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.;<br><br>Plaintiffs,<br><br>v.<br><br>SANDOZ INC.; SANDOZ INTERNATIONAL GMBH; and SANDOZ GMBH;<br><br>Defendants. | ) | Civil Action No.: 2:16-cv-01118-CCC-MF<br><br>**PLAINTIFFS' POST-TRIAL BRIEF** |

# TABLE OF CONTENTS

# TABLE OF AUTHORITIES

**Page(s)**

**Cases**

**Rules and Statutes**

## Table of Abbreviations

| Parties | |
|---|---|
| Immunex | Plaintiff Immunex Corporation |
| Roche | Plaintiff Hoffmann-La Roche Inc. or corporate affiliates |
| Plaintiffs | Plaintiffs Immunex, Amgen Manufacturing, Limited and Plaintiff Hoffmann-La Roche Inc. |
| Sandoz | Defendants Sandoz Inc., Sandoz International GmbH, and Sandoz GmbH |
| **Patents/Patent Publications** | |
| '182 patent | U.S. Patent No. 8,063,182 [JTX-1] |
| '522 patent | U.S. Patent No. 8,163,522 [JTX-2] |
| Roche Patents | '182 patent and '522 patent |
| EP121 | European Patent No. 0 939 121 [PTX-1536] |
| asserted claims | claims 11-12 and 35-36 of the '182 patent and claims 3, 8, 10 of the '522 patent |
| **Defined Terms** | |
| A&S | 2004 Accord and Satisfaction [JTX-12] |
| ATCC | American Type Culture Collection |
| ADCC | antibody-dependent cell-mediated cytotoxicity |
| CDC | complement-dependent cytotoxicity |
| DNA | deoxyribonucleic acid |
| cDNA | complementary DNA |
| FDA | U.S. Food and Drug Administration |
| FOF | Plaintiffs' Proposed Finding of Fact |
| GATT | General Agreement on Tariffs and Trade |
| Ig | immunoglobulin |
| CH1 | first constant domain of the heavy chain of an Ig |
| CH2 | second constant domain of the heavy chain of an Ig |
| CH3 | third constant domain of the heavy chain of an Ig |
| kD | Kilodalton |
| MPEP | Manual of Patent Examining Procedure |
| ODP | Obviousness-type double patenting |
| POSA | Person of Ordinary Skill in the Art on August 31, 1990 |
| PTO | U.S. Patent and Trademark Office |
| Board | Patent Trial and Appeal Board (formerly the Board of Patent Appeals and Interferences) |
| RA | rheumatoid arthritis |
| SEQ ID NO | sequence identifier number |

| | |
|---|---|
| TNF | tumor necrosis factor |
| TNF-BP | TNF binding protein |
| TNFR | TNF receptor |
| p55 | p55 TNFR |
| p75 | p75 TNFR |
| **Sandoz's Obviousness-Type Double Patenting References** | |
| Finck patents | U.S. Patent Nos. 7,915,225 [DTX-11], 8,119,605 [DT-12], and 8,722,631 [DTX-13] |
| Jacobs '690 patent | U.S. Patent No. 5,605,690 [JTX-42] |
| '279 patent | U.S. Patent No. 5,610,279 [JTX-5] |
| **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) [JTX-24] |
| Smith '760 | U.S. Patent No. 5,395,760 [JTX-65] |
| Bryn 1990 | Byrn R et al., Biological properties of a CD4 immunoadhesin, Nature 344: 667-670 (1990) [JTX-56] |
| Capon '964 | U.S. Patent No. 5,116,964 [JTX-61] |
| Seed '262 | European Patent Application Publication No. 0 325 262 [JTX-57] |
| Karjalainen '827 | European Patent Application Publication No. 0 394 827 [JTX-60] |
| Traunecker 1989 | Traunecker A et al., Highly efficient neutralization of HIV with recombinant CD4-immunoglobulin molecules, Nature 339:68-70 (1989) [JTX-25] |
| Watson 1990 | Watson S 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) [JTX-59] |
| **General References** | |
| Capon 1989 | Capon D et al., Designing CD4 immunoadhesins for AIDS therapy, Nature 337:525-31 (1989) [JTX-58] |
| Dembic | Dembic Z et al., Two Human TNF Receptors have similar extracellular, but distinct intracellular, domain sequences, Cytokine 2:231-237 (1990) [JTX-23] |
| **Citations** | |
| PTX | Plaintiffs' Trial Exhibit |
| DTX | Defendants' Trial Exhibit |
| JTX | Joint Trial Exhibit |

## INTRODUCTION AND SUMMARY

The Roche inventors were the first to file patent applications describing and claiming TNFR fusion proteins, including the one now known as etanercept—a combination of parts of the p75 TNFR and an IgG1 antibody. Immunex did not develop etanercept until after Roche's patent filing, and it recognized Roche's dominant patent position by licensing the Roche patent applications.

As the trial record showed, etanercept met a long-felt need and dramatically changed the lives of thousands of patients by providing relief from the debilitating pain and joint-damage caused by RA. As an *anti*-inflammatory medicine targeting TNF, etanercept defied conventional wisdom because its IgG1 portion was known to cause inflammation. Etanercept's structure and its resulting, dramatic therapeutic effects were wholly unexpected.

Sandoz finally admitted, on the eve of trial, that its etanercept biosimilar infringes Roche's patents, making its scattered invalidity challenges the trial's focus. But Sandoz's presentation fell far short of providing the clear and convincing evidence required to prove any of them. Its experts ignored the claim construction Sandoz agreed to, misconstrued the patent disclosures, took inconsistent positions, and retreated from their assertions on cross-examination. Sandoz offered no reply to the testimony of several of Immunex's witnesses. And nothing in Sandoz's trial presentation confronted the reality that arguments advanced by Sandoz had already

been rejected by the PTO Board. Sandoz entirely failed to meet its heavy burden in proving invalidity.

Sandoz's challenge to the Roche Patents' disclosure was two-fold—first, that the written description did not establish the inventors possessed the claimed p75 TNFR:IgG1 fusion and, second, that it did not enable it. But Sandoz's experts admitted the p75 TNFR and IgG1 sequences were both well known, and Sandoz has said nothing in rebuttal to the compelling testimony of Immunex's experts that the patents not only identified both but described how to combine the precise parts of each to yield the claimed p75 TNFR-IgG1 fusion. That is all the law of written description requires. Sandoz's experts also admitted a POSA could readily practice the claimed inventions, thereby dooming its enablement challenge.

Sandoz's obviousness challenges ask the Court to credit arguments and prior art the PTO repeatedly found insufficient to show obviousness even under its lower "preponderance of the evidence" standard. The trial evidence showed that Sandoz's witnesses improperly used hindsight to pick and choose bits of the prior art to reconstruct the claimed inventions without any motivation for doing so, and contrary to conventional wisdom. Sandoz also had no answer to the compelling, real-world evidence of non-obviousness established at trial—that etanercept exhibits entirely unexpected binding and clinical properties, addressed a long-felt need for effective RA treatment, and had tremendous commercial success. Sandoz instead alleges

"simultaneous invention" by other research groups to contend a POSA would not be deterred from pursuing the claimed fusions. But except for Immunex, which did its work after the Roche inventors and took a license to the Roche Patents, all those other groups pursued *different* constructs that were never developed clinically; this other work, considered objectively, shows the Roche inventions to be inventive, not obvious.

Sandoz finally argues that the Roche Patents should be held invalid under the judge-made doctrine of ODP, which prevents a common inventor or owner from securing multiple patents on a single invention. Sandoz's first ODP challenge, based on the parent of the Roche Patents, is barred by the safe harbor provisions of 35 U.S.C. § 121 because the PTO found the p55 and p75 fusions to be patentably distinct and forced Roche to seek claims to these different inventions in separate patents; the trial evidence included admissions from Sandoz and its experts supporting the PTO's position that p55 and p75 are patentably distinct.

Sandoz also argues that ODP applies between the Roche Patents and certain Immunex patents. But this argument ignores the requirement of ODP for common ownership or inventors of these patents. Instead of proving that, Sandoz asks this Court, for the first time ever, to use instead an "all substantial rights" test taken from "prudential standing" cases as a proxy for common ownership and to thereby extend ODP, also for the first time, to patent licensees. No court has ever applied ODP in

that manner and for good reason. The "all substantial rights doctrine" is used in the standing analysis to determine who can bring a lawsuit and how patent rights may be efficiently enforced; it has nothing to do with proving a patent invalid. Sandoz is also wrong when it argues the Federal Circuit has always evaluated "patent ownership" using the "all substantial rights" test; that Court instead routinely looks to state law to determine issues of patent ownership.

To justify this dramatic expansion of the law, Sandoz portrays ODP as a sweeping doctrine for ridding the world of patents whose terms are deemed too long by would-be copyists. But ODP is a narrow doctrine, filling a specific gap in the statutory framework governing validity. Sandoz's repositioning of it would create chaos—turning common, post-invention licensing and even patent settlements into a trap to retroactively invalidate patents properly obtained by different inventors working separately at different times and owned by separate legal entities. Sandoz's reimagined ODP doctrine is legally and factually unfounded, has never been accepted before, and should not be accepted now.

In any event, the trial evidence shows that Immunex does not hold all substantial rights to the Roche Patents; Roche retained meaningful rights, including the right to enforce the patents and perform significant research. It also shows the Roche Patents' claims are not obvious over any claims of the Immunex patents, when both sets of claims are considered as a whole as the law requires. Sandoz failed

to prove the "chimeric antibody" of Immunex's Jacobs patent claim 3, given its admittedly distinct structure, made the Roche fusion obvious, and likewise failed to prove that any of the Finck patent claims render Roche's production and product claims obvious.

The Court should reject Sandoz's defenses, confirm the patents' presumptive validity, and enter judgment holding that Sandoz infringes the asserted claims.

## STATEMENT OF FACTS

### I. Enbrel® (etanercept)

Enbrel® was the first FDA-approved fusion protein. FOF 10. Its active ingredient is etanercept, a novel bio-engineered fusion protein that combines the extracellular region of p75 TNFR with the exon-encoded hinge–CH2–CH3 portion of the heavy chain of human IgG1. FOF 113-14. Etanercept owes its success to several unexpected properties tied to its unique structure, including that its two TNFR arms work together to tightly bind and neutralize TNF without causing aggregation. FOF 252-254.

Enbrel® is entirely unlike earlier RA drugs—it treats the cause of RA, not just its symptoms, and helps stop disease progression. FOF 10, 240-241. The best of those earlier drugs, methotrexate, produced favorable responses in only ~30% of patients, many of whom could not tolerate it over extended periods. FOF 240. The long-term outlook for RA was "depressing." FOF 241. The approval of Enbrel® in

1998 changed everything. *Id*. Its efficacy in ~70% of patients was hailed as a true "breakthrough." *Id*. In Sandoz's own words to the FDA, Enbrel® "changed the practice of medicine." FOF 239.

## II. The State of the Art by August 31, 1990

### A. Cytokines and Rheumatoid Arthritis

Auto-immune and inflammatory disorders arise when an overactive immune system attacks the body. FOF 32. In August 1990, little was known about their cause or progression except that many factors were involved, such as cell-signaling, formation of antibody complexes, and triggering of effector functions. FOF 29, 151, 211.

TNF is a cytokine. FOF 28. Cytokines are proteins that act as messengers in the body, and many were known to exist. FOF 27. They were believed to play a role in inflammation, but because they exhibit a wide array of distinct (and often overlapping) activities, it was difficult to pin down any given cytokine's role in any particular disease, much less identify one as a viable therapeutic target. FOF 27, 150. The role of TNF was particularly unclear—it was implicated in "diverse biological processes," including normal, beneficial ones. FOF 29. And while TNF was potentially implicated in auto-immune disorders such as RA, many others were as well, with IL-1 being the one with the "strongest link." FOF 151.

The physiological role of TNFRs also was not established. From *in vitro* work

with soluble forms of TNFRs, researchers were "tempt[ed] to speculate" they acted as TNF inhibitors, but could not rule out a "converse" role as reservoirs that could "prolong the [body's] exposure" to TNF, thus aggravating disease. FOF 31.

By mid-1990, two human TNFRs (p55 and p75) had been identified and sequenced. FOF 36-41. They also were known to have distinct structures—they were no more similar to each other than to an unrelated protein, nerve growth factor receptor. FOF 290. *In vitro* studies confirmed those distinctions mattered; p55 blocked TNF five times more effectively than p75. FOF 289.

### B. Immunoglobulin Fusion Proteins

The first immunoglobulin (Ig) fusion proteins were developed as potential therapies for AIDS. FOF 173. Capon 1989 explained the concept underlying these hybrid molecules—combine part of a receptor that targets HIV-infected T-cells (CD4) with parts of an antibody that activate cell-killing "effector" functions (*i.e.*, antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC)). FOF 176-178.

The Ig parts in these early fusions varied widely: some were a complete Ig heavy chain, some lacked the first domain (CH1) and part of the hinge, and some omitted the entire CH1 and hinge domains. FOF 177, 183, 186-187-8, 193. Certain fusions even added a third "linker" sequence between the receptor and Ig components. FOF 184. Critically, there was no evolving consensus about which part

of an Ig should be used in fusion proteins in August of 1990. FOF 158-159.

If there was consensus about anything then, it was that Ig effector functions were critical and should be preserved. FOF 208. The July 1989 Seed '262 publication emphasized that "any" Ig fragment could be used "as long as the remaining fragment has antibody effector function." FOF 182, 219. Dr. Capon's '964 patent, filed in November 1989, listed immunoglobulin effector functions "such as complement binding, cell receptor binding, and the like" as the "object" of its innumerable Ig fusion protein designs (FOF 185) and its two "particularly preferred" fusion proteins "contain[ed] the effector functions of immunoglobulin $G_1$" (FOF 187). The proven effector activity of Ig fusion proteins even prompted concerns — a June 1990 paper by Zettlmeissl warned that "[o]ne of the most important issues confronting these [receptor-Ig fusion] agents is the extent of autoimmune damage arising" from their use. FOF 198.

## III. The Roche p75 TNFR-Ig Fusion Protein Invention

### A. Roche's Invention of the p75 TNFR-Ig Fusion Protein

The Roche Patents claim priority to a European application filed on August 31, 1990, and benefit of a U.S. application filed September 10, 1990 (the "priority applications"). FOF 51. The named inventors are scientists who formed the core of Roche's TNF research project in the late 1980s and early 1990s. FOF 46. Led by Dr. Werner Lesslauer, they sought to develop a molecule to block TNF. *Id.*

Dr. Lesslauer had the insight in late 1989 to combine the extracellular region of either p55 or p75 with the hinge-CH2-CH3 portion of an immunoglobulin, preferably IgG1 or IgG3. *Id.* His idea was far from self-evident. The Roche inventors were aware that earlier Ig-based fusion proteins were designed to induce inflammatory immune responses, the opposite of what they were seeking. FOF 46-47. And their colleagues were skeptical about including the *pro*-inflammatory part of an immunoglobulin in a molecule intended for use as an *anti*-inflammatory. FOF 48. Nevertheless, Dr. Lesslauer intuited that his fusion protein would not aggregate TNF and would not induce effector functions as the earlier CD4 fusion proteins did. *Id.* Later studies confirmed his intuition. FOF 48, 252, 255.

The inventions arose out of the Roche's early work to identify and characterize both TNFRs; the inventors worked on p55 and p75 in parallel and made foundational contributions to the knowledge of each. FOF 36-39. They were the first to experimentally prove there are two distinct human TNFRs, and the molecular weights they published for each became the shorthand name of each TNFR. FOF 36. They were the first to publish the amino acid sequence of the p55 TNFR and the second to do so for the p75 TNFR. JTX-21; JTX-23; FOF 39-40.[1]

[1] While researchers at Immunex published the complete p75 TNFR sequence two months earlier, both groups reported the same 235 amino acid extracellular region for p75 and the same boundary between its extracellular and transmembrane regions. JTX-24; JTX-23; FOF 40-41.

The Roche inventors also documented their work on the two TNFRs in the examples in their patents. FOF 58. Examples 1-8 describe the path they took to isolate, purify, sequence, and clone the two TNFRs. FOF 58, 62-64. Examples 9 and 10 describe their work to recombinantly express p55. FOF 58. Example 11 describes a fusion protein they made that combined the extracellular region of one of the TNFRs (p55) with the exon-defined hinge-CH2-CH3 domains of a human IgG heavy chain (IgG3). FOF 58-60, 118. That example was based on p55 simply because they cloned p55 first. FOF 49. The inventors, however, clearly described fusions based on both p55 and p75 and later made a p75 fusion using that same method. *Id.* They also pointed to Example 11 as a recipe to follow for making p55 and p75 fusions using deposited examples of IgG1 and IgG3 vectors. FOF 101, 104-105. The patent disclosure thus identified four preferred fusions, one of which combines the p75 extracellular region with an exon-defined IgG1 heavy chain constant region lacking only the CH1 domain, precisely as the claims specify. FOF 106-107.

### B. Immunex's Development and Licensure of Roche's Invention

Immunex did not make etanercept until November or December 1990, several months after the August 31, 1990 priority date of Roche's patents. FOF 69. Etanercept was FDA-approved for treating RA in November 1998. JTX-27; JTX-28; JTX-29; JTX-30; FOF 10.

Recognizing Roche's superior position, Immunex sought to license Roche's pending patent applications in 1999, effective back to the approval date of Enbrel®. FOF 70. Immunex paid Roche tens of millions of dollars under this license. FOF 70. Amgen acquired Immunex in 2002. FOF 71. Roche obtained patent claims to p75 TNFR fusion proteins in 2003 in its related EP121 patent; Amgen expected that similar claims would issue in the U.S. FOF 72. As part of an effort to reduce Enbrel®'s royalty burden, Amgen negotiated a buy-out of the future royalties under the Roche Patents via the 2004 Accord & Satisfaction ("A&S"). FOF 71.

Amgen and Roche had only recently concluded a hard-fought patent litigation involving other products. FOF 300. While Roche was willing to assign its pending applications to Amgen outright (as it did for Wyeth for the ex-North America patents), Amgen, wary of future conflicts with Roche, wanted Roche to remain owner of the applications so that Roche would owe a duty of candor to the PTO and be a party to any litigation involving patents that might issue from them. FOF 300. Roche retained important rights reflecting continued ownership of its U.S. patents. FOF 303-309. Pursuant to the A&S, Amgen took control of prosecution, working diligently to secure patents covering etanercept. FOF 71. The PTO Board ultimately determined that p75 TNFR-Ig fusions were patentable, and the Roche Patents issued in 2011 and 2012. FOF 74. Amgen later consolidated and transferred all its rights in the 2004 A&S to Immunex. FOF 301 n.5.

### C. Sandoz's Deliberate Copying of Roche's Invention

Sandoz claims it was surprised when the Roche Patents issued, but used privilege claims to block discovery of that claim; uncontested facts show it to be implausible. Immunex disclosed the Enbrel® license from Roche in a 1999 10-K filed publicly with the SEC. PTX-365 at 49. Sandoz also studied the Roche patent estate carefully. FOF 78. The first Roche priority application published in March 1991 disclosed p75 fusion proteins. FOF 266. The file history of the Roche's '279 patent (JTX-9), made public in 1997, disclosed the serial numbers of the applications that later issued as the Roche Patents. FOF 80. Roche was issued claims to p75 fusion proteins in its 2003 European '121 ("EP121") patent. FOF 56. Sandoz thus knew of both the EP121 and '279 patents when it began its biosimilar work, and actually named its biosimilar "GP2015" based on the EP121 patent's expiration date. FOF 79. And after spending considerable efforts developing alternatives to Enbrel® that it believed would avoid Roche's patents, Sandoz ultimately chose to simply copy Enbrel®, as it freely admits. FOF 245-249.

## ARGUMENT

### I. Sandoz Failed to Prove Its Written Description or Enablement Defenses

At trial, Sandoz argued the Roche inventors never contemplated p75-Ig fusion proteins; it claims that Immunex, after it "purchased Roche's applications" executed a strategy of "transforming" these supposedly deficient disclosures to cover and enable etanercept. Sandoz Tr. Br. at 1. That is a false narrative. From the very first

filing in August of 1990, the contents of the applications leading to the Roche Patents (collectively "the disclosure") described and enabled the p75 TNFR and fusions based on it. Sandoz's written description and enablement challenges rehash matters decided by the PTO, mischaracterize what the patents state and was known in August of 1990, and conflict with governing case law.

### A. The Roche Patents Demonstrate Possession of the Claimed Fusion Proteins and Their Claimed Methods of Production

It is well settled that a patent need not include, and preferably omits, what was already known in the art. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006). The Federal Circuit has applied this maxim to hold that a patent's written description need not reproduce known amino acid or DNA sequences within its four corners if the invention lies in combining parts of those known sequences to yield a new and inventive sequence. Indeed, in a case involving one of Dr. Capon's own patents, *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005), the Federal Circuit reversed a PTO Board decision using this precise rationale, holding "[t]he Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes." *Id.; see also Falkner,* 448 F.3d at 1368 ("where, as in this case, 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."). The disclosure describes the claimed p75-IgG1 fusion because it identifies both parts of the claimed p75-IgG1 fusion protein (*i.e.*, the known p75 extracellular region and exon-encoded IgG1 hinge-CH2-CH3 portions) and describes how to combine them as the claims specify.

### 1. The Two Components of the Claimed p75-Ig Fusion Proteins Were Known and Available before August 1990

Many of the facts that dispose of Sandoz's written description challenge are undisputed. By August 1990, it was known that p75 was one of two human TNFRs, weighed about 75 kD, and bound TNF. FOF 36-37. The full amino acid sequence of p75 had been published twice and its extracellular region had been identified. FOF 39-41. A cDNA sequence encoding the p75 was published and publicly accessible from GenBank, FOF 40, and sending either of two 18-amino acid sequences disclosed in the patents (*i.e.*, SEQ ID NOs: 7 or 10) to GenBank would prompt return of that known p75 sequence, FOF 90. And the amino acid and DNA sequences of the IgG1 heavy chain constant region and its allelic variants were also known, FOF 99, as was its exon-defined CH1 domain, FOF 100.

### 2. The Disclosure Identifies Soluble Fragments of the Known p75 TNFR to Use in TNFR/IgG Fusions

Starting in the Abstract, the disclosure consistently identifies "soluble fragments" of the known p75 TNFR as one of two "TNF binding protein" (TNF-BP)

parts to use in TNFR-IgG fusions (the other being the p55 TNFR). FOF 88-98, 103. The disclosure makes this crystal clear when it identifies as a source of these soluble fragments "especially preferred" TNF-BPs that weigh "about 55 or 75 kD" and that one of them (p75) contains "at least one of the following amino acid partial sequences: … (IIA) […] (SEQ ID NO: 7)" and "(IID) […] (SEQ ID NO: 10)." FOF 88. As Dr. Naismith explained, by referring to a human TNF-BP that weighs about 75 kDa and contains SEQ ID Nos. 7 and 10, the disclosure unambiguously identified the p75 TNFR reported in Smith 1990 and in Dembic. FOF 89-91. *See Yeda Research & Dev. Co. v. Abbott GmbH & Co.,* 837 F.3d 1341 (Fed. Cir. 2016) (written description adequately identifies a known protein by describing a partial amino acid sequence and protein's functional properties).

The disclosure recognizes there can be allelic variants and other inconsequential variations in a DNA sequence that encodes the p75 TNFR that do not affect its ability to bind TNF—that is why the disclosure states "the invention embraces not only allelic variants, but also those DNA sequences which result from deletions, substitutions and additions from one or more of the sequences in FIG.1 or FIG.4, whereby, in the case of proteins coded thereby there come into consideration … TNF-BP." FOF 67, 129. A p75 TNFR encoded by a DNA containing the partial cDNA in Figure 4 is one of these. FOF 127, 129.

The disclosure, however, is not limited to using a p75 TNFR DNA sequence

containing the Figure 4 partial cDNA. Dr. Naismith explained a POSA would have read the disclosure as also describing the known p75 TNFR cDNA the Smith authors had deposited with Genbank and made publicly available to other researchers in May of 1990. FOF 90-92, FOF 128.[2] That conclusion flows naturally from how the disclosure refers to p75 DNA sequences—it says "there are also preferred DNA sequences which code for a protein of about 75/65 kD, whereby those which contain the partial cDNA sequences shown in FIG. 4 are preferred." FOF 98. In other words, a DNA sequence encoding the p75 TNFR that contains the Figure 4 sequence *may* but *does not have to* be used—it is just "preferred." Indeed, that is made crystal clear by the subsequent indication in the disclosure that a cDNA encoding a TNFR soluble fragments can be made from either sequence; as it states: "[o]n the basis of *the thus-determined sequences and of the already known sequences for certain receptors*,

[2] Another p75 cDNA was the one in the N227 plasmid the inventors made before August 31, 1990, deposited with the ATCC (PTA 7942) and identified in the disclosure. FOF 94; *Enzo Biochem, Inc. v. Gen-Probe Inc*., 323 F.3d 956, 965-66 (Fed. Cir. 2002) (public deposit of DNA forms part of patent's written description). The extracellular region of that deposited cDNA encodes the identical extracellular region sequence reported in Smith 1990 and Dembic. FOF 68, 93. Sandoz argues that deposit was improper, which renders claims 35 and 36 of the '182 patent invalid as anticipated because those claims refer to that sequence. But the PTO Board found the deposit amendment complied with all PTO rules: the PTA 7942 plasmid contains a p75 cDNA identified in the specification (it is a "DNA sequence[] encoding the 75/65 kD"), it was made before August 31, 1990 and it was properly deposited with the ATCC. FOF 42, 68, 93-95. The deposited plasmid is part of Roche Patents' written description as from their 1990 priority dates. *In re Lundak*, 773 F.3d 1216, 1223 (Fed. Cir. 1985).

those partial sequences which code for soluble TNF-BP can be determined and cut out from the complete sequence using known methods." (emphasis added) FOF 92.

### 3. The Disclosure Identifies the Exon-Defined Ig Hinge-CH2-CH3 Portion as the Second Part of the Fusions

The disclosure also identifies the Ig part of the claimed fusion proteins, indicating it consists of all domains except the first of a human IgG1 or IgG3 heavy chain constant region. FOF 99. It unquestionably describes these as *exon-defined* Ig domains—it discloses deposited vectors including "pCD4-Hγ1," which contain DNA sequences encoding the *exon-defined* hinge, CH2, and CH3 part of a human IgG1 heavy chain. FOF 101. The sequencing work done by Sandoz's own expert, Dr. Kittendorf, confirmed that is what is in the pCD4-Hγ1 vector. FOF 61. And because that deposited vector is identified in the disclosure, it provides a sufficient written description of the exon-encoded hinge-CH2-CH3 of the IgG1 heavy chain constant region. *Enzo*, 323 F.3d at 965.

### 4. The Roche Patents Describe the Claimed p75-Ig Fusions

The disclosure, in addition to identifying both components, says to combine them to yield the claimed p75-Ig fusions—as it states (and echoes in two other locations), the invention includes "*a combination* of two partial DNA sequences with one … coding for those soluble fragments of non-soluble proteins which bind TNF (see above)" (*i.e.*, p55 or p75) and the other "coding for all domains other than the first domain of the constant region of the heavy chain of … in particular $IgG_1$ or

$IgG_3$ subtypes." FOF 103. It also describes using examples of vectors encoding parts of IgG1 and IgG3 heavy chains (pCD4-Hγ1 and pCD4-Hγ3) to make fusion proteins consisting of "a soluble fragment of non-soluble TNF-BP" (i.e., p55 or p75) and "all domains except the first of the constant region of the heavy chain." FOF 104. And by pointing to Example 11 as a recipe for "TNF-BP" fusions, it describes use of the extracellular region of either the p55 or p75 "TNF-BP" in these fusions. FOF 104-106. The disclosure clearly demonstrates possession of the claimed p75-IgG1 fusion protein. FOF 107.

#### 5. The Roche '522 Patent Describes Its Claimed Methods

Sandoz offered no evidence at trial that the steps of the claimed methods of the '522 patent were not adequately described; it only asserted the '522 patent failed to describe the p75 fusion that results from performing those steps. As that fusion protein is described, Sandoz's challenge to the '522 patent fails.[3]

### B. Sandoz's Written Description Challenge Fails as It Rests on a Misreading of the Disclosure and Ignores Applicable Precedent

Sandoz, relying on Dr. Capon, argues the disclosure is defective because it does not reproduce the known p75 sequence within its four corners—they contend

[3] Dr. Capon criticized amendments to the '522 patent specification, but each was approved by the PTO, FOF 53, and Dr. Capon has no basis for suggesting the PTO erred in approving them. Regardless, the amendments were proper because they added nothing beyond what the priority applications identified—the known p75 sequence in Smith 1990. *Id.* Sandoz's complaints also, at most, relate to claims 8 and 10; claim 3 and its parent claim 1 do not refer to SEQ ID NO: 27.

the only TNFRs it describes are p55 and a "truncated and mutated" p75 in Figure 4 that is not the known p75 TNFR published before August of 1990. D.I. 603 at 41 ("the only amino acid sequence in the specification that is related to the p75 TNF receptor is disclosed in Figure 4."); 9/13A, 22:1-7.

Dr. Capon's trial testimony cannot be reconciled with the claim language specifying that the p75 TNFR extracellular region portion of the fusion must contain the amino acid sequence listed in SEQ ID NO: 10, which Dr. Capon acknowledged the Figure 4 sequence does not contain. FOF 134. The Roche inventors isolated the partial cDNA in Figure 4 along with several other cDNAs as described in the disclosure. FOF 64-65. By their terms the claims referencing SEQ ID NO: 10 exclude the Figure 4 partial cDNA because it omits that sequence. FOF 134. Dr. Naismith also testified without contradiction that SEQ. ID NO: 10 would have pointed the POSA to the known p75 TNFR sequence published in Smith 1990 and Dembic, not Figure 4 (FOF 90, 141) and the disclosure unambiguously identifies the known p75 sequence as one source of "soluble fragments" of "TNF-BP" to use in fusion proteins, as explained above (FOF 127-28, 88-98, 103).

Dr. Capon's testimony about multiple, different sized p75 TNFRs is also inconsistent with scientific evidence published before August 1990 showing that HL60 cells only make one p75 mRNA "message." FOF 44, 131. That, as Dr. Naismith explained, means that HL60 cells only make *one* p75 TNFR, *not two*

*different sized* p75 TNFRs. FOF 131. The disclosure identifies HL60 cells as the source of not only the "75/65 kD" receptor which the inventors isolated and found to contain SEQ ID NOs: 7 and 10 but the cDNA library from which the Figure 4 partial cDNA was isolated. FOF 58, 63-65, 132. This evidence also rules out Dr. Capon's claim that the two different sized bands in Example 6 contained two different TNFRs. FOF 132. The disclosure stated that both bands bound TNF and reacted with an anti-P75 TNFR antibody, and Dr. Naismith explained the size difference was due to different patterns of glycosylation of the *single* p75 TNFR protein present in both bands, FOF 62, 140; Indeed, the disclosure uses the label "65/75 kD" to refer to this *single* p75 TNFR found in both bands. FOF 62.

Dr. Capon's testimony about theoretical impacts of differences between the Figure 4 and known p75 sequences also was not credible. The first difference he points to—that Figure 4 omits the "first 70 amino acids" of p75 TNFR—cannot be reconciled with how the disclosure actually refers to Figure 4; it calls it a "partial cDNA" of p75, not a complete p75 TNFR sequence.[4] FOF 65, 126. Next, he testified that three amino acid differences in the extracellular region of each sequence might introduce "drastic" changes affecting the protein's biological functions. That, however, was ruled out by experimental evidence published before and after August

[4] A POSA also would not have counted the 22 amino acids leader sequence as part of the p75 TNFR protein sequence, as Dr. Capon did. FOF 134 n.7.

31, 1990; allelic variants of p75 TNFR with one or two of those changes bound TNF tightly. FOF 133, 137-139. The disclosure itself refutes Dr. Capon's theory that a third "conservative" amino acid change might affect glycosylation and thus TNF binding—Example 6 reports that p75 TNFR with differing patterns of glycosylation bound TNF. FOF 140.

Finally, Dr. Capon did not offer credible testimony that a POSA would have read the disclosure's reference to a "deletion" in Smith 1990 as affirmatively discouraging use of the known p75 TNFR. FOF 125. Doing that requires reading the disclosure in a knowingly incorrect manner—that when it says Smith 1990 discloses a "deletion," it is saying Smith is describing a *smaller* sequence than that in Figure 4; the Smith 1990 sequence, however, is indisputably *larger* than the Figure 4 sequence. Trial Tr. (Capon) at 37:20-25 (for "75 you start with Figure 4, and you go smaller.") The plausible reading is what Dr. Naismith provided—this passage is simply identifying Smith 1990 as a source of soluble fragments of the known p75 TNFR to use in fusion proteins. 9/18P 52:10-53:7.

### C. Sandoz Enablement Challenge Fails, as Its Own Experts Concede

Although Sandoz contended before trial that the claims were not enabled, its two experts, Drs. Blobel and Capon, conceded that a skilled person could have produced the claimed fusion proteins without undue experimentation by using known methods as of August 1990. FOF 111. Those concessions doom Sandoz's

enablement challenge. The asserted claims are enabled.

## II. The Asserted Claims Are Not Obvious

To overcome the presumption of validity, Sandoz was required to provide proof—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." 35 U.S.C. § 103. That is a question of law based on factual determinations including: (1) the scope and content of the prior art; (2) differences between the prior art and claims at issue; (3) the level of ordinary skill in the art; and (4) objective indicia of nonobviousness such as unexpected results, commercial success, long felt but unsolved needs, and failure of others, etc. *Graham v. John Deere Co. of Kan. City,* 383 U.S. 1, 17 (1966).

The "genius of invention is often a combination of known elements which in hindsight seems preordained," *Polaris Indus., Inc. v. Arctic Cat, Inc.,* 882 F.3d 1056, 1078 (Fed. Cir. 2018). As nearly all inventions are "combinations of what, in some sense, is already known," a claim cannot be held obvious "merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Intl. Co. v. Teleflex Inc.,* 550 U.S. 398, 418-19 (2007). Instead, the challenger must prove a POSA would have been motivated to combine prior art teachings to achieve the claimed invention, and would have had a reasonable expectation of success in doing so. *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.,* 876 F.3d 1350, 1359-61

(Fed. Cir. 2017). That task is particularly difficult when, as here, the same prior art has already been considered by the PTO. *Shire LLC v. Amneal Pharm., LLC*, 802 F.3d 1301, 1307 (Fed. Cir. 2015).

Sandoz's obviousness case was an exercise in pure hindsight. It failed to show why a POSA would have been motivated to use any part of either p75 or an Ig to treat inflammation, much less the particular parts selected by the Roche inventors, or to make the claimed combination. In truth, the "genius of invention" of the Roche Patents was a combination that not only had never been made before, but defied conventional wisdom to produce unexpected results that, in Sandoz's own words, "changed the practice of medicine." FOF 235. Sandoz fell far short of its burden of proving obviousness by clear and convincing evidence.

### A. Sandoz's Proof Failed, as Its Expert Did the Wrong Analysis.

Before even getting to the *Graham* factors, Sandoz's obviousness expert, Dr. Blobel, violated the most fundamental precept of any validity analysis—that the prior art be compared to the *properly construed* claims of the patents. *See, e.g.*, *Medichem, S.A. v. Rolabo, S.L.*, 353 F.3d 928, 933 (Fed. Cir. 2003) ("The first step … is a proper construction of the claims."). Ignoring the agreed claim construction, Dr. Blobel testified the claimed fusion protein could include a linker and that its hinge could have two *or* three cysteine residues; he then proceeded to rely on prior art that included those features. FOF 184, 187-188, 193, 201. But the claims use the

closed language "consist" or "consist essentially of"—which means the fusions *only* have two parts and exclude unrecited elements, such as a linker. And Sandoz's acceptance of the "exon-encoded" construction for IgG domains (D.I. 618) means the claimed fusions must have a hinge with three cysteines. Dr. Blobel's own testimony confirms his errors make a difference; he repeatedly emphasized it would *not* have been obvious to choose a three-cysteine hinge over a two-cysteine hinge. FOF 264. Opinions based on an "incorrect understanding of the claim construction" are worthless, and the Court should "disregard that testimony." *Cordis Corp. v. Boston Sci. Corp.*, 658 F.3d 1347, 1357 (Fed. Cir. 2011). Sandoz's only witness on obviousness was Dr. Blobel; his testimony cannot, as a matter of law, support Sandoz's case.

### B. The Evidence Demonstrates the Claims Were Not Obvious

#### 1. Level of Ordinary Skill.

Plaintiffs' experts identified a POSA as 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, protein expression, protein, purification, cell culturing, and basic immunology. FOF 18. Sandoz's definition was not materially different. *Id*.

#### 2. Scope and Content of the Prior Art.

Sandoz's obviousness case starts with the premise that a POSA seeking new therapies for auto-immune disorders would have picked TNF as an agent to target,

and then would have picked one of the TNFRs as a TNF-inhibitor. Because no prior art disclosed etanercept or any other similar TNFR/IgG fusions, Sandoz and Dr. Blobel were forced to rely on prior art they alleged to separately disclose etanercept's component parts. FOF 147, 160-195. They arranged the references—all of which had been considered by the PTO (FOF FN. 4)—in six combinations, each including a reference that disclosed the p75 TNFR (the Smith 1990 article and Smith '760 patent) and one or more references that described unrelated Ig fusions (Seed '262, Byrn 1990, Watson 1990, Karjalainen '827,[5] Capon '964, and Traunecker 1989). FOF 147.

The record refutes this foundation of Sandoz's theory and exposes "the 'insidious' exercise of decisional hindsight" at the heart of Sandoz's case, *In re Ethicon,* 844 F.3d 1344, 1355-56 (Fed. Cir. 2017), for it was only the post-invention knowledge of the TNFR/IgG1 combination *in etanercept* that led Sandoz and Dr. Blobel to "pluck[]" these references "out of the sea of prior art," *WBIP, LLC v. Kohler Co*., 829 F.3d 1317, 1337 (Fed. Cir. 2016).

As Plaintiffs' expert, Dr. Wall, an expert in immunology, explained, dozens of cytokines, including TNF, had been identified by August 1990 and many were

[5] At trial, Dr. Blobel conceded that Karjalainen '827, published after August 1990, was not prior art. FOF 191. Under 35 U.S.C. § 103(c)(1), it also cannot be used for obviousness because Hoffmann-La Roche AG owned both the claimed invention and the subject matter of Karjalainen '827 as of August 1990. *Id*.

believed to potentially be associated with auto-immune disorders. FOF 27, 29, 150. The cytokine network, however, is highly complex, and the numerous and redundant properties of cytokine made it exceedingly difficult to isolate the role of any given cytokine in different diseases. FOF 150. For that reason, even the Brennan 1989 paper on which Dr. Blobel relied made clear that not just TNF, but a host of cytokines, were potentially implicated in auto-immune disorders and that the "relative importance" of each remained "unclear." *Id*. As two of the Brennan 1989 authors later reported, it is a "misconception" to think that TNF was an "obvious therapeutic target" given the "plethora of possible cytokine therapeutic targets" and the "prevailing view" in the early 1990s that "blocking any one pro-inflammatory mediator in isolation would not be beneficial as those remaining would drive the biological processes." FOF 149.

Even if a POSA had selected TNF as a starting point for research, that would not have led to use of TNFRs as potential therapies. Though the amino acid sequences of p55 and p75 were published before August 1990, their physiological role had not been established, according to Dr. Wall's unrebutted testimony. FOF 31. Researchers speculated that soluble TNFRs might be useful for treating TNF-related disorders (FOF 31), but the prior art—including a paper cited by Dr. Blobel—also warned that TNFRs could exacerbate TNF-related conditions (FOF 31). The prior art therefore did not identify TNFRs as the "most promising to modify

in order to improve upon its … activity and obtain a compound with better activity." *Otsuka Pharm. Co. v. Sandoz, Inc*., 678 F.3d 1280, 1291 (Fed. Cir. 2012). And, as here, when the prior art "as a whole" points in "many directions," the choice of a particular compound, like TNFRs, as a starting point is not obvious. *Takeda Chem. Indus. v. Alphapharm Pty.,* 492 F.3d 1350, 1363 (Fed. Cir. 2007).

The unfounded hindsight in Sandoz's focus on TNFRs is evident as well in its selection of IgG fusion references to include in its combinations. The prior art Ig fusion proteins were developed as potential therapies for HIV/AIDS. FOF 171-174. To the extent their potential had been considered at all, it was to *elicit* immune system effector functions to kill HIV-infected cells. FOF 173-174. Such effector functions, like CDC and ADCC, provoke inflammatory processes as part of their disease-fighting mechanism—precisely what a treatment for auto-immune disorders like RA seeks to *prevent*. FOF 156, 206-208.

Researchers at the time also specifically warned of the possible adverse auto-immune impact of such Ig fusion proteins in therapy:

> One of the most important issues confronting these agents is the extent of autoimmune damage arising from the interaction of the fusion protein with its native ligand [*i.e.,* binding partner].

FOF 198, 209, 223. Although Dr. Blobel failed to consider this when formulating his opinions, he did recognize that such concerns were something a POSA would "take into consideration for sure." FOF 2114. This evidence refutes the idea that a

POSA would have looked to the IgG fusion protein literature as a "natural choice for further development efforts." *Otskua Pharm.,* 678 F.3d at 1291.

Sandoz attempted to explain away such concerns by wandering beyond Dr. Blobel's expertise. By his own admission, Dr. Blobel is "not an immunologist." FOF 211. Moreover, his contention that inflammation concerns would not have applied in the context of soluble molecules, like TNF, was directly refuted by (1) a general immunology textbook from the relevant period (Paul 1989), and (2) Plaintiffs' expert, Dr. Wall, who *is* an immunologist. FOF 211. Sandoz's supposed distinction between soluble and membrane-bound targets was both misplaced and ultimately irrelevant. FOF 212.

The undisputed evidence, including testimony from Plaintiffs' expert, Dr. Greene, showed that Ig fusion proteins contain the structural elements known to elicit effector functions and had repeatedly been shown to trigger those functions by August 1990. FOF 173, 210, 255. Given that, a POSA would have expected a TNFR fusion targeting TNF to also exhibit effector functions. FOF 255. Dr. Blobel acknowledged both points—IgG fusions included all the elements necessary for effector functions and were specifically designed to have cell-killing activity. FOF 181. While no further confirmation is needed, the fact that the FDA required Sandoz to test its etanercept biosimilar for effector activity confirms the gravity of the risks of inflammation for RA patients even today. FOF 259.

### 3. Differences between the Prior Art and the Claimed Invention.

The difference between the prior art and the claimed invention is undisputed: the claims require a fusion protein consisting of the extracellular region of the p75 TNFR and the exon-defined hinge, CH2, and CH3 human IgG1 domains while the prior art disclosed no such structure. To bridge this chasm, Sandoz argues that a POSA would have been motivated to make a fusion that combined these separate and unrelated structures. Sandoz's theory faces two insurmountable problems.

First, the prior art as of August 1990 taught that an IgG1, and in particular its hinge and CH2 domains, activated effector functions leading to inflammation; a consequence contrary to the goal of treating auto-immune disorders. FOF 156, 174-177, 206-210. Isolated statements, with no data, speculating that, perhaps, certain very different fusion proteins might be used for anti-inflammatory purposes cannot override this clear understanding in the art. FOF 193-195, 223, 237.

Second, none of the specific motivations Dr. Blobel advanced for combining a TNFR with an IgG fragment—namely, extending plasma half-life, improving its binding affinity, and facilitating purification—would have prompted a POSA to ignore the effector function and pro-inflammatory effects of an Ig. FOF 209-210, 224. Worse, Dr. Blobel admitted that *all* these supposed motivations "could have been achieved by making the chimeric antibody disclosed in Smith's '760 patent instead of etanercept." FOF 225. And there were many other known ways in the art

to achieve those goals (*e.g.*, polyethylene glycol). FOF 166, 169, 204, 233-234.

As a threshold matter, a supposed solution to a problem cannot provide a motivation to modify prior art if "the problem was not known, the possible approaches to solving the problem were not known or finite, and the solution was not predictable." *Leo Pharm. Prods., Ltd. v. Rea,* 726 F.3d 1346, 1356-57 (Fed. Cir. 2013). Sandoz and Dr. Blobel also failed to identify anything in the prior art showing that their three proposed motivations were necessary or desirable for the recently cloned TNFRs. Far from it: the evidence to which Sandoz points is Dr. Loetscher's testimony that the *inventors* believed fusing a soluble TNFR to an IgG component might enhance its half-life and binding affinity. FOF 46. But "the path that leads an inventor to the invention is expressly made irrelevant to patentability by statute," *Life Techs., Inc. v. Clontech Lab., Inc.,* 224 F.3d 1320, 1325 (Fed. Cir. 2000), as "[i]nventors, as a class, … possess something … which sets them apart from the workers of *ordinary* skill," *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) (emphasis in original).[6]

Beyond their failure to establish a credible motivation to combine a TNFR with an IgG, Sandoz fails to show why a POSA would have been motivated to combine the *specific* parts of each that make up etanercept—*i.e.,* the extracellular

[6] In any event, Dr. Loetscher testified the inventors in fact did not know whether their modifications would actually enhance these properties. FOF 46.

portion of p75 and the *exon-defined* hinge, CH2, and CH3 domains of human IgG1. The required motivation, after all, is a motivation to combine prior art teachings "to achieve *the claimed invention*," with "a reasonable expectation of success in doing so." *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.,* 688 F.3d 1342, 1360 (Fed. Cir. 2012) (emphasis added).

Neither motivation nor reasonable expectation was established here. Regarding the extracellular TNFR component, its role in the body was uncertain (FOF 31); even if POSA were motivated to develop this molecule, two distinct TNFRs (p55 and p75) with quite different structures were known, each exhibiting different relative potencies in neutralizing TNF in laboratory tests, with soluble p55 being five times more effective. FOF 289-290. Sandoz and Dr. Blobel offered no reason, other than hindsight, why a POSA would have picked p75 over p55 with a reasonable expectation of developing a therapeutic.

A POSA who sought to use an IgG part despite known concerns about their effector functions faced even more choices. Why omit the light chains or CH1 domain, especially when retaining CH1 seemed to reduce the effector function in CD4 fusion proteins (FOF 179-181)? And Sandoz's claim of an "evolution" towards IgG fusion proteins lacking the CH1 domain after Traunecker 1989 did not hold up at trial. FOF 158-159. The evidence instead showed that many different Ig components were known in the prior art, and there was no clear trend toward use of

one. Notably, Dr. Blobel after using a demonstrative to contend there was an "evolutionary" trend toward one, acknowledged his demonstrative had material errors and omissions—he not only mis-ordered the timeline of publications, but omitted prior art structures in them that did not fit into his storyline. FOF 158. Dr. Blobel's testimony that removal of CH1 was considered preferable to address "secretion" issues was also misleading: fusion proteins retaining CH1 were made before *and* after Traunecker's 1989 paper and were even labeled "particularly preferred." FOF 235.[7]

Obviousness cannot be established where the prior art provided no "reason to select (among several unpredictable alternatives) the exact route" that led to the invention. *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 (attempts to solve problem by trying "a variety of things [] over a course of a number of years" supported finding of no motivation to combine). Even Sandoz's highly curated selection of prior art identified no such reason here. Sandoz failed to satisfy its heavy burden to establish a *prima facie* case of obviousness for any of the asserted claims.

[7] Sandoz failed to prove its alternative theory that a POSA would have been motivated to remove the CH1 domain and light chains from the "chimeric antibody molecule" in the Smith '760 patent. FOF 167. Smith '760 teaches that its "chimeric antibody molecule" should have "unmodified constant region domains." FOF 167. The notion that a POSA would have found it obvious to use this molecule to treat auto-immune disease but decide before testing that it was not suitable for that purpose absent modification makes no sense. FOF 168.

**4. Objective Indicia Confirm Non-Obviousness of the Claims.**

Multiple objective indicia reinforce the non-obviousness of the patented inventions. Such evidence "can be the most probative evidence of nonobviousness in the record," and can "enable 'the court to avert the trap of hindsight'"—the very trap that Sandoz seeks to lay. *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017). Sandoz's attempt to dismiss this probative evidence at trial utterly failed.

*Nexus*. There is no serious dispute that all of the secondary indicia have a nexus to the claims—they are all linked to etanercept, which the claims effectively define. *WBIP*, 829 F.3d at 1329 (nexus between the patented invention and objective indicia can be presumed when the asserted claims cover the product).

*Unexpected Results*. Unexpected results are a "superior property or advantage that [a skilled artisan] would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). That reflects common sense: "that which would have been surprising … would not have been obvious." *Id*. Etanercept exhibits at least three such unexpected properties: (1) a lack of aggregation; (2) 50-fold higher binding affinity and 1000-fold higher TNF neutralization activity; and (3) little to no ADCC and CDC activity. FOF 252-254.

First, a POSA would have expected etanercept, like antibodies, to bind TNF in a "mode" that resulted in aggregation. FOF 230-31, 252-53, 260. The prior art

showed that antibodies and other fusion proteins were able to "cross-link" different targets and cause aggregation. FOF 231. And that is what was generally expected for bivalent molecules, save for extremely rare instances in which both the binding molecule and its multivalent target had exactly the right structures and orientation to each other. FOF ¶ 253. Etanercept had such a structure; it exhibited this unique "mode 2" binding to TNF that does not cause aggregation. *Id*.

Second, etanercept exhibited an unexpected 50-fold increase in its affinity for TNF and a 1000-fold increase in its TNF neutralization activity. FOF 254. Neither property would have been expected in August of 1990. *Id*.

Finally, etanercept exhibits little to no ADCC or CDC activity. FOF 255. That was unexpected, according to Plaintiffs' expert Dr. Greene, because etanercept includes structural features that elicit these effector functions, as seen in prior art IgG fusion proteins. *Id*.

On each of the binding properties, Dr. Naismith provided compelling and objective testimony grounded on his careful study of etanercept and TNF. FOF 230-231, 252-254. Dr. Skerra's opinions, by contrast, lacked any credibility because they were based *on the wrong molecule*. He was told, but remarkably did not independently investigate, what etanercept's properties were—he believed (incorrectly) that it had only 185 of the 235 amino acids in the p75 extracellular region, an assumption even he recognized was material to his opinions. FOF 232.

When he attempted at trial to dismiss the impact of adding back the missing 50 amino acids in etanercept, he was impeached with his deposition testimony, where he had testified those extra 50 amino acids would have led a POSA to expect it to *cause* aggregation—contrary to his trial testimony. *Id*.

*Long-felt, but Unmet Need and the Failure of Others*. A desire for a "safer, less toxic, and more effective" alternative to existing therapies is a basis for finding long-felt but unmet need, *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc*., 471 F.3d 1369, 1380 (Fed. Cir. 2006), as is "the failure of others to develop" a safe and effective drug, *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).

Dr. Fleischmann gave unrebutted testimony that etanercept satisfied a long-felt, but unmet medical need. FOF 240. A 1991 article, for example, called the outlook for RA treatment "depressing" without "any specific 'targeted' therapy." FOF 241. Prior art therapies in use since the late 1800s were of limited utility, and the most common therapy, methotrexate, approved in 1988, helped only a small minority of patients. FOF 240. Other research groups, including those interested in TNFRs, failed to develop a therapeutic before the invention. FOF 242. The approval of Enbrel® in 1998 was a game-changer. Enbrel's efficacy in ~70% of patients was hailed as a true breakthrough. FOF 241. It plainly met a need and succeeded where others had failed for decades.

*Praise and Clinical Success*. "Industry participants, especially competitors, are not likely to praise an obvious advance over the known art," and so evidence of such praise "weighs against an assertion that the same claim would have been obvious." *WBIP*, 829 F.3d at 1334. There was no dispute at trial that Enbrel® received widespread praise, even from Sandoz. FOF 239. It was hailed as a "truly breakthrough" drug that ushered in a "new era" of treatment and which Sandoz said "changed the practice of medicine." FOF 239, 241. Evidence of a drug's success among doctors and patients is similarly telling. *See, e.g.*, *Janssen Prod., L.P. v. Lupin Ltd.*, 109 F. Supp. 3d 650, 671 (D.N.J. 2014), *modified*, 2016 WL 1029269 (D.N.J. Mar. 15, 2016). Enbrel®'s clinical and commercial success were undisputed. It was widely prescribed from the start, and prescriptions rose rapidly through 2008, despite supply shortages and the entry of two major competitors, Humira® and Remicade®. FOF 243-244. The evidence showed, moreover, 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). FOF 244; *see also WBIP*, 829 F.3d at 1329 (nexus between the patented invention and objective indicia can be presumed when the asserted claims cover the product).

*Copying*. Copying is probative of non-obviousness because the "tribute of [an alleged infringer's] imitation" suggests that the invention was superior to other options. *Diamond Rubber Co. v. Consol. Rubber Tire Co.*, 220 U.S. 428, 450 (1911).

Even for pharmaceuticals, copying is relevant when it is not required for regulatory approval and 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). Sandoz's copying fits that profile. Soon after the Roche Patents issued, Sandoz initiated a design-around program and identified candidates it believed would avoid the Roche Patent claims and could secure FDA approval. FOF 245-246. Sandoz ultimately abandoned those efforts and copied not only etanercept's exact amino acid sequence but the method used to make it. FOF 247-248.

*Licensing*. "Recognition and acceptance of the patent by competitors who take licenses under it to avail themselves of the merits of the invention is evidence of nonobviousness." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1539 (Fed. Cir. 1983). Here, Immunex and Amgen paid Roche large sums to practice etanercept under the 1998 license and the 2004 A&S. FOF 250-251.

*Alleged Simultaneous Invention*. "Simultaneous invention" is relevant only in "rare instances," and cannot make up for a failure to make out a *prima facie* case of obviousness. *Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010). Rather than helping Sandoz, the allegedly "simultaneous" work simply confirms that the claimed fusion protein was *not* obvious.

There is no dispute that Behringwerke, U. Texas, and Genentech never made

the claimed invention.[8] FOF 264, 267, 269-270. These groups could not have "simultaneously invented" a protein they never made or proposed. *See, e.g.*, *Shire* 2018 WL 2684097 at *20 ("Because NPC 16731 and icatibant are two different peptides, NPC 16731 cannot demonstrate near-simultaneous invention."); *see also Endo Pharm. Inc. v. Amneal Pharm., LLC*, 224 F. Supp. 3d 368, 381 (D. Del. 2016). That these researchers, who include a Nobel Laureate, all went "in different ways" is in reality "strong evidence" the claimed invention was not obvious. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.,* 676 F.3d 1063, 1082 (Fed. Cir. 2012).

Immunex's late 1990 development of etanercept also does not help Sandoz. That work was motivated by post-priority data from Behringwerke (FOF 263)—a different state of the art than what the Roche inventors faced—and is not an example of near-simultaneous invention. *See In re Nuvasive*, 842 F.3d 1376, 1384 (Fed. Cir. 2016) (disclosures after an invention's priority date cannot serve as motivation to make the invention). A single instance of near-simultaneous invention also cannot

[8] Even if they had developed the same molecule—which they did not—Sandoz did not prove any of this work occurred before Roche Patents were filed, and two were not before publication of the Roche invention in March of 1991. That diminishes what little probative value it might have, as it may have simply reflected a "shift in the state of the art." FOF 266, 268; *Eli Lilly & Co. v. Teva Pharms. USA*, No. IP 02-0512-C-B/S, 2004 WL 1724632, n.23 (S.D. Ind. Jul. 29, 2004); *Shire Orphan Therapies LLC v. Fresenius Kabi USA, LLC*, No. CV 15-1102-GMS, 2018 WL 2684097, 2018 WL 2684097, *20 (D. Del. June 5, 2018) (research "after the first invention has been publicized has little probative force.").

prove obviousness—if it did, there would be no reason to resolve prior inventorship disputes among two or more applicants via interference proceedings under the pre-AIA statute. *Envtl. Designs v. Union Oil Co.*, 713 F.2d 693, 698 n.7 (Fed. Cir. 1983). In any event, Immunex recognized that Roche's invention came first and took a license, acknowledging its inventive nature.

## III. Sandoz's ODP Arguments Based on the Roche '279 Patent Fail.

Sandoz's first ODP challenge is based on claim 5 of the '279 patent owned by Roche. At trial, Sandoz stipulated the safe harbor of 35 U.S.C. § 121 protects the '522 patent against a challenge based on the '279 patent. FOF 277. That leaves only Sandoz's challenge to the '182 Patent, which fails on the facts.

### A. The Safe Harbor of 35 U.S.C. § 121 Protects the Asserted Claims from ODP Based on the '279 Patent.

Under 35 U.S.C. § 121, the '279 patent cannot be used against the '182 patent if the '182 patent issued from a divisional application "filed as a result of" a "requirement for restriction." *Id.* That is exactly what happened here.

Steven Kunin, an expert on PTO practice, testified without contradiction that the '182 patent issued from a divisional application filed as a result of a PTO restriction requirement in the prosecution of the '279 patent. FOF 278-82. That restriction required Roche to elect between prosecuting claims to either the p55 or the p75 TNFR. FOF 280. In response, Roche elected the p55 species and eventually was granted the '279 patent with claims to it, while the p75 claims were pursued in

a divisional application that led to the '182 patent. FOF 285.

In its pre-trial brief, Sandoz raised only one issue—whether Roche was entitled during prosecution of the '182 patent to amend its pending claims to bring them into consonance with the restriction requirement. *See* D.I. 603 at 39. In Sandoz's view, that it took time to do so forever bars access to the safe harbor. But there is nothing in § 121—or in any case applying it—that imposes such a time limit. Mr. Kunin's unrebutted testimony instead established that the PTO *does* permit applicants to amend claims to invoke the safe harbor at any time. FOF 284. *Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc.*, 592 F.3d 1340 (Fed. Cir. 2010), also instructs that the proper inquiry is on the *issued* claims—the Court found the safe harbor to apply in that case even though claims had been presented (but never issued) that were *not* consonant. *Id.* at 1354. Because consonance of the issued claims here is undisputed, FOF 283, the safe harbor applies.

### B. The Claims of the '182 Patent Would Not Have Been Obvious in Light of Claim 5 of the '279 Patent.

Even without the safe harbor, Sandoz's ODP challenge would fail. The '279 patent claims a p55 fusion protein, and Sandoz has argued p55 is "an entirely different receptor" than p75. D.I. 603 at 1. The PTO found during prosecution the two TNFRs are "unobvious in view of each other." FOF 291. There would have been no reason to modify a p55 fusion protein to get to a p75 fusion protein, because as Dr. Greene explained, p55 was known to be a *more active* TNF inhibitor than p75.

*See* FOF 289-290. The p75 TNFR-IgG fusion of the claims is patentably distinct from p55 and fusions based on it. FOF 288-292. Sandoz cannot establish ODP by clear and convincing evidence.

## IV. Sandoz's ODP Arguments Based on the Immunex Patents Fail.

Sandoz advances a novel theory of ODP to suggest that Immunex's patents related to etanercept can be used as ODP references against the Roche Patents. It argues that Immunex's exclusive license—taken 14 years after the Roche invention—transferred sufficient rights to Immunex such that the resultant Roche Patents, created by different inventors working at a different company at a different time, are invalid in light of Immunex's independently developed and patented inventions. Sandoz draws on the "all substantial rights" test from prudential standing law to argue that Immunex is the "owner" of the Roche Patents for ODP purposes. This theory has no support in the law or the facts of this case.

### A. The Immunex and Roche Patents Are Not "Commonly Owned" By Immunex, Whether for ODP Purposes or Otherwise.

The Immunex patents Sandoz seeks to use as ODP references against the Roche Patents are Jacobs '690 and three Finck patents. None are available to use against the Roche Patents, as none have any common inventors with the Roche Patents, and because they and the Roche Patents are not, and have never been, "commonly owned." FOF 295-298.

ODP is grounded in the text of the Patent Act, which gives an inventor the

right to seek "*a* patent" for his or her invention. 35 U.S.C. § 101 (emphasis added). Prototypical ODP occurs when an *inventor* seeks two patents for essentially the same invention. *See Gilead Scis., Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1212 (Fed. Cir. 2014). Indeed, at one time, "common ownership" was not a recognized basis for ODP at the PTO. *See* Commissioner's Notice, 834 O.G. 1615, 1615 (Jan. 31, 1967) (ODP "should not be applied to situations involving commonly owned cases of different inventive entities"). The PTO saw no need for ODP rejections absent common inventors, as "Sections 102 and 103 [already] … preclude[d] the granting of two or more patents" for essentially the same invention. *Id.* at 1616.

Things changed when Congress enacted 35 U.S.C § 103(c)(1). That provision treats certain commonly-owned work as if it was done by a single inventor, barring the use of one inventor's work as prior art against another. Its enactment opened a potential gap in the law, because it could lead to the issuance of multiple patents covering essentially the same invention. Congress expected that ODP would fill this narrow statutory gap. S. Rep. No. 98-663, at 8 (1984).

Consistent with this gap-filling purpose, ODP cases have applied a strict "common ownership" test that mirrors § 103(c)(1)'s requirements; it requires proof the inventions were wholly owned by the same entity at the time the invention was made. *See Novartis Pharms. Corp. v. Noven Pharms., Inc.*, 125 F. Supp. 3d 474, 487 (D. Del. 2015) (applying test from Manual of Patent Examining Procedure (MPEP)

§ 706.02(*l*)(2)); *Ex parte Brookhart*, No. 2005-2463, 2005 Pat. App. Lexis 2485, *4 (B.P.A.I. Sept. 19, 2005) (same). The PTO applies this same strict test in ODP, *see* MPEP § 804.03(II); *see also Gilead*, 753 F.3d at 1216-17 (looking to MPEP guidance on ODP); *In re Hubbell*, 709 F.3d 1140, 1146 (Fed. Cir. 2013) (same), and Congress likewise expected courts would, too. *See* S. Rep. No. 98-663, at 8 ("The term 'commonly owned' means wholly owned by the same person, persons, or organization at the time the invention was made.").

Sandoz argues these common-ownership cases are really about "commonness" rather than "ownership." 9/11/2018 AM 30:12-13 ("This is about what 'common' is."). But there is no reason why "common ownership" would mean one thing in "commonness" cases and another in "ownership" cases. Nor do the cases reflect Sandoz's distinction. *Novartis*, for example, did not examine "commonness"; it simply applied the prevailing "common ownership" standard. *See, e.g.*, 125 F. Supp. 3d at 487.[9]

Because Sandoz cannot prove common ownership under the prevailing standard, it asks this Court to be the first to import the "all substantial rights" test from prudential standing cases into the double-patenting context, substituting

[9] Sandoz pointed to MPEP § 804.03 (¶ 8.28), *see* 9/11/2018 AM 31:13-32:9, which says a pro forma ODP rejection should "also be included" when there is "no evidence of common ownership." But as the very next part of § 804.03 makes clear, this is done to simply elicit information about *whether* such common ownership existed or not. *See* MPEP 804.03, ¶ 8.28.01.

"effective" common ownership for actual ownership at the time of invention. *But see Advanced Cardiovascular Sys. v. Medtronic, Inc.*, No. 95-cv-3577, 1996 WL 467293, *9 (N.D. Cal. July 24, 1996) (expressly refusing to "broaden[] the concept of double patenting to include 'effective' common ownership").

Sandoz also argues the all-substantial-rights test is the "only test the Federal Circuit has ever applied." 9/11/2018 AM 22:4-5. Not so—the Court's general rule for patent ownership issues looks to state law. *See Jim Arnold Corp. v. Hydrotech Sys., Inc.*, 109 F.3d 1567, 1572 (Fed. Cir. 1997) ("the question of who owns the patent rights and on what terms typically is a question exclusively for state courts"); *MyMail, Ltd. v. America Online, Inc.*, 476 F.3d 1372, 1376 (Fed. Cir. 2007).[10] The all-substantial-rights test addresses a particular, practical problem of "prudential" standing: sorting out when an exclusive licensee must join the patent owner as a co-plaintiff and when the licensee can sue on its own. *See Prima Tek II, L.L.C. v. A-Roo Co.*, 222 F.3d 1372, 1377 (Fed. Cir. 2000).

By using it as a new way to invalidate patents, Sandoz seeks to turn the all-substantial-rights test—a doctrine developed to facilitate the efficient enforcement of patent rights—on its head. Importing a standing doctrine into ODP would create

[10] Applying state law here would require "effectuat[ing] the parties' intent" in the 2004 A&S, *Lorillard Tobacco Co. v. Am. Legacy Found.*, 903 A.2d 728, 739 (Del. 2006); JTX-12 at 16 (§ 11.12) (choosing Delaware law to govern A&S), which was *not* to transfer ownership. *See* FOF 299-300.

a regime of contagious patent invalidity, with absurd and wide-ranging consequences. Patents valid when issued could spontaneously self-destruct upon transfer or license, destroying existing statutory rights, discouraging licensing as a means of resolving patent disputes, and disrupting settled expectations. *Cf. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002) ("courts must be cautious before adopting changes that disrupt the settled expectations of the inventing community"). Worse, Sandoz's new, untethered rule would discourage those in the best position to bring life-changing therapies to market—companies that have done similar research and obtained patents of their own—from licensing rights under patents owned by others covering such therapies, as well as compounds or methods of making them.

In any event, Sandoz cannot pass its own test, and certainly not by clear and convincing evidence. Based on "the intention of the parties" and "the substance of what was granted" under the 2004 agreement, *Alfred E. Mann Found. for Sci. Research v. Cochlear Corp.*, 604 F.3d 1354, 1359 (Fed. Cir. 2010) (internal citations omitted), Roche owns the Roche Patents.

Stuart Watt, who negotiated the 2004 A&S for Immunex and Amgen, testified without contradiction that Immunex did not seek an assignment from Roche because Immunex wanted to maintain a license. FOF 300. This was corroborated by John Parise at Roche, who explained that Immunex wanted a license, not an assignment.

FOF 300. Immunex wanted Roche to remain the owner so that Roche would have a duty to disclose information to the PTO in prosecution and would participate as a party in any litigation. FOF 300.

The agreement reflects the parties' intent. FOF 301. At Roche's insistence, FOF 304, Roche retained a substantial right to practice the patent for internal non-clinical research under § 3.2. *See* FOF 304; *AsymmetRx, Inc. v. Biocare Med., LLC*, 582 F.3d 1314, 1320 (Fed. Cir. 2009) (noting retained right "to make and use the p63 antibodies" for "academic research"). Roche likewise retained the substantial right to sue on 180 days' notice to Immunex under § 3.6. *See* FOF 305; *Alfred E. Mann Found.*, 604 F.3d at 1361-63 (second right to sue was substantial retained right). Sandoz contends this right is illusory because Immunex could moot a Roche suit by granting the defendant a license, but, as Mr. Watt explained, that would *not* be consistent with Roche's sole right to rectify infringement under § 3.6, or with Immunex's duty to cooperate. FOF 305. To be sure, Immunex has the first right to sue or license, but it cannot simply indulge infringement if Roche elects to sue. *See Abbott Labs. v. Diamedix Corp.*, 47 F.3d 1128, 1132 (Fed. Cir. 1995) (noting absence of "right to indulge infringements").

Roche also retained the absolute right to refuse to permit Immunex to assign rights under the A&S—including the right to direct prosecution—to a third party. FOF 306. If Immunex were the owner, it could have chosen to prosecute the

applications itself or sold them to someone else who wanted to prosecute them. Likewise, if Immunex already owned the patents, Roche could not demand an additional payment for an assignment.[11] FOF 307; *cf. DDB Techs., L.L.C. v. MLB Advanced Media, L.P.*, 517 F.3d 1284, 1290 (Fed. Cir. 2008) (distinguishing between an "assignment" and "merely a promise to assign").

Roche has never owned any of the Immunex patents, and Immunex has never owned any of the Roche Patents. Because there is no common ownership, the Immunex patents cannot be used as ODP references against the Roche Patents.

### B. The Post-GATT Finck Patents Cannot Be Used, in Any Event, to Cut Short the Pre-GATT Roche Patents' Statutory Term.

The Finck patents cannot be used against the Roche Patents for a second, independent reason. ODP addresses the "unjustified timewise extension" of a patent right. *Boehringer Ingelheim*, 592 F.3d at 1347. But the main reason the Roche Patents expire after the Finck patents is that the law defining the term of patents changed—the Roche Patents are "pre-GATT" and have a 17-year-from-issuance term,[12] *see* 35 U.S.C. § 154(c)(1), whereas the "post-GATT" Finck patents expire 20 years after their earliest filing date, *id.* § 154(a)(2); FOF 310. *See, e.g.*, *Abbott*

[11] If Immunex owned the Roche Patents, it also would not need provisions to protect its license in the event of Roche's bankruptcy. *See* FOF 308.

[12] "Pre-GATT" refers to patents issuing from applications filed before the June 8, 1995 effective date of the Uruguay Round Agreements Act, Pub. L. No. 103-465, 108 Stat. 4809 (Dec. 8, 1994), which implemented agreements reached during the Uruguay Round of the General Agreement on Tariffs and Trade.

*Labs. v. Lupin Ltd.*, No. 09-cv-152, 2011 WL 1897322, *10 (D. Del. May 19, 2011) ("no undeserved, extended patent term" where longer term was due to Congress). The post-GATT Finck patents cannot cut short the pre-GATT Roche Patents' statutory term.

### C. Sandoz Has Not Proven by Clear and Convincing Evidence That the Immunex and Roche Patents Claim Indistinct Inventions.

Even if the Immunex patents were proper ODP references, Sandoz still failed to prove that the Roche Patents claim patentably indistinct inventions.

#### 1. The Inventions of the Asserted Claims Would Not Have Been Obvious in Light of Claim 3 of the Jacobs '690 Patent.

Sandoz failed to establish by clear and convincing evidence that the inventions claimed in the Roche Patents are obvious variations of claim 3 of the Jacobs '690 patent. FOF 327-28. The Roche Patents claim etanercept and methods of making it, but Jacobs claim 3 is to a method of lowering active TNF-α by administering a "chimeric antibody" made up of part of a TNFR fused to "the constant domain of an immunoglobulin." JTX-42 at 26; FOF 327-30. As Dr. Blobel admitted, Jacobs claim 3 differs from the Roche Patents because the latter excludes both CH1 and the light chain, whereas the Jacobs claim 3 does not. FOF 327. In fact, the Jacobs "chimeric antibody" construct is the same one shown in Smith '760, and would not have made etanercept obvious for the same reasons Smith '760 did not. FOF 168, 205, 224-228, 235.

### 2. The Inventions of the Asserted Claims Would Not Have Been Obvious in Light of the Claims of the Finck Patents.

Sandoz also failed to establish by clear and convincing evidence that the claims of the Finck and Roche Patents are patentably indistinct. ODP looks to what a claim "*defines*," not what it "*discloses*." *Gen. Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1280 (Fed. Cir. 1992). Claims also must "be read as a whole," not by picking out statements "as though it were a prior art reference." *Id.* at 1278, 1280. Sandoz complied with neither requirement—it improperly used the "disclosure" of etanercept in the Finck patent claims and considered the claims piecemeal rather than "as a whole."

Applying the proper analysis, claim 10 of the '522 patent—a method of culturing a CHO cell with DNA that encodes etanercept and purifying the product—is very different from claim 1 of the Finck '225 patent—a method of treating a psoriasis with etanercept, for example. *See* FOF 316; *compare* JTX-2 at 46, *with* JTX-39 at 16; *see Astellas Pharma, Inc. v. Ranbaxy Inc.*, 2007 WL 576341 No. 05-2563 (MLC) (D.N.J. 2007), *4-9 (compound distinct from process for making it). Sandoz offered *no* evidence the Roche claims *as a whole* are obvious variants of the Finck ones. FOF 313. Sandoz ignores *General Foods*, which held that a later claimed method was distinct from an earlier method that "disclosed" each step of the later one, when the claims were considered *as a whole*. 972 F.2d at 1280-81.

In any event, the two-way test applies here. Sandoz's challenge is premised

on the theory that *Immunex* unjustly extended the Finck patents' term via the Roche Patents. But Immunex only obtained control over prosecution of the Roche Patents in 2004 and worked diligently to get them issued. *See* FOF 321. Sandoz's failure to identify *any* applicant-caused delay after 2004 means Sandoz is required to prove that there is no patentable distinctness under the "two-way test." *See In re Braat*, 937 F.2d 589, 593 (Fed. Cir. 1991) (two-way test avoids penalizing applicants who do not control the "rate of progress of the applications through the PTO").[13] Sandoz did not even attempt to establish that the Finck claims would have been obvious in light of the Roche claims, and thus its ODP challenge fails.

## CONCLUSION

The Court should enter judgment that the Roche Patents are valid and infringed.

[13] Sandoz suggests the two-way test cannot apply for any Finck patent issued after a Roche Patent, inferring this rule from cases involving only pre-GATT patents. D.I. 603 at 36. But the Federal Circuit has never addressed that issue because it has never held a pre-GATT patent invalid over a post-GATT patent, period.

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
(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.*

*s/ Liza M. Walsh*
Liza M. Walsh
Marc D. Haefner
Christine I. Gannon
Eleonore Ofosu-Antwi
Colleen M. Maker
WALSH PIZZI O'REILLY FALANGA LLP
One Riverfront Plaza
1037 Raymond Boulevard, 6th d
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*