercept works in the body. PTX-915 at 34; 9/24P (Skerra) 7:16-9:20. Sandoz's own testing also showed that "[i]n an assay more closely representing physiological conditions (target cells with low amounts of membrane-bound TNF or endogenously expressing TNF), GP2015 and Enbrel did not mediate ADCC." DTX-403 at 55.

260. Dr. Skerra testified a POSA would have expected etanercept to not cause aggregation in the presence of TNF trimers despite acknowledging the three dimensional shape of the p75 extracellular region and many parameters of how it might bind to TNF were unknown in August of 1990. 9/24A (Skerra) 99:6-10, 99:17-25, 102:3-16, 107:16-18. He admitted that he had not independently investigated the makeup of the etanercept molecule, leading him to erroneously conclude it contained only 185 of the 235 amino acids of p75's extracellular region. *Id.* at 79:12-18, 81:6-14. Dr. Skerra's opinions about etanercept's lack of ADCC and CDC activity were based on his assumptions about its ability to cause aggregation, which, in turn, were based on the same, incorrect protein (i.e., the one lacking 50 amino acids of the p75 extracellular region). *Id.* at 81:6-10. When he attempted to dismiss the significance of those missing 50 amino acids to his opinion,

he was impeached with his deposition testimony, where he testified that a POSA would have expected a version of etanercept that added back in the missing 50 amino acids of his 185-amino acid version of etanercept to cause aggregation. *Id.* at 81:11-82:5, 83:7-15; PTX-1582.

261. The USPTO, including an appeal decision by the Board during prosecution of the Roche Patents, reached these same technical conclusions: these properties were unexpected. PTX-6-6.456 (Board Decision) at 7.

3. Asserted "Simultaneous Invention"

262. Defendants asserted four instances of asserted "simultaneous invention" of etanercept: work done by Dr. Beutler (later, a Nobel Laureate) at the University of Texas; work done by Dr. Ashkenazi at Genentech; work done by Dr. Lauffer of Behringwerke in the course of a collaboration with Immunex; and work done by Immunex's Dr. Goodwin.

263. None of this work qualifies as prior art, as Dr. Blobel recognized. Only Dr. Goodwin made etanercept—months after the priority date. JTX-74 (Goodwin) 53:9-10, 53:12-18, 53:20-22. And Dr. Goodwin made etanercept because he was motivated by non-public data from Behringwerke, available after the priority date, showing a different TNFR fusion protein had 50- to 100-fold "higher affinity" for TNF when compared to the soluble receptor alone. *Id.* at 51:25-52:16, 52:19-20; DTX-90 at 2 ("The inhibition constants of the TNFRFc protein are really

surprisingly low. . .”). That single instance does not suffice to render the Claims obvious. The other three constructs were different from etanercept, and Drs. Greene and Wall testified that the differences would not have made the Claims obvious.

264. Dr. Beutler’s work does not constitute a simultaneous invention. Contrary to etanercept, his fusion protein: used the p55 receptor rather than the p75; used mouse IgG rather than human; used a partial, two-cysteine hinge rather than the full, exon-encoded, three-cysteine hinge; and contained what his patents called a “specifically cleavable linker [] functionally interposed” between the hinge and CH2 that constituted six extra amino acids. JTX-67 at 15 (col. 7:5-8); JTX-68 at 1; 9/18P (Greene) 103:12-21; 9/20A (Wall) 89:19-90:1; 9/12P (Blobel) 33:8-34:13. As Dr. Greene testified at trial, without rebuttal or contradiction by Sandoz, there were technical reasons for such choices. Experimental evidence before the priority date that reported that the p55 inhibits TNF significantly more than p75. 9/18P (Greene) 108:21-109-24, 113:2-15; JTX-47 at 3 (Table 1). Dr. Capon testified that the p55 was “a completely different gene product and a completely different protein, very different from p75” from the p75. 9/13A (Capon) 69:15-17. As Dr. Greene explained, the linker would have allowed the fusion to be turned off by separating the receptor and Ig components, in case effector functions were an issue. 9/18A (Greene) 109:25-110:14. Dr. Blobel admitted it would have been “not so obvious” to choose a two-cysteine hinge over a three-cysteine hinge, and Dr. Beutler’s choice

confirmed this. 9/12P (Blobel) at 34:8-9; 39:24-40:11. Dr. Beutler declared that he did not invent the fusion protein of the Claims. PTX-1545 at 1-2, ¶ 4.

265. Defendants submitted a paper, a patent, and three declarations from Dr. Beutler in an apparent attempt to show that his work was before the priority date, but defendants failed to prove that. Dr. Beutler's paper (Peppel 1991), whose lead author was Peppel, was not received for publication until August 8, 1991, nearly a year after the priority date. JTX-68. His patent, US Patent No. 5,447,851, was not filed until April 1992, some 19 months after the priority date. JTX-67; 9/12P (Blobel) 32:6-22. His August 18, 2017 declaration, obtained by Sandoz during this litigation, placed his "invention" of his fusion—he did not define what he meant by "invention"—in a sixteen-month window between August 11, 1990 and December 1, 1991, but did not include any dated documents to corroborate that assertion. DTX-1164 at 2; 9/12P (Blobel) 90:16-91:9. Dr. Beutler's July 22, 1993 declaration, submitted during prosecution of his patent, stated that he conceived of his fusion protein "prior to December 1991," without reaching back to August 1990, but again attached no dated documents to corroborate that. DTX-658. Finally, in his June 19, 2017 declaration, submitted in opposing Sandoz's request to depose him, Dr. Beutler stated that he conceived of his fusion proteins "in or around 1991." PTX-1546 at 3; PTX-1545; 9/12P (Blobel) 93:2-94:19. Based on that record, the Court must conclude that Sandoz has failed to show a prior invention by Dr. Beutler, and that

his work does not constitute a "simultaneous invention."

266. In addition, Dr. Blobel's testimony failed to account for a POSA's knowledge. The Patents-in-Suit claim priority to the EP707 Application, filed on August 31, 1990 and published on March 20, 1991. JTX-6; JTX-7 (certified translation); 9/18A (Naismith) 41:3-22. The EP707 Application discloses p55 and p75/Ig fusion proteins where, as in the Claims, the Ig component is made of "all the domains except the first of the constant region of the heavy chain." JTX-7 at 2 (Abstract, entry 57). The specification of this European patent application is essentially the same as the specification of the Patents-in-Suit. 9/18A (Naismith) 41:14-22. Thus, as of its publication on March 20, 1991, a POSA would have been aware of TNF receptor/IgG fusion proteins that used, as the Ig component, "all of the domains except the first of the constant region of the heavy chain." Based on the record, Sandoz has not proved that Dr. Beutler's work came before March 1991.

267. Like Dr. Beutler and his colleagues, Dr. Ashkenazi and colleagues at Genentech did not make etanercept. Rather, their fusion constructs, like Dr. Beutler's used the p55 receptor and a truncated, partial hinge that contained only two cysteines. JTX-69 at 2; 9/12P (Blobel) 39:9-23, 50:11-51:4; 9/18P (Greene) 103:25-104:3; 9/20A (Wall) 89:9-18. As noted above, Dr. Greene testified without rebuttal or contradiction by Sandoz that there were sound technical reasons to have selected the p55 receptor rather than the p75—which may explain why both a future

Nobel Laureate and a premier biotechnology company were both focused on p55 rather than p75. 9/18P (Greene) 108:21-109:17. In short, neither the contemporaneous art nor the contemporaneous artisans treated p55 and p75 as interchangeable or as obvious variants of one another. And, again, Dr. Blobel admitted on cross-examination that it would have been "not so obvious" to choose a three-cysteine hinge over a two-cysteine one. 9/12P (Blobel) 34:5-13; 39:24-40:11.

268. The Genentech work on which Dr. Blobel relied was first submitted for review on June 13, 1991, JTX-69 at 1—nearly a year after the priority date of August 30, 1990. And Dr. Blobel's testimony failed to account for a POSA's knowledge gained by the March 1991 publication of the EP707 Application.

269. Based on his deposition testimony played at trial and the contemporaneous written record, the construct that Behingwerke's Dr. Lauffer conceived and made was not etanercept. His construct, like Dr. Beutler's, added a linker that functionally facilitated the joining of the two fusion components. JTX-78 (Lauffer) 112:22-113:07; 9/12P (Blobel) 50:24-51:4; 9/18P (Greene) 104:8-16; 9/20A (Wall) 88:14-23; PTX-6.321 at 2.

270. Dr. Lauffer also deleted the last five amino acids of the C terminus of the TNF receptor portion. JTX-78 (Lauffer) 112:22-113:07; 9/12P (Blobel) 50:20-23; 9/18P (Greene) 104:8-16; 9/20A (Wall) 88:14-23; PTX-6.321 at 2. Dr. Blobel tried to minimize these differences, but as explained above (FOF 184), there were

technical reasons for an artisan to have included a linker. They also demonstrate the different choices that a POSA would have made other than the ones that lead to the claimed inventions. Even if Dr. Blobel's testimony removal of linker sequences would have been obvious "to prevent antigenicity," 9/12A (Blobel) 32:2-9, this is irrelevant because Dr. Lauffer's construct is admittedly not prior art. 9/12P (Blobel) 41:10-16. Moreover, concerns about problems caused by unnatural amino acid sequences, would have led POSA away from making a fusion protein in the first place, as Dr. Wall explained. 9/20A (Wall) 80:7-14.

271. Dr. Lauffer also deleted the last five amino acids of the C terminus of the TNF receptor portion. JTX-78 (Lauffer) 112:8-21; 9/12P (Blobel) 50:20-51:4; 9/20A (Wall) 88:14-23; PTX-6.321 at 2. Dr. Blobel tried to minimize these differences, but as explained above (FOF 184), there were technical reasons to have included a linker. This was among the many choices that a POSA would have to have made to arrive at the Inventions. Dr. Blobel testified that removing linker sequences would have been obvious "to prevent antigenicity," 9/12A (Blobel) 32:2-9, but Dr. Lauffer's construct is not prior art. 9/12P (Blobel) 41:10-16. Moreover, concerns about problems caused by unnatural amino acid sequences would have led a POSA away from making a fusion protein in the first place, as Dr. Wall explained. 9/20A (Wall) 55:19-54:10; 80:12-14.

272. Dr. Blobel never provided a reason why it would have been obvious for

a POSA to use the full extracellular region rather than a truncated version, as Dr.Lauffer did. FOF 159. Based on the record, that never occurred to Dr. Lauffer or anyone else at Behringwerke over this project's many months.

273. Defendants also appeared to suggest at trial that Dr. Lauffer conceived or and perhaps even made his construct before the priority date. Defendants waived and conceded that Dr. Lauffer's work is not § 102(g) defenses, D.I. 597, which its counsel confirmed at trial, 9/11P 94:1-4.

274. Nor does the July 1990 letter (DTX-114) show the conception or the reduction to practice of any fusion protein, let alone any Claim, before August 31, 1990. Although the letter makes reference to "TNFR:Fc," it fails to provide any information that identifies the specific structure of the protein. 9/12P (Blobel) 45:7-10; 9/18P (Greene) 106:2-25. The reported test results do not prove the presence of a fusion protein because the testing lacked controls sufficient to determine what was actually in the test tube. 9/18P (Green) 106:2-25. Indeed, the finding that binding with the test molecule was "comparable" to soluble TNF-R (*i.e.*, a non-fusion protein) (DTX-114 at 1) is consistent with the conclusion that the tube contained soluble receptor, because as Dr. Blobel testified, a dimeric TNF-R Ig fusion protein would have been expected to exhibit significantly higher binding affinity than TNF-R alone. 9/11P (Blobel) 99:20-100:23.

275. The PTO considered this issue, having been supplied the October 1989

meeting minutes and July 1990 letter. JTX-3.1; JTX-4.1; 9/12P (Blobel) 51:5-8.

XIV. SANDOZ HAS FAILED TO PROVE THE PATENTS-IN-SUIT INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

276. Sandoz has failed to prove that the Claims are invalid for obviousness-type double patenting ("ODP"), whether based on the '279 Patent, the Jacobs '690 patent, or the Finck Patents.

A. '182 Patent Claims Aare Not Invalid in Light of the '279 Patent

277. As Defendants stipulated that the safe harbor set forth in the third sentence of 35 U.S.C. § 121 protects the claims of the '522 Patent from an ODP challenge based on the claims of the '279 Patent, 9/21 9:7-16, Defendants challenge only '182 Patent's Claims in light of the '279 Patent.

1. '279 Patent Not ODP Reference as per § 121 Safe Harbor

278. The unrebutted testimony of Steven G. Kunin establishes that the '182 Patent, like the '522 Patent, is also protected by the § 121 safe harbor from an ODP challenge based on the '279 patent.

279. The § 121 safe harbor protects applicants from the unfairness of facing ODP challenges when they are forced to pursue inventions in separate patent applications as a result of a restriction requirement. 9/21 (Kunin) 70:25-71:7.

280. The examiner issued a restriction requirement during the prosecution of the '640 application, which issued as the '279 patent—the parent of the '182 Patent. 9/21 (Kunin) 83:5-84:16; JTX-9 at 116-20. The examiner determined that

p55 and p75 proteins were patentably distinct inventions and thus that claims to those proteins had to be pursued in separate applications. 9/21 (Kunin) 83:25-84:16; JTX-9 at 118-19. The examiner never allowed claims to the genus covering both p55 and p75 to issue, which means the examiner's "election of species" requirement constitutes a restriction requirement. 9/21 (Kunin) 84:17-22.

281. The '182 Patent issued from an application that was filed as a divisional of the '640 application. 9/21 (Kunin) 85:15-22; PTX-6.14.

282. The divisional application was filed after the restriction requirement, 9/21 (Kunin) 85:23-86:2, and the applicants expressly referred to the restriction requirement in filing their divisional application. JTX-3 at 9. In addition, Mr. Kunin testified without contradiction that the claims of the '182 Patent could not have been pursued with the claims of the '279 patent, based on the restriction requirement. 9/21 (Kunin) 86:3-7. Accordingly, the '182 Patent issued from a divisional application that was filed as a result of a restriction requirement.

283. There is no dispute that, although the original claims of the '790 application were *not* consonant with the restriction requirement, the issued claims of the '182 Patent *are* consonant. 9/21 (Kunin) 88:11-89:6. The only dispute is whether an applicant can amend claims during prosecution to overcome an ODP rejection and obtain the protection of the safe harbor.

284. Mr. Kunin testified without contradiction that the PTO permits

applicants to amend claims to bring them into consonance with a restriction requirement. 9/21 (Kunin) 76:21-78:1. Indeed, prosecution is an iterative process in which applicants are expected to amend claims to overcome rejections on any number of grounds, including rejections based on ODP. *Id.* at 77:15-78:1. To confirm his understanding of PTO procedure, Mr. Kunin did a case study of the file histories involved in *Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc.*, 592 F.3d 1340 (Fed. Cir. 2010). 9/21 (Kunin) 78:2-7. In those file histories, Mr. Kunin found that the PTO permitted an initial lack of consonance to be cured through amendment, following an ODP rejection. 9/21 (Kunin) 80:19-82:14. The application of the safe harbor in the *Boehringer Ingelheim* file histories was consistent with Mr. Kunin's understanding of PTO procedure 9/21 (Kunin) 82:6-14.

285. As in *Boehringer Ingelheim*, the '182 Patent applicants amended claims to bring them into consonance after an ODP rejection. 9/21 (Kunin) 89:7-90:9; PTX-6.280 at 9; PTX-6.332 at 5-6. Consistent with the restriction requirement, the '182 Patent claims proteins incorporating a portion of p75, whereas the '279 patent claims proteins incorporating a portion of p55. 9/21 (Kunin) 88:19-24.

286. Because the '182 Patent is protected by the § 121 safe harbor, Sandoz cannot advance an ODP challenge based on the '279 patent. 9/21 (Kunin) 91:17-22.

2. Claims Patentably Distinct from Claim 5 of the '279 Patent

287. Defendants' ODP challenge is based solely on claim 5 of the '279

Patent. JFPTO at pp. 30-32.

288. The '182 Patent Claims differ substantially from Claim 5 of the '279 patent, which incorporates p55 instead of p75. 9/18P (Greene) 111:9-113:15; 9/11P (Blobel) 123:7-12. Sandoz acknowledges that p55 is "an entirely different receptor" from p75. D.I. 603 at 1.

289. A POSA would not have been motivated to replace p55 with p75 because, as between the two receptors, a POSA would have preferred p55. 9/18P (Greene) 109:18-24. Contemporaneous scientific data demonstrated that the p55 extracellular domain was five times more active as a TNF inhibitor. 9/18P (Greene) 108:21-109-24, 113:2-15; JTX-47 at 3 (Table 1).

290. p55 and p75 were also known to be very different proteins even though they both bind to TNF. 9/18P (Greene) 111:9-113:15, 114:5-8. Dr. Capon agreed that they are "completely different." 9/13A (Capon) 69:13-18. The immune system recognizes p55 and p75 as distinct. 9/18P (Greene) 111:20-112:4. Their extracellular regions also have very different amino acid sequences. 9/18P (Greene) 112:7-23 ("they are 70 to 75 percent different."). The amino acid sequence of p55 is more related to nerve growth factor than it is to p75. *Id.* at 112:16-20. They also have different biological functions as evidenced by the difference in their ability to inhibit TNF. 9/18P (Greene) 113:2-15.

291. The PTO also concluded that p55 and p75 are patentably distinct:

> The proteins are unobvious in view of each other, they have no common core sequence, this difference in primary sequence predicts a difference in tertiary structure. The difference in structure would affect the folding of the protein. These folding characteristics and sequences are not obvious in view of one another therefore they are novel and patentably distinct, from one another.

JTX-9 at 118; *see also* 9/21 (Kunin) 83:5-84:16.

292. Furthermore, the '279 Patent's claim 5 encompasses a broad genus of TNFR portions to be used in the fusion protein, namely, "a soluble fragment of the insoluble TNF receptor protein." JTX-5 at 20. Claim 5 reads on a p55 extracellular domain fragment of any size that binds TNF. *Id*.; 9/21 (Kunin) 86:25-87:4.

293. Sandoz thus did not prove, by clear and convincing evidence, that the '182 Patent Claims would have been obvious in light of claim 5 of the '279 patent.

B. The Roche Patents Are Not Invalid in Light of Immunex's Patents

1. Immunex's Patents are Not Proper ODP References

294. Sandoz has failed to prove by clear and convincing evidence that the three Finck patents or Jacobs '690 patent (together, the Immunex Patents) are available as ODP references to the Patents-in-Suit.

295. The Patents-in-Suit and Immunex Patents do not share any common inventors. *Compare* JTX-1 & JTX-2, *with* JTX-39, JTX-40, JTX-41, & JTX-42.

296. The Immunex Patents are assigned to Immunex, JTX-39; JTX-40; JTX-41; and JTX-42, and it is undisputed that Immunex did not own the Roche Patents, or the applications from which they issued, at the time the any of the inventions of

the Immunex Patents were made. JTX-13 at 9 (§ 3.1); 9/24P (Watt) 22:4-10. The Jacobs '690 Patent is also assigned to Immunex, JTX-42 at 1, and it is undisputed that Immunex did not own the Roche Patents, or the applications from which they issued, at the time that any of the inventions of the Jacobs '690 Patent were made.

297. Sandoz has not argued that the Immunex Patents are available as ODP references if the Court decides that ODP based on "common ownership" requires (1) that such ownership must exist *at the time of invention*, and/or (2) that the reference patent and asserted patents must be *entirely owned* by the same entity.

298. Even if the Court were to adopt Sandoz's theory that ODP can arise based on a license agreement entered into many years after the inventions were made—which the Court has not (*see* CoL VII., VIII.)—Sandoz has failed, in any event, to prove by clear and convincing evidence that Roche transferred "all substantial rights" to the Patents-in-Suit under the 2004 A&S in light of the intentions of the parties and the substance of what was granted under that agreement.

a. The parties to the 2004 Accord and Satisfaction did not intend to assign away the Roche Patents

299. Based on its substance and his demeanor, Mr. Watt's testimony regarding the parties' intent to maintain a license relationship with regard to the patent applications from which the Patents-in-Suit issued was credible, supported by Roche's Mr. Parise, and unrebutted.

300. Amgen did not seek an assignment from Roche in 2004, because

Amgen wanted to maintain a license relationship. 9/24P (Watt) 29:9-31:5. In particular, Amgen wanted Roche to retain ownership of the patents so that Roche would have a duty to disclose information to the PTO during prosecution and an obligation to participate in litigation as a party. *Id.* Amgen did not want to rely on a mere contractual duty to cooperate, particularly because it anticipated—correctly—that Roche and Amgen, having recently concluded hard-fought patent litigation involving a different product, would be adverse to one another in patent litigation again shortly after the 2004 A&S was executed. *Id.* at 30:6-31:14.

301. As Mr. Watt testified, the 2004 A&S reflects the parties' intent to maintain a license relationship. 9/24P (Watt) 32:7-10. Whereas Wyeth was assigned Roche patents outside North America, *id.* at 27:24-28:5; JTX-12 at 3 (§ 2.1), Immunex was granted an exclusive license to the U.S. Roche Patents.[4] 9/24P (Watt) 28:20-29:1; JTX-12 at 4 (§ 3.1).

302. John Parise, who was involved in the 2004 negotiations on behalf of Roche, similarly testified that the Roche Patents-in-Suit were licensed under the 2004 A&S because Amgen and Immunex did not want all rights; they preferred a license. JTX-80 (Parise) 62:21-24, 66:19-23; 67:1-5.

b. Under the 2004 Accord and Satisfaction, Roche

[4] The 2004 A&S granted a license to "Amgen and its Affiliates," JTX-12 at 4 (§ 3.1), but all rights were consolidated and granted to Immunex under a later intra-company agreement. 9/24P (Watt) 29:2-8; JTX-14.

retained substantial rights to the Patents-in-Suit

303. In addition, Roche retained substantial rights to the Roche Patents-in-Suit under the 2004 A&S, and a number of provisions are in fact inconsistent with an intent to convey all rights but are consistent with a license.

304. One substantial right that Roche retained was the right to practice the patents for internal, non-clinical research. JTX-12 at 4 (§ 3.2). This right was valuable—e.g., allowing Roche to do research to develop a next-generation etanercept molecule—and Roche insisted on retaining it. 9/24P (Watt) 32:14–33:25.

305. Another substantial right that Roche retained was the right to sue infringers, control such litigation, and collect any damages in the event that Immunex failed to rectify infringement within 180 days of receiving notice from Roche. JTX-12 at 6 (§ 3.6). Because Roche's right to rectify infringement after 180 days' notice to Immunex was "solely within the control of Roche," and because Immunex had a duty to then "cooperate with Roche in any such suit," Immunex could not moot such litigation brought by Roche by subsequently granting the defendant/infringer a sublicense. *Id.*; 9/24P (Watt) 39:2-25.

306. Another substantial right that Roche retained was the right to choose its partner under the license agreement, *i.e.*, the absolute right to refuse to consent to Immunex's assignment of *Immunex's* licensed rights—including, for example, the right to direct prosecution—to an unrelated third party. JTX-12 at 14 (§ 11.4);

compare id. (§ 11.5, providing that Wyeth, a party to the agreement with regard to ex-North American patents, could freely assign those patents).

307. Roche also retained the right to insist upon additional consideration in the event that Immunex sought an assignment. JTX-12 at 5 (§3.3). That the agreement sets forth certain terms and conditions upon which the parties might transfer ownership in the future further confirms that the parties did not intend to transfer ownership upon execution. JTX-80 (Parise) at 107:13-15; 107:18-108:02.

308. Mr. Watt's unrebutted testimony also establishes that there are provisions in the 2004 A&S that were included to protect Immunex as a licensee but would not have been necessary if Immunex had been granted an assignment. For example, § 5.3 protects Immunex's customers from an infringement suit brought by Roche. JTX-12 at 7. Mr. Watt testified that this would not have been needed if Roche had assigned the patents, because Roche would not have been able to sue anyone. 9/24P (Watt) 40:20-41:16. Similarly, § 11.1 protects Immunex's license to the Roche patents in the event of Roche's bankruptcy. JTX-12 at 13. This, too, would not have been needed if the patents had been transferred to Immunex outright, because the patents would no longer be Roche assets over which a bankruptcy trustee could assert control. 9/24P (Watt) 41:17-42:11.

309. In light of the parties' intentions and the rights granted under the agreement, the 2004 A&S did not transfer "all substantial rights" in the Roche

Patents-in-Suit to Immunex, and Sandoz has failed to prove, by clear and convincing evidence—even under its novel theory of "common ownership"—that the Immunex Patents and Patents-in-Suit are or ever were "commonly owned."

2. The Roche and Immunex Patents' Claims Are Distinct

a. The Claims of the Roche Patents are patentably distinct from the claims of the Finck Patents'

310. The Finck Patents are all post-GATT patents, expiring 20 years from their earliest filing date because they were filed after June 8, 1995. JTX-39; JTX-40; JTX-41. The claims of the Finck patents are generally directed to methods of treating psoriasis and psoriatic arthritis using etanercept. JTX-39; JTX-40; JTX-41.

311. The Claims differ from the claims of the Finck Patents because they cover etanercept and a method of making etanercept, rather than a method of treating psoriasis or psoriatic arthritis. JTX-1 and JTX-2.

312. The examiner of the Finck patents was aware of the disclosure of the Roche Patents-in-Suit when he allowed the Finck patents to issue. JTX-39 at 1; JTX-40 at 1; JTX-41 at 1.

313. Sandoz has failed to offer any evidence to suggest that the inventions of the '182 Patent (etanercept) and the '522 Patent (a method of making etanercept) are patentably indistinguishable from the inventions of the Finck patents (methods of treating psoriasis or psoriatic arthritis using etanercept) when the claimed inventions of each patent are considered as a whole.

314. Instead of addressing the patentable distinctness of the claimed inventions as a whole, Sandoz only offered expert testimony to the effect that a particular element "disclosed" in the Finck patents—"TNFR:Fc"—renders obvious the inventions of the Roche Patents-in-Suit. 9/11P (Blobel) 36:16-40:1; 42:21-44:23, 9/12P (Blobel) 74:11-18.

315. But neither Dr. Blobel nor any other witness ever testified that the inventions claimed in the Roche Patents-in-Suit are essentially the same as—*i.e.*, patentably indistinct from—the inventions claimed in the Finck patents, even under the one-way test for patentable distinctness.

316. The Roche Patents' issuance did not effect an unjustified timewise extension of the Finck Patents. The Roche Patents' longer term is due to the governing law. *See* 35 U.S.C. § 154(c)(1). Moreover, one who practices the '522 Patent's claimed invention to make etanercept would not, without more, infringe the Finck patents, because merely making etanercept would not result in treating psoriasis. JTX-2 at 45-46. And one could practice the Finck Patents without infringing all of the Claims in the Roche Patents-in-Suit. For example, one could make etanercept using a host cell other than a CHO cell, as required by claim 10 of the '522 Patent, and use that etanercept to treat psoriasis or psoriatic arthritis. JTX-2 at 48 (claim 10).

317. The objective evidence supporting the nonobviousness of the Claims,

discussed *infra* at CoL 57, also supports the conclusion that the Claims would not have been obvious in light of the Finck Patents' claims.

318. Moreover, Sandoz has not proven, or attempted to prove, that the Roche Patents-in-Suit are invalid under the two-way test for patentable distinctness.

319. The Finck Patents share no common inventors with the Roche Patents-in-Suit and thus could not have been prosecuted in a single patent application. JTX-1; JTX-2; JTX-39; JTX-40; JTX-41.

320. Sandoz's ODP theory based on the Finck Patents depends entirely on Immunex's asserted control over the applications leading to the Roche Patents-in-Suit beginning with the execution of the 2004 A&S. It is undisputed that the Finck Patents were not available as ODP references while Roche controlled prosecution.

321. Mr. Watt testified without contradiction that Immunex "worked diligently" to get the applications leading to the Roche Patents-in-Suit to issue as soon as Immunex took over prosecution. 9/24P (Watt) 104:15-22; *see also id.* at 104:23 (counsel for Sandoz acknowledging, "You certainly did.").

322. In light of the applicant's undisputed diligence during the relevant period, any delay in the'182 Patent's issuance from the time Immunex took over prosecution was solely attributable to the USPTO, and in particular to the examiner's repeated issuance of unjustified rejections, which forced the applicants to pursue a successful but time-consuming appeal to the PTO Board, which reversed all grounds

for rejection that the examiner advanced. PTX-6.456. Even before Immunex had taken over, the USPTO delayed examination by, at one point, losing the file for application leading to the '182 Patent for roughly two years. 9/21 (Kunin) 105:2-18.

323. Likewise, in light of the applicant's undisputed diligence during the relevant period, any delay in the issuance of the '522 Patent from the time Immunex took over control of prosecution was solely attributable to the USPTO, in particular to the examiner's issuance of unjustified rejections and failure to engage in substantive examination of the claims. Although the applicants did not have to pursue a separate appeal in the '522 Patent's prosecution, they did face similar rejections, which they overcame by citing the Board's decision. JTX-4 at 4994, 4985-93, 4952-82 (March 15, 2011 submission)[5]; *see id.* at 4952 (noting that the "claimed subject matter [had] been pending for nearly eleven years" and that applicants had attempted to "expedite" and "advance prosecution," but that the examiner had maintained rejections that were unjustified for the reasons identified by the Board). In addition, the relevant Technology Center Director at the USPTO sent a letter to the applicants on August 11, 2010 acknowledging that the examiner had issued only one substantive office action in more than five years, and directing the examiner to "treat this application as special and expedite its prosecution to

[5] The pages in the certified file history are out of order but have been cited in the order in which they would have been submitted.

conclusion." JTX-4 at 4239-40. Even before Immunex had taken over, the USPTO delayed examination by, at one point, failing to act on the application for a period of several years, leading the applicants to submit six status inquiries in an effort to advance prosecution. 9/21 (Kunin) 104:21-105:1; JTX-4 at 354-55.

324. Because the USPTO is responsible for any relevant delays in prosecution, the two-way test for patentable distinctness applies. Sandoz did not offer any evidence to suggest that the Claims would be invalid for ODP under the two-way test.

325. Sandoz has failed to prove by clear and convincing evidence that any of the Claims are invalid for ODP based on the Finck Patents' claims, under either the one-way test or the two-way test for patentable distinctness.

b. The Claims of the Roche Patents are patentably distinct from Claim 3 of the Jacobs '690 Patent

326. ODP challenge with regard to the Jacobs '690 Patent is based solely on claim 3 of that patent. JFPTO at p. 29, ¶¶ 108-09 and 111.

327. Claim 3 does not cover etanercept or its use because etanercept is not a "chimeric antibody" having a "constant domain of an immunoglobulin molecule." 9/12P (Blobel) 68:6-18. Etanercept does not have any light chains or the CH1 of the heavy chains. 9/12P (Blobel) 20:11-17, 70:12-15.

328. A "chimeric antibody" as described in the Jacobs '690 patent specification (as well as in the Smith '760 patent) has an antibody structure with four

chains (two heavy chains and two light chains), where the variable regions of either or both the heavy and light chains are substituted with the sequences of a TNFR. JTX-42 at 7:42-46; JTX-65 at 10: 53-57; 9/20A (Wall) 91:8-92:3, 118:3-23; 9/11P (Blobel) 72:14-74:25; 9/12A (Blobel) 23:20-25:19.

329. The "constant domain of an immunoglobulin molecule," as recited in Jacobs '690 Patent's claim 3, includes the CH1, hinge, CH2, and CH3. 9/12P (Blobel) 69:15-70:7. In construing claim 3, Dr. Blobel incorrectly assumed that it covers etanercept because the specification discloses etanercept in Figure 1 and the Examples. 9/12P (Blobel) 63:22-64:24. But the Jacobs '690 Patent's specification does not equate a chimeric antibody to a TNFR:Fc, as shown in Figure 1.

330. When viewed as a whole, the file history of the Jacobs '690 Patent does not support construing claim 3 to cover the use of etanercept.

331. The Jacobs '690 patent issued from a continuation-in-part application of the Smith '760 patent. JTX-42 at p. 1; 9/12P (Blobel) 62:14-17. The references to etanercept and the TNFR:Fc fusion were added to the specification when the continuation-in-part was filed in 1992. 9/24P (Watt) 100:1-11, 101:18-23. Although Immunex attempted to get claims to the fusion protein in the prosecution of the Jacobs '690 Patent, the examiner rejected them because the disclosure of the fusion protein was added too late. *Id.* at 100:12-17.

332. During prosecution of the Jacobs '690 Patent, Immunex initially

attempted to obtain a method claim reciting TNFR:Fc. DTX-18 at 17. This claim was numbered application claim 6 during prosecution. *Id.*

333. However, in response to the examiner's prior art rejection, Immunex, on May 23, 1996, cancelled application claim 6 (and other claims) in order to receive the priority date of the Smith '760 patent and to overcome the examiner's prior art rejection. DTX-18 at 294, 298-301.

334. An interview summary from 8/96 specifically recorded that "Applicant agreed to amend [the] claim language to receive priority date." DTX-18 at 388. No claim reciting TNFR:Fc issued in the Jacobs '690 patent. JTX-42 at 26-27.

335. In reaching his conclusions, Dr. Blobel incorrectly relied on a single paper in the file history prior to the cancellation of application claim 6 and ignored the rest. 9/11P (Blobel) 49:17-51:6; DTX-55 at 5. He also incorrectly relied on the Enbrel label in assuming that claim 3 covers etanercept. 9/12P (Blobel) 67:15-68:3.

336. Immunex properly listed the Jacobs '690 Patent on Enbrel's label because it reasonably believed that claims 2 and 5 cover etanercept's use. 9/24P (Watt) 44:17-45:25. Claim 3 did not contribute to Immunex's decision to maintain the Jacobs '690 Patent on the Enbrel label. *Id.* 46:1-4.

337. There would be no motivation to modify the "chimeric antibody" of Jacobs '690 Patent's claim 3—as with the "chimeric antibody of the Smith '760 patent—to arrive at the Claims. *See* FOF 205.

338. Likewise, the objective evidence supporting the non-obviousness of the Claims, discussed FOF XIII.F, also supports the conclusion that they would not have been obvious in light of claim 3 of the Jacobs '690 Patent.

PLAINTIFFS' CONCLUSIONS OF LAW

I. SANDOZ HAS NOT OVERCOME THE VALIDITY PRESUMPTION

1. The Patents-in-Suit and each Asserted Claim are presumed valid. 35 U.S.C. § 282(a); *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 110-14 (2011). Sandoz has not overcome this presumption by clear and convincing evidence.

II. THE PATENTS-IN-SUIT DESCRIBE THE CLAIMS

2. The specification of each Patent-in-Suit must "contain a written description of the invention." 35 U.S.C. § 112. In other words, it must reasonably convey to a POSA that the inventor possessed the claimed invention as of the filing date. *Ariad Pharm. Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). Examples or actual reduction to practice are not required. *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014). Written description is a question of fact. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991).

3. The written description inquiry "must be applied in the context of the particular invention and the state of the knowledge." *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005) (internal citations omitted).

4. "[A] patent need not teach, and preferably omits, what is well known in the art." *Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006). Where

"accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences…, satisfaction of the written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences." *Id.* at 1368; *see also Capon*, 418 F.3d at 1358. Identifying a protein via a partial amino acid sequence and other biological characteristics suffices. *Yeda Research & Dev. Co. v. Abbott GmbH & Co.,* 837 F.3d 1341, 1345-46 (Fed. Cir. 2016).

5. Written description is also satisfied by reference to the placement of biological material in a public depository. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 965 (Fed. Cir. 2002). If described in the application as-filed, such material may be deposited at any time before issuance. *In re Lundak*, 773 F.2d 1216, 1222 (Fed. Cir. 1985); *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.").

6. The Patents-in-Suit satisfy the written description requirement because the Patent Disclosure reasonably conveys to a POSA that the Inventors possessed the inventions of the Asserted Claims. FOF 85-109. Sandoz has failed to show the lack of any necessary disclosure that would convince a POSA otherwise. FOF 124-142. On the record as a whole, Sandoz has failed to prove by clear and convincing evidence that either of the Patents-in-Suit lacks adequate written description relative to its Asserted Claims.

III. THE PATENTS-IN-SUIT ENABLE THE CLAIMS

7. The specification of each Patent-in-Suit must also contain a written description "of 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. In other words, it must teach a POSA "'how to make and use the full scope of the claimed invention without undue experimentation.'" *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1378 (Fed. Cir. 2009) (quotations omitted). Enablement is a question of law based on underlying facts. *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991).

8. Relevant factors to weigh in assessing undue experimentation include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

9. Biological material deposited before issuance and publicly available after issuance will meet the enablement requirement. *Lundak*, 773 F.2d at 1223.

10. The Patents-in-Suit satisfy the enablement requirement because they teach a POSA in sufficient detail to make and used the claimed inventions without undue experimentation. FOF 110-123. Sandoz has failed to prove by clear and

convincing evidence that either of the Patents-in-Suit fails to enable its Claims.

IV. THE '182 PATENT'S CLAIMS 35 AND 36 ARE NOT ANTICIPATED

11. Sandoz's anticipation defense, directed only to the '182 Patent's claims 35 and 36, challenges those claims' entitlement to an effective filing date of August 31, 1990. Those claims, and the specification, reference the 2006 deposit of PTA-7942. FOF 143. The argument thus reduces to a question of whether the amendment of the specification to reference PTA-7942, approved by the PTO Board in 2010, PTX-6.456 at 9, added new matter not described in the priority application.

12. Both entitlement to the effective filing date of a priority application and the prohibition against new matter are analyzed under 35 U.S.C. § 112. *Martek*, 579 F.3d at 1369 (effective filing date); *Commonwealth Sci. & Indus. Research Org. v. Buffalo Tech. (USA), Inc.*, 542 F.3d 1363, 1380 (Fed. Cir. 2008) (new matter). Whether amending the '182 Patent's specification to refer to the 2006 deposit added new matter is a question of fact. *Commonwealth*, 542 F.3d at 1380.

13. During prosecution, the PTO Board allowed amendment to reference deposit PTA-7942, finding that it did not introduce new matter. PTX-6.456 at 9; FOF 95. That allowance is thus "entitled to an especially weighty presumption of correctness in a subsequent validity challenge based on the alleged introduction of new matter." *Commonwealth*, 542 F.3d at 1380 (quotation marks omitted).

14. Because Sandoz has failed to show that the amendment to reference

PTA-7942 introduced new matter, (1) Claims 35 and 36 are entitled to an effective filing date of August 31, 1990; (2) the '182 Patent meets the written description and enablement requirements for these claims as of August 31, 1990; and (3) Claims 35 and 36 of the '182 Patent are not anticipated by later art.

V. THE CLAIMS OF THE PATENTS-IN-SUIT ARE NOT OBVIOUS

15. To show obviousness, Sandoz must prove by clear and convincing evidence that "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." 35 U.S.C. § 103. That is a question of law predicated on factual determinations, including: (1) scope and content of the prior art; (2) differences between the claimed subject matter and the prior art; (3) level of ordinary skill; and (4) objective indicia of non-obviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

16. The first step of the obviousness analysis is a proper claim construction. *Medichem, S.A. v. Rolabo, S.L.*, 353 F.3d 928, 933 (Fed. Cir. 2003).

17. Sandoz's expert, Dr. Blobel, applied the wrong claim construction by assuming the Claims encompass a two-cysteine hinge, contrary to the agreed construction that the claims require the exon-encoded, three-cysteine hinge. FOF 220. As such, Dr. Blobel's obviousness evidence and analysis may be disregarded. *Cordis Corp. v. Boston Sci. Corp.*, 658 F.3d 1347, 1356-57 (Fed. Cir. 2011).

18. The law presumes that the PTO considered prior art listed on the face of the Patents-in-Suit. *Shire LLC v. Amneal Pharm., LLC*, 802 F.3d 1301, 1307 (Fed. Cir. 2015). Though it does not alter the ultimate burden of proof, the fact that the art Sandoz relied upon was considered by the PTO is relevant to its weight. *See Microsoft*, 564 U.S. at 111. Indeed, Sandoz "has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents." *Shire*, 802 F.3d at 1307 (quoting *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1304 (Fed. Cir. 2008)); *see also Supernus Pharm. Inc. v. Actavis Inc.*, No. CV 13-4740 (RMB/JS), 2016 WL 527838, *31 (D.N.J. Feb. 5, 2016).

19. Sandoz cannot prove any Asserted Claim obvious "merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Sandoz must prove by clear and convincing evidence that a POSA "would have had reason to combine the teaching of the prior art references to achieve *the claimed invention*, and that the [POSA] would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1068-69 (Fed. Cir. 2012) (emphasis supplied); *see also Kinetic Concepts, Inc.*

v. Smith & Nephew, Inc., 688 F.3d 1342, 1360 (Fed. Cir. 2012).

20. "[T]he obviousness inquiry must 'guard against slipping into use of hindsight and…resist the temptation to read into the prior art the teachings of the invention in issue.'" *In re Ethicon, Inc.*, 844 F.3d 1344, 1349 (Fed. Cir. 2017) (alterations in original) (quoting *Graham*, 383 U.S. at 36); *see also KSR*, 550 U.S. at 421. For that reason, an inventor's path to the invention is hindsight and should never lead to a conclusion of obviousness. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) (citing 35 U.S.C. § 103(a)).

21. Where a POSA would not have recognized the problem, she has no motivation to look to the prior art for a solution. *See Leo Pharm. Products, Ltd. v. Rea*, 726 F.3d 1346, 1353 (Fed. Cir. 2013).

22. A prior art reference must be considered as a whole, "including portions that would lead away from the invention in suit." *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987). Evidence suggesting reasons to combine cannot be viewed in isolation from evidence suggesting the opposite. *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1363 (Fed. Cir. 2017).

23. Obviousness cannot be established where the prior art provided no "reason to select (among several unpredictable alternatives) the exact route" taken by the inventors. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008); *see also Arctic Cat*, 876 F.3d at 1363 (trying options over a

course of years do not show a motivation to combine).

24. Sandoz failed to establish *prima facie* obviousness. Its obviousness case rested solely on art and arguments that the USPTO considered and repeatedly found insufficient to establish obviousness of the claimed inventions. FOF 147 n.3. A POSA would not have been motivated to combine the extracellular region of p75 with the exon-encoded hinge-CH2-CH3 of a human IgG1; in fact, recognized concerns in the art would have given a POSA reasons not to. FOF 206-15, 224-37.

25. Plaintiffs proffered evidence of objective indicia showing that the Claims would not have been obvious. Such evidence can be the most probative evidence of nonobviousness in the record, and objective indicia enable the court to avert the trap of hindsight. *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017). This evidence was probative and persuasive. Had Sandoz established *prima facie* obviousness, Plaintiffs' evidence would have overcome it.

26. Plaintiffs established nexus between the objective indicia and the claimed invention, *i.e.* they showed that the factors driving the indicia were "commensurate in scope with the claims which the evidence is offered to support." *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018). The indicia were "tied to a specific product, and that product embodies the claimed features, and is coextensive with them." *Id.* (quotations omitted); *see also WBIP LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016); FOF 8-9, 76, 238, 252-56.

27. Plaintiffs established *prima facie* nexus; the burden shifted to Sandoz to rebut it. *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1311 (Fed. Cir. 2010). Rebuttal must be with evidence; argument is insufficient. *WBIP*, 829 F.3d at 1329.

28. Sandoz, through Dr. McDuff, provided only criticism—and no evidence—to challenge *Plaintiffs' prima* facie nexus of the claimed inventions to etanercept's exceptional commercial success, and accordingly failed to rebut Plaintiffs' showing. Sandoz did not challenge the etanercept's clinical success, which led to its commercial success. FOF 243.

29. Unexpected results are a "superior property or advantage that [a POSA] would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). They are probative of nonobviousness because "that which would have been surprising…would not have been obvious." *Id.* "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.*

30. A claimed invention's unexpected properties need not have been recognized at the time of invention. *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc. U.S.A.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014).

31. Plaintiffs have demonstrated that etanercept, which is covered by the Asserted Claims, has a number of unexpected properties: (1) a tendency not to cause aggregation with TNF; (2) superior binding affinity to and inhibition of TNF; and

(3) surprisingly low effector functions. FOF 252-256.

32. Sandoz's expert, Dr. Skerra, did not refute these unexpected properties because he analyzed the wrong molecule. FOF 232, 260.

33. A desire for a safer, less toxic, and more effective alternative to existing therapies shows long-felt but unmet need. *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006). Such evidence is particularly probative when it demonstrates both that a demand existed for the patented invention which others tried but failed to satisfy. *Cyclobenzaprine*, 676 F.3d at 1082; *see also Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 876 F. Supp. 2d 295, 417 (S.D.N.Y. 2012), *aff'd in relevant part*, 723 F.3d 1363 (Fed. Cir. 2013).

34. "Evidence that the industry praised a…product which embodies the patent claims weighs against an assertion that the same claim would have been obvious." *WBIP*, 829 F.3d at 1334. In contrast, doubt or skepticism from the industry or skilled artisans about "whether or how a problem could be solved or the workability of the claimed solution…favors non-obviousness." *Id.* at 1335.

35. Evidence of a drug's widespread use supports nonobviousness. *See Janssen Prod., L.P. v. Lupin Ltd.*, 109 F. Supp. 3d 650, 671 (D.N.J. 2014), *modified*, No. 10-5954 (WHW) 2016 WL 1029269 (D.N.J. Mar. 15, 2016).

36. Etanercept has enjoyed significant praise and success. FOF 239-44. Plaintiffs' Dr. Fleischmann, testified without rebuttal or contradiction that etanercept

met a long-felt but unmet need for a safe and effective RA therapy. FOF 239-241. Others tried, but failed. FOF 242. Drs. Fleischmann and Vellturo also testified, without rebuttal, to etanercept's success and widespread adoption. FOF 243-244.

37. Copying evidences the accused infringer's recognition that the patented invention is superior to other options. *Diamond Rubber Co. v. Consol. Rubber Tire Co. of N.Y.*, 220 U.S. 428, 450 (1911). Copying supports nonobviousness when, as here, it follows attempts to design around the patented invention. *See, e.g.*, *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 731 (Fed. Cir. 2017).

38. Despite Sandoz's belief at the relevant time that FDA guidelines for biosimilars did not prohibit amino acid sequence differences or require the applicant to use the same expression system as the reference product, FOF 82, 246-248, Sandoz copied Enbrel's amino acid sequence and host cell system, FOF 77, 245, 249. It did so following attempts—subsequently abandoned—to design around Roche's patents. FOF 83, 249. Sandoz's copying is probative of non-obviousness.

39. Licensing by competitors evidences nonobviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1539 (Fed. Cir. 1983). Plaintiffs introduced evidence, without contradiction, of Immunex's licensure of the Patents-in-Suit, and the substantial amounts Immunex paid for the license. FOF 250-51.

40. Sandoz's alleged "near-simultaneous invention" cannot make up for Sandoz's failure to make out a *prima facie* case of obviousness. *Geo. M. Martin Co.*

v. Alliance Mach. Sys. Int'l LLC, 618 F.3d 1294, 1304 (Fed. Cir. 2010).

41. As obviousness is determined at the time of the invention, research after that date often has little probative value, *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 n.4 (Fed. Cir. 1986), particularly after the invention was publicized, *Shire Orphan Therapies LLC v. Fresenius Kabi USA, LLC*, No. 15-cv-1102-GMS, 2018 WL 2684097, *20 (D. Del. June 5, 2018). The later research may reflect a "shift in the state of the art," rather than its state at the time of the invention. *Eli Lilly Co. v. Teva Pharms.*, No. IP 02-0512-C-B/S, 2004 WL 1724632, n.23 (S.D. Ind. July 29, 2004), *aff'd*, No. 05–1044, 2005 WL 1635262 (Fed. Cir. July 13, 2005).

42. In rare instances, independently made, simultaneous inventions, made within a comparatively short space of time, may provide some support for obviousness, *Geo. M. Martin*, 618 F.3d at 1304-05, but a single instance cannot, as the pre-AIA statute governing interference practice, 35 U.S.C. § 135, recognized the possibility of near simultaneous invention. *Lindemann Maschinenfabrik GMBH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1460 (Fed. Cir. 1984).

43. For drugs, alleged evidence of near-simultaneous "invention" can be disregarded for obviousness if they are not the same compound as claimed. *See, e.g.*, *Shire*, 2018 WL 2684097, at *20; *Endo Pharm. Inc. v. Amneal Pharm., LLC*, 224 F. Supp. 3d 368, 381 (D. Del. 2016). But if other researchers went "in different ways," that may be strong evidence of non-obviousness. *Cyclobenzaprine*, 676 F.3d at 1082.

44. Sandoz's alleged objective indicia of obviousness lacked merit. Of the groups Sandoz alleged to be simultaneous inventors, only Immunex's Dr. Goodwin developed the claimed fusion protein (after the Priority Date) while the others developed different and unsuccessful constructs, some after publication of the Roche EP707. FOF 262-275. Sandoz's failed evidence of "simultaneous invention" only reinforces the inventiveness of the claimed inventions.

45. On the record as a whole, Sandoz has failed to prove by clear and convincing evidence that any Asserted Claim of the Patents-in-Suit would have been obvious to a POSA on August 31, 1990.

VI. THE ROCHE '279 PATENT IS NOT A PROPER ODP REFERENCE

46. The safe harbor of 35 U.S.C. § 121 protects patents issuing from divisional applications filed as a result of a restriction requirement against an ODP challenge based on the claims of a parent patent, so long as the applicant maintains "consonance" with the lines drawn by the examiner in the restriction requirement. *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1579 (Fed. Cir. 1991).

47. An issued patent's consonance is determined based on the issued claims. *Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc.*, 592 F.3d 1340, 1344 (Fed. Cir. 2010). An applicant may secure safe harbor protection by amending pending claims to make them consonant with an earlier restriction requirement. *Id.*

48. Because the '790 application, which issued as the '182 Patent, was filed

as a divisional application as a result of a restriction requirement issued during prosecution of the '640 application, which issued as the '279 patent, FOF 280-82, and the'182 Patent's issued claims are consonant with that restriction requirement, FOF 285, § 121 protects the '182 Patent from an ODP challenge based on the '279 patent. The '279 Patent is thus not available as a reference under ODP.

VII. THE IMMUNEX PATENTS ARE NOT PROPER ODP REFERENCES

49. The doctrine of obviousness-type double patenting (ODP) is assessed only for patents that, at the time of invention, shared a common inventor, inventive entity, or owner. *In re Hubbell*, 709 F.3d 1140, 1148 (Fed. Cir. 2013).

50. For ODP purposes, inventions are "commonly owned" only when it is proven, by clear and convincing evidence, that the inventions were entirely or wholly owned by the same entity at the time the invention was made. *Novartis Pharms. Corp. v. Noven Pharms., Inc.*, 125 F. Supp. 3d 474, 487 (D. Del. 2015) (applying MPEP § 706.02(*l*)(2)); MPEP § 804.03(II); S. Rep. No. 98-663, at 8).

51. Roche never owned any of the Immunex Patents and Immunex never owned any of the Patents-in-Suit, and at no point in time—much less at the time of their inventions—were any of the Immunex Patents owned by the same entity that owned any of the Patents-in-Suit. FOF 295-296. As the Immunex Patents and the Patents-in-Suit were never "commonly owned" (under ODP or otherwise), none of the Immunex Patents are available as ODP references against the Roche Patents.

52. A "post-GATT" patent cannot serve as an ODP reference against a "pre-GATT" patent because the "pre-GATT" patent's term is defined by law and there is consequently "no undeserved, extended patent term." *Abbott Labs. v. Lupin Ltd.*, C.A. No. 09-152-LPS, 2011 WL 1897322, *10 (D. Del. May 19, 2011). ("GATT" refers to Pub. L. No. 103-465, 108 Stat. 4809 (Dec. 8, 1994), effective June 8, 1995.) Thus, the post-GATT Finck Patents (FOF 310) could not have been used against the Patents-in-Suit as ODP references even if they had been "commonly owned" under the ODP doctrine.

VIII. THE ALLEGED ODP REFERENCES COULD NOT SUPPORT ODP

53. When the ODP doctrine applies, the ODP analysis involves two steps: (1) construing the claims of the challenged patent and the ODP reference patent, and (2) comparing each of those claims, as construed, to determine whether the claimed inventions are patentably distinct. *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366, 1374 (Fed. Cir. 2014).

54. ODP is concerned with what "invention [the claim] defines," and not what the patent "discloses." *Gen. Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1280 (Fed. Cir. 1992). The disclosure of an ODP reference patent "cannot be used as though it were prior art, *even where the disclosure is found in the claims*." *Id.* at 1281 (emphasis in original). Rather, "[c]laims must be read as a whole in analyzing a claim of double patenting." *Id.* at 1278.

55. In instances where "a later filed improvement patent issues *before* an earlier filed basic invention," a "two-way" test is applied to assess whether the later filed patent is patentably distinct over the basic invention. *In re Braat*, 937 F.2d 589, 593 (Fed. Cir. 1991) (emphasis). This protects an applicant from being "penalized by the rate of progress of the applications through the PTO, a matter over which the applicant does not have complete control." *Id.*

56. As with an obviousness analysis, where offered, the fact-finder considers objective indicia in analyzing ODP. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 689 F.3d 1368, 1381 (Fed. Cir. 2012). Dr. Blobel did not provide an assessment of any such objective indicia as applicable to his ODP analysis.

57. The Claims are patentably distinct from the '279 patent's claim 5. Dr. Blobel misconstrued the latter. Claim 5 is directed to a broad, open genus of IgG1 fusion proteins incorporating fragments of the p55, FOF 292, whereas the Claims are directed to a composition (and methods of making it) incorporating only p75's full extracellular region, FOF 75-76. The p55 and p75 TNFR are distinct proteins with different sequences and functions. FOF 288-291. Thus, even if the '279 Patent had been a proper ODP reference, its claim 5 could not have rendered any of the Claims invalid for ODP.

58. The Claims are patentably distinct from the Jacobs Patent's claim 3. Dr. Blobel misconstrued the latter and relied on improper documents in doing so. FOF

329, 335. That claim is directed to a treatment method with a "chimeric antibody" including an Ig heavy chain CH1 and Ig light chains, which the Claims exclude. FOF 327-334. Dr. Blobel identified no motivation to modify claim 3 of the Jacobs Patent to arrive at the claimed inventions, and objective indicia support the non-obviousness of the claimed inventions. FOF 337-338. Thus, even if the Jacobs Patent had been a proper ODP reference, its claim 3 could not have rendered any of the Claims invalid for ODP.

59. The Claims are patentably distinct from the Finck Patents' claims. Dr. Blobel misconstrued the claims of the latter by failing to consider them as a whole. FOF 314. Properly construed, the Finck Patents' claims are directed to methods of treatment with etanercept, whereas the Claims are directed to the composition and methods of making it. FOF 311-313, 316. Thus, even if the Finck Patents had been proper ODP references, their claims could not have rendered the Claims invalid for ODP under either the one-way or the two-way test. FOF 316-325.

Dated: October 23, 2018

Respectfully submitted,

s/ Charles H. Chevalier
David E. De Lorenzi
Charles H. Chevalier
Christine A. Gaddis
GIBBONS P.C.
One Gateway Center
Newark, New Jersey 07102-5310

s/ Liza M. Walsh
Liza M. Walsh
Marc D. Haefner
Christine I. Gannon
Eleonore Ofosu-Antwi
Colleen M. Maker
WALSH PIZZI O'REILLY FALANGA

(973) 596-4500

OF COUNSEL:

David I. Berl (*pro hac vice*)
Aaron Maurer (*pro hac vice*)
Thomas S. Fletcher (*pro hac vice*)
Seth R. Bowers (*pro hac vice*)
WILLIAM & CONNOLLY LLP
725 Twelfth St. NW
Washington, D.C. 20005
(202) 434-5000

Attorneys for Hoffmann-La Roche Inc.

LLP
One Riverfront Plaza
1037 Raymond Boulevard, 6th Floor
Newark, New Jersey 07102
(973) 757-1100

OF COUNSEL:

David T. Pritikin (*pro hac vice*)
Steven J. Horowitz (*pro hac vice*)
Richard M. Chen (*pro hac vice*)
SIDLEY AUSTIN LLP
One South Dearborn
Chicago, Illinois 60603
(312) 853-7000

Vernon M. Winters (*pro hac vice*)
James A. High Jr. (*pro hac vice*)
Sue Wang (*pro hac vice*)
SIDLEY AUSTIN LLP
555 California Street, Suite 2000
San Francisco, California 94104
(415) 772-1200

Jeffrey P. Kushan (*pro hac vice*)
Peter S. Choi (*pro hac vice*)
Ryan C. Morris (*pro hac vice*)
SIDLEY AUSTIN LLP
1501 K Street N.W.
Washington, D.C. 20005
(202) 736-8700

Samuel N. Tiu (*pro hac vice*)
SIDLEY AUSTIN LLP
555 West Fifth Street
Los Angeles, California 90013
(213) 896-6000

Sona De (*pro hac vice*)
SIDLEY AUSTIN LLP

787 Seventh Avenue
New York, NY 10019
(212) 839-5300

Wendy Whiteford (*pro hac vice*)
J. Drew Diamond (*pro hac vice*)
Dennis Smith (*pro hac vice*)
Joseph E. Lasher (*pro hac vice*)
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, CA 91320-1789
(805) 447-1000

Attorneys for Immunex Corporation and Amgen Manufacturing, Limited