IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANOFI-AVENTIS U.S. LLC,
GENZYME CORP. AND
REGENERON PHARMACEUTICALS, INC.,
Petitioners

v.

IMMUNEX CORPORATION,
Patent Owner

Case IPR2017-01884
Patent 8,679,487

IMMUNEX CORPORATION'S PATENT OWNER RESPONSE UNDER 37 C.F.R. §42.120

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Patent Owner Immunex Corporation ("Immunex") submits this Patent Owner Response in support of the patentability of claims 1-17 of U.S. Patent No. 8,679,487 ("the '487 Patent"; EX1001). As shown herein, the Petition for *inter partes* review filed by Petitioners Sanofi-Aventis U.S. LLC, Genzyme Corp., and Regeneron Pharmaceuticals, Inc. (collectively, "Sanofi") fails to meet its burden of persuasion that any of the challenged claims are unpatentable over the cited art.

I. Introduction

The inventors of the '487 patent generated and characterized new human antibodies that bind to human IL-4 receptor alpha chain ("IL-4R")[1] and block IL-4R-mediated cytokine activity. The 12B5 antibody is one such human anti-IL-4R antibody, and the '487 patent claims specify that an antibody with a light chain

[1] The scientific literature interchangeably uses the terms "IL-4R" and "IL-4Rα" to refer to the transmembrane receptor protein "interleukin-4 receptor subunit alpha." *See, e.g.*, EX1400, ¶39, n 1. Consistent with this usage, Immunex uses "IL-4R" to refer to that single transmembrane protein and uses "IL-4 receptor complex" or "IL-4R complex" to refer to multi-protein receptor complexes that include IL-4R.

comprising SEQ ID NO: 10 and a heavy chain comprising SEQ ID NO: 12 ("12B5") is a reference antibody.

Before May 2001, MAb230 was known and used by researchers in the field as a laboratory bench research tool to perform assays such as "neutralization," "ELISA" and "Western Blot." EX1206, 0010, 0018. At that time, no one had suggested or tried to modify Mab230 to make a human or humanized antibody that could be used for treating inflammatory diseases, and a person of ordinary skill in the art seeking to develop an antibody for therapeutic use in human patients would not have started with a murine antibody and modified it as Petitioners now argue. Indeed, before the publication of the '487 patent's disclosures, the Petitioners (and Petitioners' expert) were pursuing a range of different methods of blocking IL-4R activity. Tellingly, Petitioners and their expert never tried to humanize Mab230 or make a human version of it. Doing so was proposed for the first time in the Petition, which recreated the state of the art with full view of the patented invention—a blatant hindsight reconstruction of the art.

After the '487 patent's disclosures became public knowledge, co-Petitioner Regeneron Pharmaceuticals, Inc. ("Regeneron") made and used the 12B5 antibody as a tool to identify new anti-IL-4R antibodies that compete with 12B5. Now,

when facing litigation regarding infringement of the '487 patent, the Petitioners have filed this Petition as part of a staggered string of serial petitions, all challenging the '487 patent's claims.

Sanofi's Petition uses blatant hindsight reconstruction to first select a prior art mouse anti-IL-4R antibody (*i.e.*, MAb230) and then to modify that antibody in a manner, and for a purpose, not suggested by the prior art. The Petition argues that it would have been obvious to either humanize MAb230 or to use Mab230 to generate a human antibody with the same binding characteristics as MAb230, with the goal of generating a therapeutic for use in the treatment of allergic disorders. But Sanofi's argument that a person of ordinary skill in the art ("POSA") would have had reason to modify the murine anti-IL-4R antibody MAb230—a laboratory research tool—to generate a therapeutic, is completely unsupported by any evidence that the art has ever suggested that MAb230 should be humanized, converted into a human antibody, or used to develop a therapeutic. *See* §§III.B, IV.A below. A thorough examination of both prior art and post-filing date publications that reference MAb230 reveals that none of them have ever identified or discussed MAb230 for humanization, conversion into a human antibody, or development into a therapeutic candidate. *Id.* Some publications that reference

MAb230 use MAb230 as a reagent in *in vitro* or *ex vivo* experiments, but then go on to discuss the possibility of targeting IL-4R with *other* therapeutics. *Id.*

A full examination of MAb230's properties reveals that its properties had not been identified as making MAb230 therapeutically useful and, to the contrary, could lead to unacceptable side effects if present in a candidate therapeutic. *See* §III.C, IV.A below. Accordingly, a POSA would not have had a reason to select Mab230 or combine the disclosures of the cited art. And a POSA would not have had a reasonable expectation of success in doing so because MAb230 had not been tested in the therapeutic context and Sanofi argues only that a POSA could have generated a humanized MAb230 or a human equivalent of MAb230, while ignoring evidence suggesting that a skilled artisan would not have reasonably expected to generate a *therapeutic* antibody. *See* §III.D below. But when the sole alleged reason to combine the prior art is to develop a potential therapeutic, a demonstration of obviousness requires that "a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective." *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013).

Sanofi ignores the breadth of prior art available prior to May 1, 2001, which

presented a wide range of options for treatment of allergic disorders. Moreover, when analyzing the scope and content of the prior art, Sanofi ignores the real-world evidence that the art was focused on other, more promising strategies, such as a soluble IL-4R receptor ("sIL-4R") or mutant versions of IL-4 (i.e., "IL-4 muteins"). Petitioners' own efforts illustrate this: before May 1, 2001, Regeneron, Sanofi-Aventis U.S. LLC, and even Sanofi's expert Dr. Zurawski pursued strategies utilizing sIL-4R, soluble IL-13R protein ("sIL-13R"), or IL-4 muteins, respectively. The record evidence shows that none of them tried an antibody approach for inhibiting IL-4 signaling or used MAb230 as the basis for developing an antibody. Accordingly, Petitioner's own actions belie their present litigation-driven, hindsight-based assertions regarding what a POSA would have done before May 1, 2001.

The above deficiencies are fatal to both grounds of the Petition. Ground 1 also fails because the claims are directed to "human antibodies," and a person of ordinary skill in the art would *not* have considered it reasonable to construe "human antibody" so broadly as to include murine antibodies modified to have some characteristics of human antibodies (*i.e.*, humanized antibodies). *See* §§II and III.A below. Immunex recognizes that the Board preliminarily held that "the

broadest reasonable interpretation of the term 'human antibody' includes both partially human and fully human antibodies." Paper 14, at 8. Immunex presents further evidence and analysis here and maintains that based on the specification (*see* §§II.A-C below) and prosecution history (*see* §II.C below), "human antibody" should be construed as fully human antibodies and not include humanized antibodies. Under the proper construction of "human antibody," Ground 1 fails to teach all elements of the challenged claims. *See* §III.A.

A further deficiency for Ground 2, specifically, is that a POSA would not have had a reason to convert Hart's MAb230 into a fully human antibody using Hoogenboom's epitope imprinted selection ("EIS") methodology and would not have had a reasonable expectation of success in doing so. A POSA would have lacked a reason to combine the cited art because prior art efforts at using EIS had repeatedly altered antibodies' binding epitopes and affinity, the very properties that Sanofi alleges to have made MAb230 useful. *See* §IV.B below. And a POSA would have known that there had been very few successful efforts at performing EIS, and thus EIS had not been demonstrated to be generally effective, contrary to Sanofi's assertions of a reasonable expectation of success. *See* §IV.C below.

In sum, the Board should decline to find any of the '487 patent claims

unpatentable over the cited art, because Sanofi fails to meet its burden of persuasion.

II. The record as a whole demonstrates that the proper construction of "human antibody" is limited to fully human antibodies

The '487 patent claims are directed to "*human* antibodies." EX1001, Claim 1. As discussed below, Immunex maintains that under the broadest reasonable interpretation standard, a person of ordinary skill in the art would not have considered it reasonable to construe "human antibody" so broadly as to include murine antibodies modified to have some characteristics of human antibodies (*i.e.*, humanized antibodies). IMX2141, ¶¶24-30; IMX2185, ¶¶16-21; IMX2183, ¶¶16-49. The proper construction is limited to fully human antibodies, which reflects the fact that partially human antibodies are a separate and distinct category of antibodies from human antibodies. *See* §§III.A-D below. Moreover, Immunex's construction of "human antibody" aligns well with "construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent," as suggested in the USPTO Notice of Proposed Rulemaking on May 9,

2018. 83 Fed. Reg. 21221, 21223.[2]

Immunex recognizes that the Board preliminarily held that "the broadest reasonable interpretation of the term 'human antibody' includes both partially human and fully human antibodies." Paper 14, at 8. Immunex respectfully suggests, however, that further evidence and analysis of the meaning of the term, in view of both the intrinsic evidence in the specification and prosecution history and the extrinsic evidence, demonstrate that the broadest *reasonable* interpretation of "human antibody" is a fully human antibody.

A. The plain and ordinary meaning of "human antibody" should apply because Immunex has not acted as its own lexicographer

In claim construction, "[t]here is a 'heavy presumption' that claim terms 'carry their accustomed meaning in the relevant community at the relevant time.'"

[2] Immunex agrees with the Notice of Proposed Rulemaking's justifications for applying the *Phillips* standard, including facilitating "greater uniformity and predictability," eliminating the difference from district courts to "increase judicial efficiency," and removing the "unfairness [that] could result from using an arguably broader standard in AIA proceedings." 83 Fed. Reg. 21221, 21222-21223.

Azure Networks, LLC v. CSR PLC, 771 F. 3d 1336, 1347 (Fed. Cir. 2014); *see also*, *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F. 3d 1359, 1366 (Fed. Cir. 2002) (holding that there is a "a 'heavy presumption' that a claim term carries its ordinary and customary meaning"). To act as a lexicographer and overcome that heavy presumption, a patentee must define a term with "reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F. 3d 1475, 1480 (Fed. Cir. 1994).

The plain and ordinary meaning should apply here because the '487 patent's specification does not explicitly define the term "human antibody," and the specification uses the term in a manner consistent with the plain and ordinary meaning of human antibody being a *fully* human antibody, as set out in §II.B below. IMX2141, ¶¶24-26, 29-30; IMX2185, ¶¶16, 19-20. For example, the '487 patent's abstract refers to "human antibodies" that are "generated by procedures involving immunization of transgenic mice." EX1001, Abstract. The specification provides detail regarding such transgenic methods, which involve using mice in which "[h]uman immunoglobulin genes have been introduced into the mice to replace the inactivated mouse genes . . . [and] immunizing [the] transgenic non-human animals with an IL-4R polypeptide." EX1001, 19:38-20:8.

The '487 patent specification uses "human antibody" consistent with its

plain and ordinary meaning. *See, e.g.*, EX1001, Abstract, 19:38-20:8, 21:10-12, 42:61-62, 43:26-27, Examples 2-3; IMX2141, ¶¶24-26, 29-30; IMX2185, ¶¶16, 19-20. For example, the '487 patent refers to antibodies with entirely human sequence (*e.g.*, the 12B5 antibody) interchangeably as "human" and "fully human" antibodies. *See, e.g.*, EX1001, 21:10-12, 42:61-62, 43:26-27. The Board pointed to a specific statement in the specification considered to be an "instance" in which "human antibody" was used in the '487 patent specification to "teach[] that the 'human antibodies' generated can be 'partially human' or 'completely human.'" Paper 14, at 7. But, respectfully, the Board is incorrect in its reading of the specification. The three-sentence passage at issue discusses methods of producing an antibody in transgenic mice:

> A method for producing an antibody comprises immunizing a non-human animal, such as a transgenic mouse, with an IL-4R polypeptide, whereby antibodies directed against the IL-4R polypeptide are generated in said animal. Procedures have been developed for generating human antibodies in non-human animals. The antibodies may be partially human, or preferably completely human.

EX1001, 19:38-44. But the specification, as understood by a person of skill in the art, simply describes that transgenic mice can be used to generate antibodies that are fully human, partially human, humanized, or chimeric and that fully human antibodies were preferred. *See, e.g.*, *id.* at 1:43, 18:34-39, 19:21-51, 20:57-58, 21:1-2; IMX2141, ¶¶29-30; IMX2185, ¶20. By referring to "[t]he antibodies," rather than to "human antibodies," the antecedent basis for "the antibodies" in the last sentence is "antibodies directed against the IL-4R polypeptide" as mentioned in the first sentence, not the "human antibodies" mentioned in the second sentence. IMX2141, ¶¶29-30; IMX2185, ¶20. Therefore, the last sentence of this passage indicates that "[t]he antibodies" directed against an IL-4R polypeptide "may be partially human." IMX2141, ¶¶29-30; IMX2185, ¶20. The cited passage in the '487 patent's specification does not state or suggest that *human* antibodies may be partially human. EX1001, 19:38-51; IMX2141, ¶¶29-30; IMX2185, ¶20. To force it to have this meaning, the term "the antibodies" of the last sentence must be misread as "the *human* antibodies."

More generally, the use of the term "human antibody" in the specification alongside alternative embodiments of partially human antibodies simply is not sufficient to re-define the term to mean something other than the well-established

and ordinary meaning in the art. IMX2101, ¶¶15-21; IMX2141, ¶¶24-30; IMX2185, ¶¶16-21. The '487 patent's specification states that human antibodies (*i.e.*, fully human antibodies), partially human antibodies, chimeric antibodies, and humanized antibodies are embodiments of the invention. But "the claims of the patent need not encompass all disclosed embodiments. [The Federal Circuit's] precedent is replete with examples of subject matter that is included in the specification, but is not claimed." *Tip Systems, LLC v. Phillips & Brooks/Gladwin*, 529 F. 3d 1364, 1373 (Fed. Cir. 2008) (internal citations omitted). Therefore, when the specification states that "[t]he desired antibodies are at least partially human, and preferably fully human," there is no imputation that the claims must cover both types of antibodies, particularly given that the claims can be—and indeed were—amended. EX1001, 21:1-2; IMX2183, ¶¶16-33; EX1002, 0068.

As discussed above, the Board should apply a "heavy presumption" that the ordinary meaning applies. *Azure Networks,* 771 at 1347. The disclosures in the '487 specification do not even imply that the meaning of "human antibody" is different from its standard meaning, let alone change the meaning with "reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F. 3d 1475, 1480 (Fed. Cir. 1994). Therefore, the plain and ordinary meaning of "human antibody" as

described below should be applied.

B. The plain and ordinary meaning of "human antibody" is a fully human antibody

Documentary evidence, the testimony of Dr. Marasco, and the testimony of Dr. Finkelman all support Immunex's construction of "human antibody" to be a fully human antibody. IMX2141, ¶¶24-30; IMX2101, ¶¶15-19; IMX2185, ¶¶16-21. Immunex's expert Dr. Wayne Marasco, who has almost thirty years of antibody design and engineering experience, testifies that "the proper construction of a 'human antibody' is a fully human antibody that, because it is derived from a human sequence, has an amino acid sequence consistent with the amino acid sequence of antibodies produced by the human immune system." IMX2141 ¶¶24-30; IMX2101, ¶¶15-19. Dr. Finkelman, an eminent immunologist who has been working elucidate the biological function of antibodies and cytokines since 1975, agrees with Dr. Marasco, and opines that "the term "'human antibody' should be limited to *fully* human antibodies and exclude partially human antibodies (*e.g.*, humanized and chimeric antibodies)." IMX2185, ¶¶16-20.

As Dr. Marasco and Dr. Finkelman explain, the convention in the field before May 1, 2001 (which has continued to the present day), was to refer to

antibodies by their species of origin. IMX2185, ¶18; IMX2141, ¶¶14-27; *see also*, EX1402, at 13:5-28; IMX2103, 128, 130:Table 1; IMX2171; IMX2172; EX1206; EX1409, 7-8; IMX2140, 320-321, Fig. 1; IMX2147, 1074. For example, the World Health Organization (WHO) has recommended naming immunoglobulin-derived peptides by their species of origin and has provided antibody naming conventions distinguishing human and other species. *See, e.g.*, IMX2171; IMX2172; IMX2141, ¶¶14, 27; IMX2185, ¶18. And everything from product catalogs to general antibody reviews consistently have referred to antibodies by their species of origin since well before May 1, 2001. *See, e.g.*, EX1206 (describing antibody products by their species of origin); EX1409, 7-8 (describing subtypes of "Human IgG" and "Murine IgG"); IMX2141, ¶¶14, 27; IMX2185, ¶18. The consistent usage of species names in association with origin means that a POSA would have understood the term "human antibody" to convey that the antibody has an amino acid sequence consistent with that origin. IMX2141, ¶¶14, 27; IMX2185, ¶18.

As Immunex's expert Dr. Marasco explains, the definition of "human" antibody in a 2005 review article is representative and consistent with the conventional association of "human" as a designation of origin:

> **Human antibody**. A mAb derived entirely from a human source, currently transgenic mice or phage display. Human mAbs can also be produced from human hybridomas or human B-lymphocyte cell lines immortalized by Epstein-Barr virus.

IMX2147, 1074 (emphasis original); IMX2141, ¶14; IMX2185, ¶18.

The '487 patent also refers to antibodies with entirely human sequence (*e.g.*, the 12B5 antibody) interchangeably as "human" and "fully human" antibodies. *See, e.g.*, EX1001, 21:10-12, 42:61-62, 43:26-27. Consistent with that usage, a POSA would have viewed "human antibody" and "fully human antibody" as interchangeable terms based on their use in the art. IMX2141, ¶¶22-23; IMX2185, ¶¶17-20; IMX2123, 609; IMX2145, 34; IMX2221, 368. Indeed, prior art references used the terms interchangeably, even within single publications. *See* §II.C.4 above; IMX2145, 34, Fig. 1; IMX2221, 368; IMX2123, 607. For example, in 1998, Jakobovits used both terms to describe the same antibodies generated in transgenic mice:

> [S]uch [transgenic] mice could be used as a valuable source for generation **of fully human antibodies** with high affinity and specificity, directed against a broad

> spectrum of antigens. Furthermore, antigen-specific **human Mabs** could be easily generated from such mice by using standard mouse hybridoma technology.

IMX2145, 34; *see also*, IMX2145, at Fig. 1 (referring both to "strains producing human antibodies" and to mice "producing fully human antibodies"); IMX2141, ¶22; IMX2185, ¶18. Similarly, van Dijk *et al.* used "fully human" and "human" interchangeably with respect to antibodies, discussing "**[h]uman antibodies** as next generation therapeutics" and noting that "**fully human antibodies** are rapidly becoming the norm." IMX2221, 368; IMX2141, ¶22.

Moreover, the deposition testimony of Sanofi's proffered third-party witness, Dr. J.P. Houchins, is consistent with Immunex's construction of the term "human antibody." For example, Dr. Houchins, the Associate Director of Antibody Research at R&D Systems, reviewed the 1996 R&D Systems Catalog (EX1206), which offered antibodies for sale. IMX2212, 50:20-53:19. Dr. Houchins stated that an antibody designated as a "Mouse" antibody would have indicated to purchasers that the "antibody was derived from an immunized mouse, so its amino acid sequence is a mouse-derived sequence" and would not be viewed as a "partially" mouse antibody. IMX2212, 50:20-52:13; *see also*, IMX2212, 52:16-53:19.

Similarly, Dr. Houchins explained that a "goat antibody" would have been expected to be fully derived from a goat antibody sequence, and would not be viewed as a "partially" goat sequence. *Id.* Such testimony from Sanofi's proffered third-party witness is fully consistent with the broadest reasonable interpretation of "human antibody" being limited to a fully human antibody, not encompassing a "partially" human antibody. IMX2141, ¶¶14, 27.

Therefore, the plain and ordinary meaning of "human antibody" is an antibody in which the amino acid sequence is consistent with the amino acid sequences of antibodies produced by the human immune system. IMX2141, ¶22; IMX2185, ¶18; IMX2101, ¶19. Further, the term "human antibody" should be viewed as interchangeable with the term "fully human antibody." . IMX2141, ¶¶22, 30; IMX2185, ¶¶17-21. The specification's use of "human antibody" is consistent with this plain and ordinary meaning. While the '487 patent refers to humanized antibodies as having regions that are "derived from" human antibodies, it does not state that humanized antibodies (or any other partially human antibody) are a type of "human" antibody. EX1001, 19:21-32; IMX2185, ¶20; IMX2185, ¶¶29-30.

C. The intrinsic evidence supports Immunex's construction of "human antibody"

Prosecution history is relevant to claim construction, and the "PTO should also consult the patent's prosecution history" as evidence of what the applicant and examiner understood to be the meaning of the claim term under the broadest reasonable interpretation standard. *Microsoft Corp. v. Proxyconn, Inc.*, 789 F. 3d 1292, 1298 (Fed. Cir. 2015) *See also*, *D'Agostino v. MasterCard Int'l Inc.*, 844 F.3d 945, 949 (Fed. Cir. 2016) (overturning a Board decision in part because the panel did not recognize that "[t]he prosecution history reinforces" a narrower claim construction); *Biogen Idec. Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1095 (Fed. Cir. 2013). As discussed below, the content and evolution of the '487 patent claims during prosecution show that the claims were limited to human antibodies, thereby excluding partially human, humanized, and chimeric antibodies. IMX2183, ¶¶34-49.

Claim 1 of the '487 Patent as issued recites "An isolated *human* antibody . . . ." (emphasis added). EX1001, Claim 1. As originally filed, however, claim 1 of the application that issued as the '487 Patent lacked the "human" limitation and recited only "An isolated antibody . . . ." EX1002, 244. The scope of the claims as

originally filed included partially human antibodies. EX1002, at 0244-245. Additionally, dependent Claim 11 as originally submitted specifically claimed an antibody that is a "human, partially human, humanized, or chimeric antibody." EX1002, 245.

During prosecution, the Examiner rejected Original Claims 1 and 11, among others, as anticipated by Mosley *et al.*, U.S. Patent No. 5,717,072 ("Mosley"). EX1002, 119-120. In response to that rejection, the Applicant amended Claim 1 to recite "An isolated *human* antibody . . .," cancelled Claim 11, and argued that "the rejection fails to identify any passage in Mosley that either explicitly or inherently teaches *human* antibodies having the properties recited in the rejected claims as herein amended." EX1002, 68-69, 74 (emphasis original).[3] The Examiner agreed, stating that "Applicants' arguments that the Mosley *et al* reference does not teach

[3] Applicant further noted that the claim amendments and cancellation of claim 11 were "made without prejudice or disclaimer" and that the applicants reserved "the right to pursue amended or cancelled subject matter in one or more timely filed continuation, continuation-in-part, or divisional applications." EX1002, 72

human antibodies, has been found persuasive." EX1002, 45.

The prosecution history is significant at least because it demonstrates, via the amendments and cancellation of claim 11, that the final claims do not include partially human, humanized, or chimeric antibodies within the scope of the claims. IMX2183, ¶¶39-44. The act of cancelling claim 11, while concurrently selecting human antibodies as the type of antibody to be specified in the remaining claims, indicates that the amendments narrowed the claims to refer only to human antibodies and excluded partially human, humanized, and chimeric antibodies. *Id.* And any construction of "human antibodies" that includes partially human antibodies would be contrary to the prosecution history as reflected by these amendments. *Id.*

The Examiner recognized that Immunex had narrowed the claim scope, and the Office subsequently treated the amended claims as being limited to fully human antibodies. IMX2183, ¶¶45-46. In particular, the Office's next action was directed to art allegedly showing fully human antibodies:

> Jakobovits states that such limitations [in Mosley] could be overcome by *fully human* monoclonal antibodies, which minimize immunogenic and allergic responses . . . . Jakobovits discloses an efficient and reliable method of

> producing *fully human* antibodies . . . . The researchers engineered mice with human antibody genes to generate and select high affinity, *fully human* antibodies . . . .

EX1002, 47 (emphasis added); *see also*, *id.*, 46-51. After noting the Examiner's focus on fully human antibodies, the Applicant never challenged that focus as the appropriate approach to characterizing the "human antibody" claim limitation. *See, e.g.*, EX1002, 39 (referencing the Examiner's argument relating to "generat[ing] fully human antibodies"); IMX2183, ¶47.

Because "partially human, humanized, or chimeric" antibodies were removed from the claims as described above, and because prosecution proceeded to focus on "fully human" antibodies, the claims must be limited to fully human antibodies. IMX2183, ¶¶48-49. Stephen Kunin, an expert on US patent practice and procedure and former Deputy Commissioner for Patent Examination Policy at the USPTO concurs and has provided an analysis and opinion regarding claim interpretation in IPR2017-01884 and indicating that Immunex's construction is consistent with and complies with USPTO practice and procedure at the PTAB in Leahy Smith America Invents Act[4] ("AIA") administrative trials. IMX2183, ¶1.

[4] Pub. L. 112-29 as enacted December 16, 2011.

Based on his analysis of the prosecution history of the ’487 patent (IMX2183, ¶¶16-33), which broadly follows the same path as that described above, it is his opinion that the term “human antibody” in the ’487 patent claims should be limited to fully human antibodies. IMX2183, ¶¶34-50.

D. Sanofi’s construction of “human antibody” is not consistent with the plain and ordinary meaning of the term as reflected in the art

Defining “human antibody” is aided by an understanding of antibody structure and the types of therapeutic antibodies. IMX2141, ¶¶12-23. Sanofi’s argument that the term “human antibody” should be construed as including both fully human and partially human antibodies is not consistent with that understanding because, as Dr. Marasco explains, the names given to therapeutic antibodies (*e.g.*, human, humanized, chimeric) were created specifically to distinguish fully and partially human antibodies. IMX2141, ¶¶14-23. The discussion below describes antibody structure and the development of different types of therapeutic antibodies, and explains how the use of those terms before May 1, 2001, supports Immunex’s construction of “human antibody” (*i.e.*, a fully human antibody).

As Dr. Marasco explains, antibodies share a common structure based on

their common sequence elements and protein domains. EX1409, 4-6, 11-13; IMX2141, ¶¶12-13. Figure 1 from the Dr. Marasco's second declaration, shown below, diagrams the relative arrangement of the two heavy chains ("HC") and two light chains ("LC") that are found in a typical antibody:

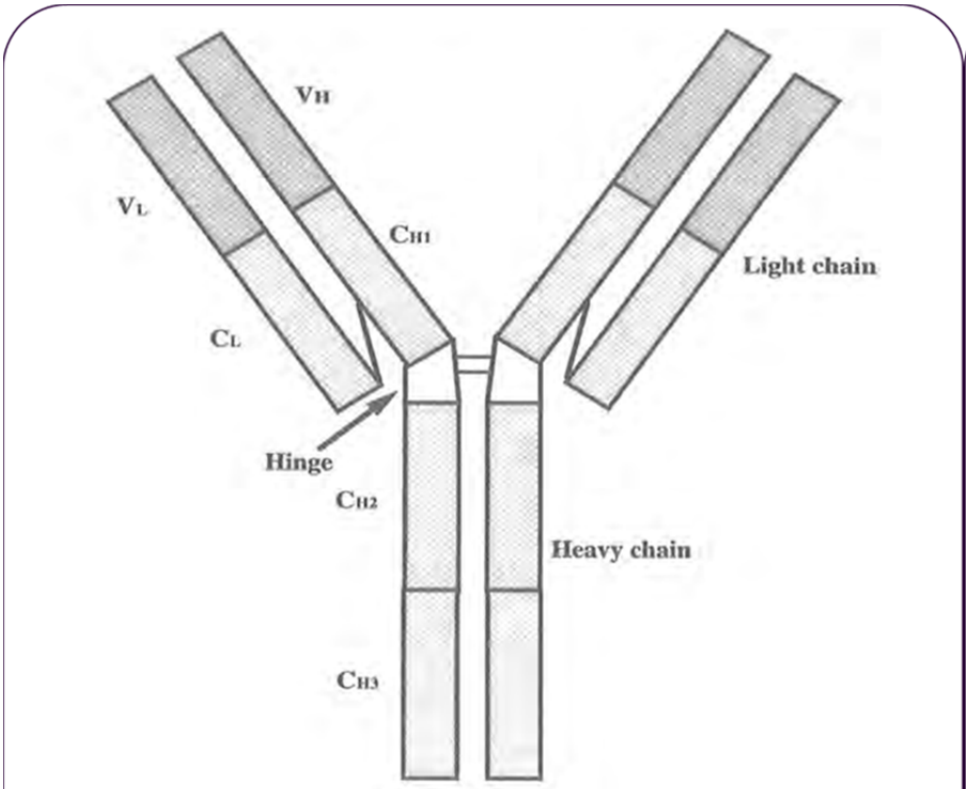


Figure 1: A representation of the organization of protein chains of an antibody molecule. The antibody includes two heavy chains and two light chains. Each light chain includes one variable region (V_L) and one constant region (C_L). Each heavy chain includes one variable region (V_H), three constant regions (C_{H1}, C_{H2}, and C_{H3}), and a hinge region. The protein chains are linked by disulphide bonds (solid lines).

IMX2141, ¶12.

Each antibody HC or LC has both a "variable region" and a "constant region." EX1409, 4; IMX2140, 320. The complementarity determining regions ("CDRs") are the portions of the variable region responsible for directly binding to an antigen, while the remainder of the variable regions consists of framework regions. EX1409, 5-6; IMX2140, 320. The locations of the CDR regions within the protein chains of an antibody are diagrammed below, in Figure 2 from Dr. Marasco's second declaration:

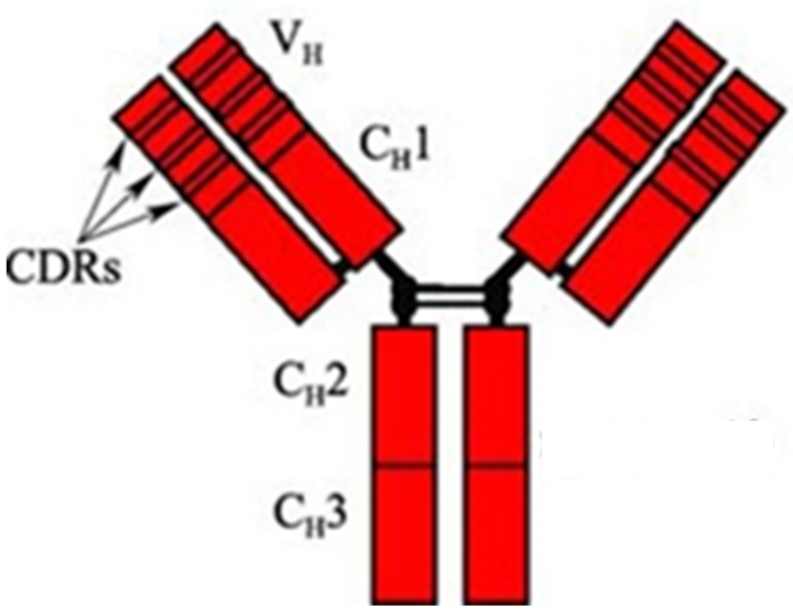


Figure 2: A representation of the organization of protein chains of an antibody molecule, including identification of the complementarity determining regions (CDRs) in the heavy chains and light chains. Each heavy chain variable region (VH) and each light chain variable region (VL) contains three CDRs.

IMX2141, ¶13.

1. Development of "chimeric antibodies"

Methods of developing monoclonal antibodies were first disclosed in 1975 by Kohler and Milstein, who had fused myeloma cell lines with B cells to create immortalized hybridomas that produced murine antibodies of consistent and predefined specificity. IMX2143; IMX2141, ¶15. After Kohler and Milstein published their work, researchers began to explore the therapeutic potential of this new reproducible source of bioactive proteins. IMX2140, 319; IMX2141, ¶15. One problem with murine monoclonal antibodies, however, was the tendency of human subjects to develop harmful immune reactions against these non-human antibodies such as pain, swelling, allergic reactions, hepatic dysfunction, and anaphylactic shock. IMX2140, 320-321, 325; EX1409, 18, 29, 31-32; IMX2144, 641; IMX2141, ¶16. These reactions developed because different species have different antibody sequences, with many differences beyond those necessary to provide antigen specificity, and the non-human antibodies were therefore recognized as foreign. *See, e.g.*, IMX2142, 455; IMX2141, ¶16.

To minimize the antibody immunogenicity problem, researchers in the early 1980's began investigating methods of producing new antibody types that are less

likely to cause an adverse immune response upon administration to a human. EX1409, 18, 29; IMX2140, 320-325; IMX2141, ¶17. One early effort in 1984 resulted in the development of chimeric antibodies. EX1409, 29; IMX2141, ¶18. Chimeric antibodies generally contain the variable region (including all six CDRs and the full framework regions) from a murine (or other non-human) antibody and the constant region from a human antibody. EX1409, 29-30; IMX2141, ¶18. Because the constant region of an antibody is the majority of the sequence of an antibody (*i.e.,* the majority of the protein), this reduces the risk of an immune reaction if administered to a human patient. EX1409, 29, 31; IMX2141, ¶18.

2. Development of "humanized antibodies"

Researchers also prepared "humanized" antibodies, a type of antibody that has more human sequence content than chimeric antibodies, as part of an effort to further reduce the immunogenicity of therapeutic antibodies. EX1409, 33-37; EX 1410, 139-141; IMX2140, 320-321; IMX2141, ¶19. Rather than containing the entire variable region of a murine (or other non-human) antibody, "humanized antibodies" are generated by transferring the CDR regions from a murine (or other non-human) antibody into the framework and constant regions of a human antibody. EX1409, 33; EX1410, 140-141; IMX2140, 320; IMX2141, ¶19.

Therefore, like chimeric antibodies, humanized antibodies retain some non-human sequence but have a reduced risk of prompting an immune reaction in a human patient. EX1409, 33, 35, 37; EX1410, 141; IMX2140, 320; IMX2141, ¶19.

3. Development of "human antibodies" as an alternative to chimeric antibodies and humanized antibodies

As technology continued to advance, researchers developed methods of producing human antibodies, *i.e.*, fully human antibodies. IMX2141, ¶¶20-22; IMX2123, 607-609; IMX2140, 321, 325; IMX2146. These methods were generated to further improve upon humanized and chimeric antibodies, with the defining feature being that the generated antibodies have an entirely human sequence. IMX2123, 609; IMX2145, 34, Fig. 1; IMX2141, ¶20. Methods of preparing human antibodies included (1) using transgenic mice in which the murine antibody genes were replaced with human antibody genes and (2) performing phage display-based methods to select useful antibodies from a library of candidate antibodies. IMX2123, 609; IMX2140, 321, 325; EX1402; IMX2146; IMX2141, ¶20.

Figures 3 and 4 below, which Dr. Marasco adopted from Murray 2000 (IMX2104) and An 2010 (IMX2140), illustrate how the art has consistently

depicted chimeric and humanized antibodies as differing from human antibodies in that they contain regions derived from mouse antibody genes (shown in black and red, respectively):

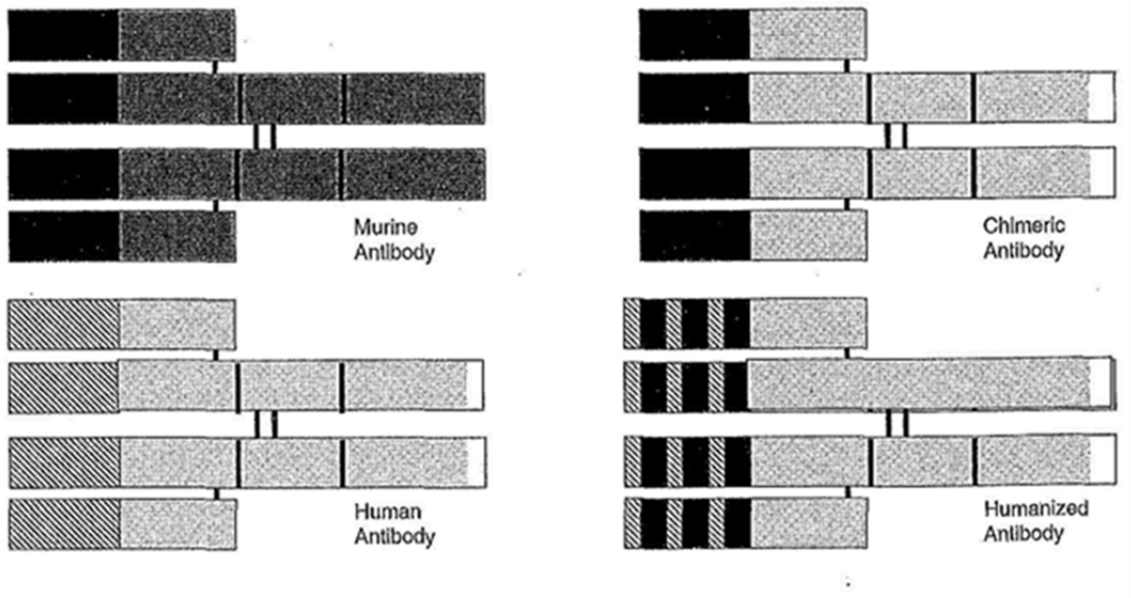


Figure 3: A schematic diagram of various types of monoclonal antibodies. The depicted regions are murine constant regions (dark grey boxes), murine variable regions (black boxes), human constant regions (light grey boxes) and human variable regions (striped boxes).

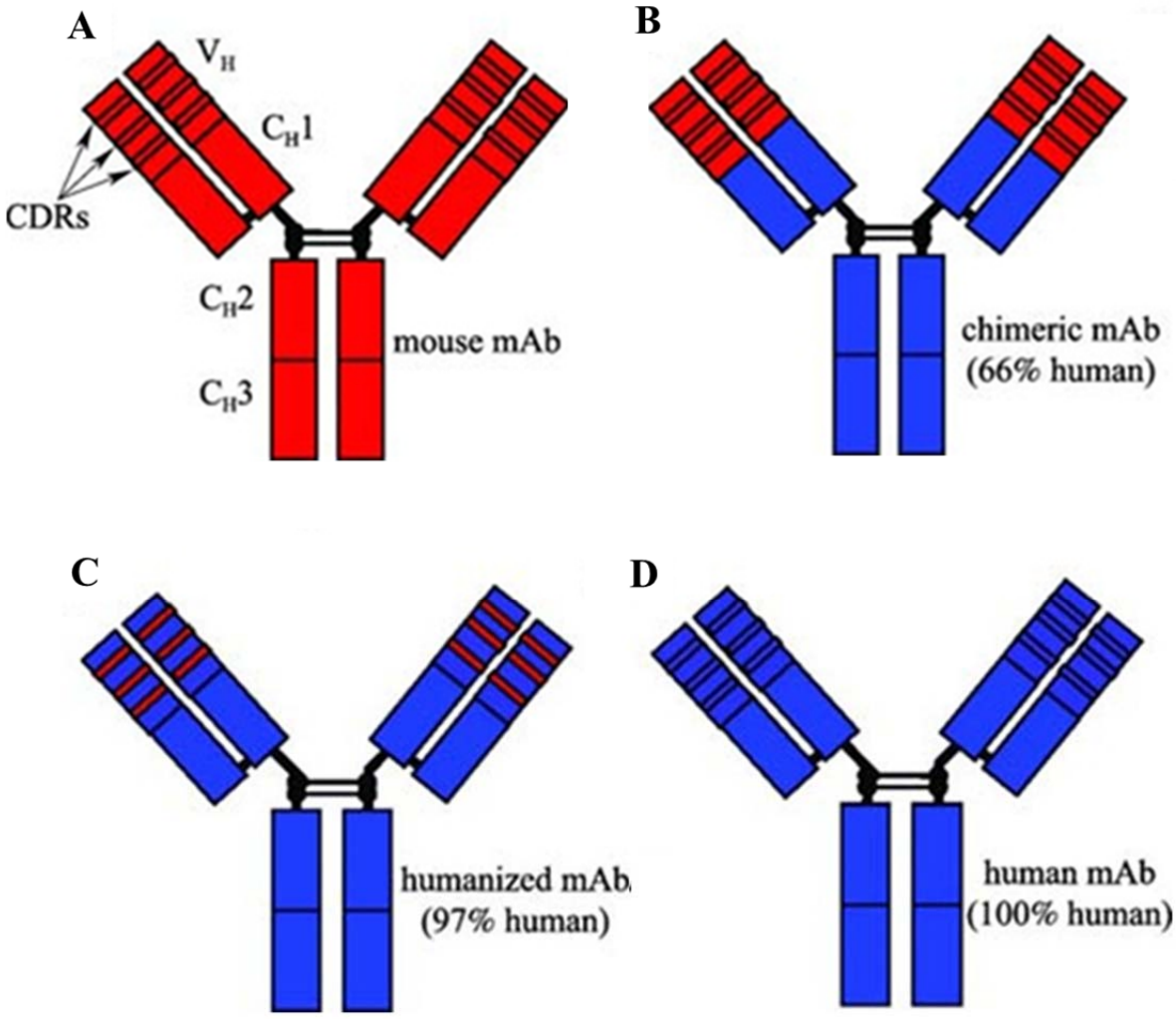
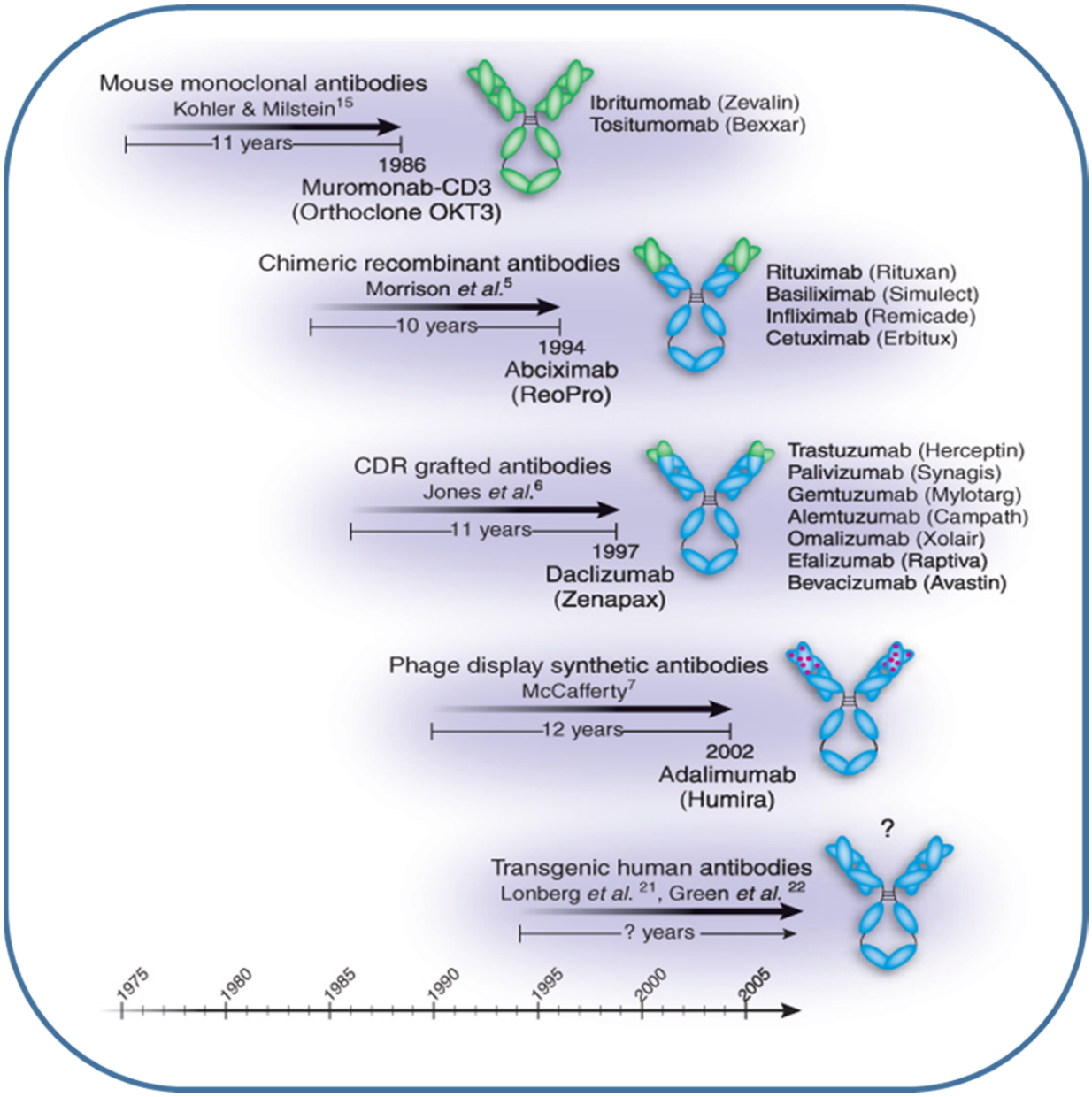


Figure 4: A schematic diagram of various types of monoclonal antibodies. The depicted regions are color coded for murine regions (red boxes) and human regions (blue boxes). Each antibody type is labelled with its approximate percent human sequence content, if any.

IMX2141, ¶22.

A timeline of the development of different types of antibody technologies is

provided below, which Dr. Marasco adapted from Lonberg 2005 (IMX2146).



IMX2141, ¶23.

* * *

For all of the reasons above, "human antibody" should be construed to mean a fully human antibody.

III. Ground 1 fails to establish obviousness

For multiple reasons, the Petition's arguments in Ground 1 fail to establish by a preponderance of the evidence that any of the challenged claims are unpatentable for at least three reasons. First, under the proper construction of "human antibody," the cited art does not teach all elements of the claims because it is directed to generating a *humanized* antibody, while the claims are directed to *human* antibodies. *See* §IV.A below. Second, Ground 1's reconstruction of an embodiment of the claimed invention is an impermissible hindsight reconstruction of the invention divorced from a full analysis of the prior art. *See* §IV.B-C below. And third, Ground 1 fails to show that a person of ordinary skill in the art would have had a reasonable expectation of success in generating the claimed antibodies. *See* §IV.D below.

A. Under the proper construction of "human antibody," Sanofi's Ground 1 fails because it is only directed to generating humanized antibodies

Ground 1 of the Petition must fail because it relies on an unreasonably broad

construction of the term "human antibody." Sanofi's premise in Ground 1 is that "it would have been obvious for a POSITA to modify Hart's MAb230 with Schering-Plough's *humanization techniques* to derive a potential therapeutic for allergic diseases." Pet., at 36 (emphasis added). But as discussed above, the proper construction of the claim term "human antibodies" does not include humanized antibodies, or any other form of partially human antibodies. Because claim 1, the sole independent claim of the '487 patent, is directed to "human antibodies," no claims of the '487 patent cover humanized antibodies.

Sanofi has neither argued nor demonstrated that the cited art in Ground 1 teaches "human antibodies" as that term is properly construed. Sanofi asserts that Hart "teaches MAb230, a murine anti-hIL-4R blocking antibody." Pet., at 35. And Schering-Plough "teaches techniques for humanizing murine anti-hIL-4R blocking antibodies." Pet., at 36. Because Schering-Plough's method starts with murine (*i.e.*, non-human antibodies), antibodies generated using that method will retain CDR's and other sequences characteristic of murine antibodies. IMX2101, ¶21. Neither Hart nor Schering-Plough discloses generating antibodies with fully human sequences, much less human antibodies that compete with the described reference antibody. Accordingly, even if a POSA would have had a reason to modify

MAb230 to make a partially human antibody according to Schering-Plough's method (which they would not, as discussed below), a POSA nonetheless would not have arrived at an embodiment within the scope of the claims.

B. Even if the Board were to accept Sanofi's claim construction, Sanofi's obviousness arguments in Ground 1 are based on impermissible hindsight

Even if the PTAB were to accept Sanofi's improper construction of "human antibody," which it should not, Sanofi's obviousness arguments in Ground 1 still fail because they rely on impermissible hindsight to arrive at the claimed invention. IMX2141, ¶¶31-33, 41; IMX2185, ¶¶22-56; IMX2101, ¶¶22-35. Sanofi's Petition and Dr. Zurawski's declaration reference IL-4's "role in the development of allergic disorders," but then immediately focus on anti-IL-4R antibodies and, in particular, a single obscure mouse antibody (*i.e.*, MAb230), rather than considering the full scope and content of the prior art as 35 USC § 103 requires. *KSR Intern. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1729-1730 (2007); Pet., at 23, 36, 43; EX1400, ¶¶130-135, 210-213. By immediately focusing on MAb230 as the purported solution to the need for treating allergic disorders, Sanofi and Dr. Zurawski engage in hindsight bias at multiple levels:

(1) they present an over-simplified view of the art that ignores the large

number of immune-cell signaling molecules involved in allergic disorders that a POSA would have considered in developing candidate therapeutic targets for treating allergic disorders;

(2) they completely ignore that the prior art taught a range of strategies for altering IL-4R signaling, of which anti-IL-4R antibodies were not among the most explored or most promising; and

(3) they completely ignore the fact that MAb230 was one of at least twelve anti-IL-4R antibodies disclosed in the prior art—and that MAb230 was not, and has not ever been, recognized in the art as a candidate for modification to create a therapeutic.

IMX2141, ¶¶31-33, 41; IMX2185, ¶¶22-56; IMX2101, ¶¶22-35.

An obviousness analysis includes examining the scope and content of the prior art. Yet, Sanofi ignores these aspects of the art, and each of these deficiencies is examined in greater detail below. *See* §§III.B.1-4. Because Sanofi's Petition picks and chooses disclosures from the art and uses *ex post* reasoning in an attempt to reconstruct the '487 patent claims, the Board should find the '487 patent claims not unpatentable.

1. Sanofi did not address the full scope and content of the art because it ignored the wide range of therapeutic strategies and targets known in the art

Sanofi's hindsight reconstruction is first evident in its failure to consider the wide range of different therapeutic strategies and targets discussed as potential treatments for allergic disorders in the prior art. IMX2101, ¶¶24-26; IMX2185, ¶¶22-23. A person of ordinary skill in the art would have been aware that "[t]he inherent complexity of allergic inflammation [had] sparked research into many potential molecular and cellular targets-in many attempts to modulate inflammation and provide clinical efficacy." EX1011, 415. Despite using "treatment of allergic disorders" as their purported rationale for combining the cited references, neither Sanofi nor Dr. Zurawski's declaration discussed any of the numerous other candidate strategies and therapeutics that were being investigated before May 1, 2001, such as cytokines, tyrosine kinases, transcription factor inhibitors, and soluble cytokine receptors. IMX2101, ¶¶25-26; IMX2185, ¶¶22-23. Nor did Sanofi or Dr. Zurawski explain why a POSA would have ignored all of these other therapeutic candidates in favor of MAb230. IMX2101, ¶¶25-26; IMX2185, ¶¶22-23. As Dr. Marasco (IMX2101, ¶25) and Dr. Finkelman (IMX2185, ¶22) explain, a POSA would have been aware of, and considered,

numerous other candidate strategies and therapeutics:

- "Recent advances in the understanding of the inflammatory and immunological mechanisms of allergic diseases [had] illuminated ***many potential therapeutic strategies*** that may prevent or even reverse the abnormalities of allergic inflammation." IMX2110, Abstract (emphasis added).
- "***Many new therapeutic agents*** have been developed either to attenuate the pro-inflammatory processes in asthma or to augment the host anti-inflammatory mechanisms . . . include[ing] heparin and inhibitors of PDEs, tyrosine kinases, and NF-kappaB, as well as antibodies and soluble receptors directed against IgE, IL-4, and IL-5." IMX2107, Abstract (emphasis added).
- "There are ***numerous therapies*** in clinical development that combat the inflammation found in asthma, specifically targeting eosinophils, IgE, adhesion molecules, cytokines (interleukin-4, -5, -13) and chemokines, inflammatory mediators, and cell signaling (kinase inhibitors)." IMX2108, Abstract (emphasis added);
- "The novel ***targets for therapy*** suggested by the current conceptual model for the activation and effector phases ***of the response to allergen are***

numerous. They include: cytokine inhibitors (anti-IL-4, IL-5, IL-13 or TNF-α), chemokine inhibitors (anti-CCR3 receptor), cell adhesion blockers (antibodies against or inhibitors of selectins, ICAM-1, VACAM-1, VLA-4), anti-inflammatory cytokines (IL-10, IFN-γ, IL-12, IL-18), transcription factor inhibitors (of NFκB, of NF-AT, of MAP-kinases, of Tyrosine kinases, of STAT-6)." IMX2109, 338 (emphasis altered).

By neglecting the wide range of other possibilities in treating allergic disorders, Sanofi and Dr. Zurawski improperly focus on IL-4R as a single option in a field replete with options. IMX2185, ¶23. When an obviousness argument provides "'no direction as to which of many possible choices is likely to be successful,' courts should reject "hindsight claims of obviousness.'" *In re Cyclobenzaprine Hydrochloride*, 676 F. 3d 1063, 1071 (Fed. Cir. 2012) (quoting *In re Kubin*, 561 F.3d 1351, 1359 (Fed.Cir.2009)). Accordingly, Sanofi's failure to consider the full scope of knowledge is an indication that hindsight has been used to define and follow a path to the claimed invention.

2. Sanofi improperly ignored the range of strategies known in the art for altering IL-4R signaling, and used hindsight to focus on anti-IL-4R antibodies.

Even if a POSA would have considered targeting IL-4R signaling as a

therapeutic strategy to treat allergic disorders (and Sanofi has not demonstrated that one would have), Sanofi's hindsight-driven analysis is further apparent in Sanofi's failure to indicate why a POSA would have chosen to develop an anti-IL-4R antibody as a method of targeting IL-4R activity. IMX2101, ¶¶27-31; IMX2185, ¶¶24-38. Sanofi's obviousness arguments do not properly consider the scope and content of the art because the relevant art is not limited to anti-IL-4R antibodies; it includes a wide range of targets and a wide range of therapeutic strategies. IMX2185, ¶¶24-27. This oversight is particularly egregious given that the Petitioners and Dr. Zurawski were engaged in various therapeutic efforts for treating allergic disorders—none of which involved an anti-IL-4R antibody. IMX2185, ¶28.

The range of different methods to modulate IL-4R activity in a therapeutic context described in the art before May 1, 2001, included at least administering:

- soluble IL-4 receptor protein,
- soluble IL-13 receptor protein,
- antibodies that bind IL-4,
- antibodies that bind IL-13,
- antibodies that bind IL-4R,

- IL-4 muteins (*i.e.*, IL-4 variants that bind to IL-4R but do not induce a biological response),
- IL-13 muteins,
- small molecules that inhibit IL-4-induced signal transduction, or
- therapeutics that target downstream effectors of IL-4 signaling such as the transcription factor STAT-6.

EX1011, 409-410; EX1429, 2:12-15; IMX2110, 1043; IMX2101, ¶29; IMX2185, ¶¶25-26. These options had been discussed side-by-side in prior art publications and considered for use as part of the same therapeutic methods. *See, e.g.*, EX1011, 409-410; IMX2107, 1326; IMX2185, ¶25.

These alternatives are all part of the relevant art because they are "from the same field of endeavor" and because they are "reasonably pertinent to the particular problem with which the inventor is involved." *Wyers v. Master Lock Co.*, 616 F. 3d 1231, 1237 (Fed. Cir. 2010). Yet, Sanofi's Petition does not even mention these alternative options. Of the range of different strategies, the most established, most explored, most clinically advanced strategy before May 1, 2001, was to block endogenous cytokine activity was using soluble IL-4R extracellular domain ("sIL-4R") to capture cytokines without signaling—a strategy that Sanofi

and Dr. Zurawski have ignored. IMX2109, 339; EX1011, 411; IMX2101, ¶28; IMX2185, ¶26. Agosti *et al.* noted in May, 2000, that "clinical trials using one of these approaches [to targeting IL-4 activity] already have commenced," referring specifically to using sIL-4R. EX1011, 409. The clinical trials with sIL-4R were "promising" and "tantalizing," and "support[ed] the potential therapeutic use of sIL-4R in allergic inflammation." IMX2109, 339; EX1011, 411; IMX2101, ¶28; IMX2185, ¶26. Despite this and despite citing Agosti *et al.*'s publication (EX1011) for other purposes, Dr. Zurawski admitted at deposition that he was unaware of whether "any molecules that inhibit IL-4 receptor-mediated signalling [sic] [had] been used in clinical trials." IMX2132, 29:23-30:5.

Contrary to the Petitioners' hindsight-driven characterization of anti-IL-4R antibodies as the obvious path, even co-Petitioner Regeneron was pursuing sIL-4R as a therapeutic, undermining the petition's argument that it would have been obvious to convert mAb230 into a therapeutic. In particular, Regeneron was developing a sIL-4R–based therapeutic known as an IL-4/IL-13 cytokine trap before May 1, 2001, and continued to do so well after that date. IMX2126. Economides et al. (IMX2111), published by Regeneron in December 2002, is a review article explaining the approach of using cytokine traps to target cytokines

such as IL-4 or IL-13. The authors state that "[t]raps potently block cytokines in vitro and in vivo and represent a substantial advance in creating novel therapeutic candidates for cytokine-driven diseases." IMX2111, Abstract. Regeneron touted this approach as providing "the most potent blockers of cytokine action that have been reported." IMX2111, 51 (emphasis added); *see also*, IMX2111, 51 (noting that the affinity of cytokine traps "compares favorably with monoclonal antibodies"). Notably absent from Regeneron's publications in this time frame is any discussion of anti-IL-4R antibodies. Similarly, Petitioner Sanofi-Aventis was pursuing a soluble IL-13 Receptor polypeptide based therapeutic. *See, e.g.*, IMX2134 at 0001. Therefore, the Petitioners' own actions contradict their *post-hoc*, litigation-driven assertions regarding what a POSA would have done in attempting to develop an anti-IL-4-based therapeutic.

Sanofi's petition and Dr. Zurawski's declaration also ignore the strategy of blocking IL-4R-mediated activity by administering mutant versions of IL-4 or IL-13. IMX2185, ¶28. These mutant proteins, called "muteins," bind to their receptors without activating them, thereby preventing endogenous IL-4 or IL-13 from binding to and activating their receptors. IMX2136, 5:16-18; IMX2185, ¶¶27-28. Again, contrary to Dr. Zurawski's hindsight-driven characterization of anti-IL-4R

antibodies as the obvious path, Dr. Zurawski himself chose to investigate IL-4 muteins as candidate therapeutics. IMX2128, 2123; IMX2132, 96:25-97:7; IMX2185, ¶28. As early as 1993, Dr. Zurawski stated that "it is likely that antagonistic mutant IL-4 proteins [(*i.e.*, IL-4 muteins)] may have potential clinical use in the treatment of IgE-mediated allergic diseases." IMX2128, Abstract; EX1400, ¶9; IMX2101, ¶29. Dr. Zurawski advocated for using muteins as therapeutics, arguing that "mutated cytokines have the potential to act as powerful antagonists in vivo." IMX2139, 4169. Dr. Zurawski's pursuit of the mutein model is further demonstrated by his obtaining a U.S. patent directed to IL-13 muteins. IMX2136; *see also*, IMX2148 (disclosing IL-2 muteins); IMX2149.

During deposition, Dr. Zurawski wrongly dismissed most of the therapeutic options for targeting IL-4R activity other than anti-IL-4R antibodies (*e.g.*, IL-4 muteins and anti-IL-4 antibodies) as not being part of the "relevant art." IMX2132, 28:8-29:17.[5] Dr. Zurawski's denial of IL-4 muteins as being part of the relevant art

[5] Dr. Zurawski gave a series of conflicting answers as to precisely which strategies for modulating IL-4R activity were part of the "relevant art" over the course of his deposition testimony in this case and in IPR2017-01879. IMX2135,

is remarkable given that Dr. Zurawki published papers on IL-4 muteins before May 1, 2001, and described himself as being "arguably, the first person to show . . . the potential utility for therapeutic application [of IL-4 muteins]." IMX2132, 28:19-22, 144:13-145:21. Dr. Zurawski even reminded himself of these efforts because, instead of investigating the relevant art in general, Dr. Zurawski's "main focus" in his searches was identifying ***his own*** papers—*i.e.*, "publications that [he] was particularly involved in that spoke to the biological activity of IL-4 and IL-13." IMX2132, 16:8-18:4.

Also during his deposition, Dr. Zurawski insinuated that by May 1, 2001, IL-4 muteins were not favored because "they had fundamentally decreased affinity" and had "a very short half-life" *in vivo*. IMX2132, 96:23-98:25;

77:12-88:18; IMX2142, 22:40-29:17. For example, in his first deposition, Dr. Zurawski asserted that IL-4 muteins were part of the relevant art, but in his second deposition, Dr. Zurawski stated exactly the opposite: that IL-4 muteins were not part of the relevant art. IMX2135, 84:8-19; IMX2132, 28:19-22. Dr. Zurawski's shifting testimony underscores the lack of credibility in his analysis of the prior art, particularly given that the art discusses muteins together with other strategies.

IMX2185, ¶29. Prior art publications in the period immediately before May 1, 2001, flatly contradict Dr. Zurawski's assertions because those publications recommend using IL-4 muteins as therapeutics without reservation. *See, e.g.*, IMX2107, 1324; EX1011, 412; IMX2150, Abstract 209; IMX2185, ¶29. For example, directly contradicting Dr. Zurawski's testimony, an abstract from Fitch *et al.* in February, 2001 reported results with an IL-4 mutein called BAY 16-9996—a preclinical candidate "being developed for the treatment of human bronchial asthma." IMX2150, Abstract 209; IMX2185, ¶29. Fitch stated that BAY 16-9996 "bind[s] with high affinity" to IL-4R and that it "is a potent inhibitor of lL-4 and IL-13-induced effects." *Id.*; *see also*, IMX2107, 1324 (stating that an IL-4 mutein bound to IL-4R with "high affinity"). Fitch continued to state that "[s]tudies conducted to evaluate the duration of effect of BAY 16-9996 demonstrated protection for up to 17 days post-administration: a surprisingly long duration despite a relatively short plasma half-life." IMX2150, Abstract 209. In contrast to this prior art evidence, Dr. Zurawski could not identify any publications supporting his litigation-driven view of the potential therapeutic utility of IL-4 muteins. IMX2132, 146:5-18.

In further contrast to Sanofi's unjustified focus on anti-IL-4R antibodies,

many reviews relating to the treatment of allergic diseases did not even mention anti-IL-4R antibodies. IMX2101, ¶30; IMX2185, ¶30. For example, in 2001 Tokura *et al.* published a series of six essays answering the question: "What are the most promising strategies for the therapeutic immunomodulation of allergic diseases?" IMX2113, Title. None of the essays mentioned anti-IL-4R antibodies, despite discussing a wide range of other therapeutic strategies including anti-IL-4 antibodies and sIL-4R. *Id.*, 134; ; IMX2185, ¶30. Other review articles published just before the May 1, 2001 priority date similarly disregarded anti-IL-4R antibodies in their extensive discussions of current and future targets of allergic disease and asthma treatments, instead focusing on other targets and therapeutic modalities. *See, e.g.*, IMX2110, 1043; IMX2108, 167; IMX2109, 339; IMX2112. S588:Table II; IMX2185, ¶30.

Rather than addressing why a POSA would have selected anti-IL-4R antibodies as a therapeutic strategy, Sanofi's hindsight-driven arguments simply ignore the other strategies discussed in the art. Sanofi immediately focused on anti-IL-4R antibodies despite such antibodies being just one aspect of the field prior to May 1, 2001. Regeneron's and Dr. Zurawski's own research efforts reflect how the field instead focused on other potential therapeutic targets for treating immune

disorders and other methods of inhibiting IL-4R mediated signaling, particularly sIL-4R and IL-4 muteins.

3. A POSA would not have selected MAb230 for developing a therapeutic candidate

Finally, even if a POSA were to have chosen to develop anti-IL-4R antibodies as a therapeutic strategy (though Sanofi has not demonstrated that one would), Sanofi's petition nonetheless is premised on impermissible hindsight. This is apparent in Sanofi's failure to justify selecting MAb230 from the known murine anti-IL-4R antibodies. IMX2101, ¶¶32-35; IMX2141, ¶¶31-33; IMX2185, ¶¶39-41. For example, Schering-Plough discloses nine different murine anti-IL-4R antibodies (*i.e.*, murine antibodies produced from hybridomas S103, 0361, S17, 0296, S456, S924, S697, 0497 and 0735). EX1007, Abstract, 2:32-33. Despite the fact that Dr. Zurawski was involved in the early testing of these nine antibodies, neither Sanofi nor Dr. Zurawski discuss them as candidates for modification to become therapeutics. EX1010, 13874:Table 1; IMX2101, ¶33. And neither Sanofi nor Dr. Zurawski discuss other murine anti-IL-4R antibodies disclosed in the prior art. *See, e.g.*, EX1019, Abstract (describing the X2/45 anti-IL-4R antibody); EX1205, 59:16-30 (describing the M57 anti-IL-4R antibody); IMX2125, 5054

(describing the CDw124 "monoclonal mouse IgG1 anti-human IL-4 receptor"); IMX2101, ¶¶32-33.

4. Sanofi has not identified *any* prior art patent or publication that suggests modifying MAb230 to make a therapeutic antibody

Despite Sanofi's sole rationale to modify MAb230 being linked to an alleged desire to make a therapeutic, and despite MAb230 being commercially available for over 20 years, and over five years before the filing date, Sanofi has not identified ***any*** patent or publication that suggests modifying MAb230 to make a therapeutic antibody. IMX2101, ¶34; IMX2141, ¶¶31-33; IMX2185, ¶¶39-41.[6] Further, there is no evidence that anyone has ever humanized MAb230. To the contrary, R&D Systems, which manufactured MAb230, stated in bold terms in its catalog that MAb230 is for "RESEARCH USE ONLY," specifically for in vitro

[6] During deposition, the only document Dr. Zurawski could identify that suggests modifying MAb230 was his own declaration for this proceeding. IMX2132. Dr. Zurawski further admitted that he could not recall having ever used MAb230 and could not recall having ever discussed the MAb230 antibody with anyone, undermining Dr. Zurawski's allegations of how POSAs viewed Mab230. IMX2132, 38:13-40:22.

assays such as "neutralization," "ELISA" and "Western Blot." EX1206, 0010, 0018. And Hart describes using MAb230 in a method of "[a]ssessment of functional responses to IL-13." EX1401, 2094. Hart was a study of the "IL-13 receptor complex on human monocytes," but in no way suggests converting any of the disclosed molecules into therapeutic candidates. EX1401, 2087.

Contrary to Sanofi's and Dr. Zurawski's unsupported views of MAb230, Dr. Marasco and Dr. Finkelman discuss the results of a comprehensive literature search for MAb230-related publications. IMX2141, ¶¶31-33; IMX2185, ¶¶39-41. That literature search revealed approximately 40 publications disclosing MAb230, all of which describe having used MAb230 as a non-clinical research reagent. IMX2141, ¶¶31-33; IMX2185, ¶¶39-41; IMX2101, ¶34; IMX2114, 1453 (using MAb230 "in flow cytometry"); IMX2115, 31448 (using MAb230 to purify recombinant proteins); IMX2116, 5660 (using MAb230 for "Flow cytometric analysis and FACS"); IMX2117, 451, 454 (using MAb230 in flow cytometry and as a signal blocking reagent); IMX2118, 630 (using MAb230 "to block endogenous cytokines"); IMX2119, 414, 416 (using MAb230 for immunohistochemistry); EX1401, 2094 (using MAb230 in a method of "[a]ssessment of functional responses to IL-13"). Similarly, publications

mentioning MAb230 after May 1, 2001, also describe MAb230 only in terms of its use as a research tool. *See, e.g.*, IMX2141, ¶¶31-33; IMX2185, ¶¶39-41; EX1401; IMX2114-IMX2119; IMX2187-IMX2211; IMX2213; IMX2215-IMX2220; IMX2151-IMX2156. Many of these publications even discuss the potential usefulness of targeting IL-4 or IL-4R with therapeutics after having used MAb230 as a non-clinical research tool, yet make no suggestion or even hint about developing MAb230 itself into a therapeutic agent. *See, e.g.*, IMX2141, ¶¶31-33; IMX2185, ¶¶39-41; IMX2151, C2037, C2038, C2037; IMX2152, 397, 399; IMX2153, 464, 468; IMX2154, 1, 3; IMX2152, 7; IMX2156, 524, 531; IMX2216, 3270, 3275; IMX2217, ¶¶[0273], [0275]; IMX2218, Example 12; IMX2219, Example 2; IMX2220, 3:6-10.[7] In short, Sanofi's arguments are driven by Sanofi's litigation strategy, not by a fair consideration of the prior art for all that it teaches.

Unlike Immunex's experts' comprehensive search of the Mab230-related art,

[7] IMX2154, IMX2155, and IMX2156 do not explicitly reference using MAb230, but generally refer to using an anti-IL-4R antibody from R&D systems and are listed on R&D's web page as having used the MAb230 product. IMX2157; IMX2141, ¶31, n. 2.

the only searching Dr. Zurawski could recall performing used his own name as a search term. IMX2132, 16:14-17:18. Dr. Zurawski makes broad assertions about the favorability of MAb230, yet by his own admission he could not recall performing searches for MAb230 literature, and couldn't recall ever having discussed MAb230 with anyone else. IMX2132, 39:5-40:22. Dr. Zurawski's results-driven analysis contrasts with scientific papers that provide real world evidence that a POSA thought of MAb230 simply as a research reagent, not a starting point for developing a therapeutic.

Sanofi's hindsight-driven focus on MAb230 is exemplified by Dr. Zurawski's immediate focus on MAb230 in his discussion of anti-IL-4R antibodies:

> Prior to May 1, 2001, it was well-known that antibodies could be raised against IL-4Rα. One such anti-h1L-4Rα antibody that was well-known to skilled artisans before May 1, 2001 is disclosed in Ex. 1204 ("Hart"). . . . Hart describes the use of a mouse anti-h1L-4Rα antibody called MAb230 (also known as clone 25463.11) to investigate the signaling complexes induced by IL-4 and IL-13 in monocytes and monocyte-derived macrophages ("MDMac").

EX1400, ¶¶43-44 (internal citations omitted); IMX2101, ¶32. Only hindsight allowed Dr. Zurawski to leap straight to discussing Mab230, given all of the other known murine anti-IL-4R antibodies.

Sanofi's assertion that "[e]very murine antibody is both a laboratory reagent and potential parent to a humanized antibody with therapeutic potential" is misleading and does not relate specifically to whether a POSA would have had reason to select MAb230. Pet., at 47. Sanofi bears the burden of demonstrating that MAb230 has characteristics that would have made it desirable as a starting point for developing a therapeutic. As discussed in Section IV.C below, MAb230's characteristics would not have provided a reason to selected Mab230 and modify it in accordance with the cited art. Thus, despite its blustering, Sanofi has not demonstrated that a POSA would have had reason "to generate a humanized version of MAb230 as a potential therapeutic for allergic diseases," let alone a human version of MAb230 as required by the claims. Pet., at 48.

Sanofi's assertion that a POSA would have selected MAb230 is further undermined by Regeneron's own actions in developing anti-IL-4R antibodies. Rather than humanizing MAb230—which Sanofi argues was the obvious choice based upon art that was all available by 1999—Regeneron's initial efforts to

develop a therapeutic inhibitor of IL-4 signaling, in the May 2001 time frame, used soluble IL-4R fragments that Regeneron termed "cytokine traps." IMX2111, 47; IMX2126. Regeneron pursued a cytokine trap targeting IL-4 and IL-13 until approximately 2006, but upon discovering that it was "a molecule that did not live up to expectations," Regeneron abandoned its cytokine trap in favor of developing anti-IL-4R antibodies. IMX2158; EX1006, ¶[0001]. And in developing human anti-IL-4R antibodies, Regeneron relied on Immunex's disclosure of the 12B5 antibody—not on MAb230, again undermining its current, litigation-driven obviousness theories. *See, e.g.*, Regeneron's anti-IL-4R antibody patent application, EX1006, ¶¶[0003], [0065], FIG. 1A-1C; IMX2124, 14:5-57, Tables 1-3. With Immunex's public teachings in hand, Regeneron made and used the same 12B5 antibody[8] as a "control" (*i.e.,* reference antibody) to screen and identify

[8] While Regeneron did not expressly disclose the name "12B5" in EX1006, Regeneron disclosed using the variable light chain and variable heavy chain sequences of 12B5: "Control antibody: a fully human anti-IL-4R antibody (U.S. Pat. No. 7,186,809; SEQ ID NOs: 10 and 12)." EX1006, ¶[0065]. U.S. Pat. No.

antibodies that compete with 12B5 for binding to human IL-4R. EX1006, ¶¶ [0003], [0065], FIG. 1A-1C. Accordingly, Regeneron first failed at developing its own IL-4R targeted therapeutic, but at no point did Regeneron disclose using MAb230 as a therapeutic candidate. It is only now, when facing accountability regarding its infringement of the '487 patent, that Regeneron and the other petitioners have alleged that MAb230 would have been selected for development into a therapeutic. Petitioners, it seems, are hoping MAb230 will be more useful to its defense strategy than it was to its research efforts.

C. The purportedly favorable properties of MAb230 would not have provided a reason to combine the cited references

Obviousness arguments should be rejected when "hindsight provides the only discernable reason to combine the prior art references." *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F. 3d 1342, 1369 (Fed. Cir. 2012). That maxim applies here because neither of the properties of MAb230 Dr. Zurawski identifies as making MAb230 a "promising candidate" actually would have provided reason to select MAb230. EX1400, ¶136; IMX2185, ¶¶42, 50-56. This leaves Sanofi's

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7,186,809 is a parent patent to the '487 Patent and shares a specification. *See* EX1001, at 1.

hindsight reconstruction as the sole reason to combine the prior art references.

1. Sanofi has not met its burden because it disregarded prior art teachings that blocking both IL-4 and IL-13 activity increased risk of parasitic infection, the development of inflammatory disorders, and cancer

Prior art studies had indicated that both IL-4 and IL-13 play important positive roles in the immune system, and that blocking their activity could lead to unacceptable side-effects. IMX2185, ¶¶43-49. As discussed below, the normal role of IL-4 and IL-13 included defense against parasitic infection, counterbalancing the inflammatory activities of T_H1 cytokines, and protecting against the development of cancer. IMX2185, ¶¶43-49. Accordingly, a POSA would have expected that blocking both IL-4 and IL-13 activity carried with it an increased risk of unacceptable side effects. *See, e.g.*, IMX2159, 773; IMX2222, 181; IMX2160, 4; IMX2223, 375; IMX2110, 1046.

While both IL-4 and IL-13 had been identified as playing a role in allergic disorders, before May 1, 2001, the art suggested that inhibiting the actions of *both* of these cytokines would have deleterious effects on the immune system. Dr. Zurawski's contention that concurrent suppression of both IL-4 and IL-13, which are both T_H2 cytokines, would be a "promising" therapy depends on an incomplete

analysis of the art. Dr. Zurawski does not account for the fact that these cytokines also serve valuable positive roles in the immune system:

> **[T]he goodness or badness of a particular cytokine response is situation dependent**: either T_H1 or T_H2 cytokines can promote protective immunity or exacerbate infection, depending on the pathogen involved, and the effector mechanisms through which a T_H1 or T_H2 cytokine response defends against infection are the same processes that cause inflammatory disease when induced inappropriately or in an exaggerated form.

IMX2159, 773.

As Dr. Finkelman explains, while T_H2 cytokines such as IL-4 and IL-13 are seen as "bad" in the sense that they promote undesired allergic responses, they are also "good" in the sense that they are "required both for host protection against a class of parasites and for suppression of T_H1 cytokine–induced immunopathology." IMX2159, 773; IMX2185, ¶¶45-49. In a healthy individual, the immune system maintains a "reciprocal antagonism between T_H1 and T_H2 cytokines." IMX2159, 772; IMX2185, ¶45. Therefore, "just as an imbalance toward T_H2 cytokine production may be responsible for allergic disease, insufficient T_H2 cytokine

production may predispose to other inflammatory disorders." IMX2159, 776; IMX2185, ¶45. Dr. Zurawski agreed that IL-4 and IL-13 were "thought to play a role in defending against pathogens" and stated that "under . . . certain circumstances, IL-4 and IL-13 can suppress inflammatory signals." IMX2132, 58:18-62:12.

Similarly, IL-4 and IL-13 were known to play a positive role in preventing tumor growth and development. IMX2185, ¶47. A POSA would have known that "IL-4 is a key enzyme not only for Th2 type immune reactions but also for tumor cell growth itself in human breast cancer." IMX2222, 181; IMX2185, ¶47. And both "IL-4 and IL-13 exert antitumoral properties *in vitro* and possibly *in vivo*." IMX2214, 3103; IMX2185, ¶47. Therefore, a POSA would have known that maintaining IL-4 and IL-13 activity is important for full protection from tumors. IMX2185, ¶47

Because both IL-4 and IL-13 were known to have important protective effects, a POSA would not have had a reason to modify an antibody that blocked both IL-4 and IL-13 activity and would not have had a reasonable expectation of success in doing so. IMX2185, ¶¶48-49. Researchers in the field prior to May 1, 2001, were concerned that inhibiting both IL-4 and IL-13 together would present

safety risks via a dysregulation of the T_H1-T_H2 cytokine balance. IMX2185, ¶¶48-49As Sanofi's Head of Development for Immunology noted, "[s]uch a dual IL-13/IL-4 mechanism of action was 'unheard of' when companies started to target cytokines with biologics . . . [and] [t]he safety implications were not understood at the time." IMX2160, 4; IMX2185, ¶¶48-49. In 1995, Dr. Zurawski also expressed doubt about inhibiting both IL-4 and IL-13, noting that "the in vivo repercussions of the inhibition of both IL-13 and IL-4 responses needs to be determined." IMX2223, 375; IMX2185, ¶¶48-49.

Moreover, a POSA would not have had a reason to combine the cited art or a reasonable expectation of success doing so in inhibiting both IL-4 and IL-13 because the relative roles of IL-4 and IL-13 were not well understood by May 1, 2001. IMX2185, ¶¶32-38, 44. Both were known to be T_H2 cytokines, and researchers had determined that the receptor complexes for each cytokine shared a component (IL-4Rα). IMX2185, ¶¶32-38, 44. But as Dr. Zurawski himself noted in 1998: "the exact constitution of the receptor complexes engaging the individual cytokines is poorly understood, though it is apparent that IL-13 has its own primary binding chains (IL-13Rα1 and IL-13Rα2), to which IL-4 does not bind." IMX2137, 423. And the relative role of each cytokine in the immune system

remained unclear, with some functions overlapping and other functions specific for one cytokine or the other. *See, e.g.*, EX1010, 13869 (noting that IL-4 can promote a Th2 response and inhibit a Th1 response in T cells, while IL-13 cannot because IL-13 receptors are not expressed by T cells); IMX2185, ¶¶32-38, 44. Dr. Zurawski summarized this uncertainty in 1998, noting that IL-4 and IL-13 have a complex interaction: "[i]t is evident that complex interrelated roles exist for IL-13 and IL-4 in the development of immune reactions, and though initially thought redundant, these cytokines elicit specific responses." IMX2137, 430; IMX2185, ¶¶32-38, 44.

To the extent that Sanofi is relying upon the supplemental information submitted as EX1455, neither Dr. Houchin's declaration nor the datasheet attached to his declaration provide any new arguments or data that would provide a reason to modify MAb230 into a therapeutic. Further, the datasheet's assertion that MAb230 has the "ability to block the human cell surface IL-4 receptor-mediated bioactivities induced by IL-4 or IL-13" is limited to *in vitro* activities and was not supported by any data relating to IL-13. IMX2212, 35:15-20, 36:22-37:15, 42:21-43:8, 59:16-23. The data provided in EX1455 also should be given little to no weight because Dr. Houchins had no first-hand knowledge of the experiments

performed, had not analyzed the underlying data, and could not say who performed the experiments. IMX2212, 28:19-29:8, 32:7-33:16, 36:16-38:6. Similarly, Dr. Zurawski admitted during deposition that he had no knowledge of who performed the experiments or where they were conducted, and could only offer that the experiments were performed "somewhere on the planet." IMX2132, 125:20-126:25, 136:8-19; 37 C.F.R. §42.65.

2. Even if a POSA were inclined to pursue a therapeutic that could block both IL-4 and IL-13 activity in spite of the risk of serious side effects, that characteristic would not have led to MAb230

Even if a POSA were inclined to pursue a therapeutic that could block both IL-4 and IL-13 activity in spite of the risk of serious side effects, that characteristic would not have led to MAb230. IMX2185, ¶¶50-53. As discussed below, the ability to block both cytokines was available in other antibodies and other methods. IMX2185, ¶¶50-53. Therefore, the ability to block both IL-4 and IL-13 activity would not have been sufficient to lead to MAb230 in particular. IMX2185, ¶¶50-53.

Multiple prior art anti-IL-4R antibodies were known to block both IL-4 and IL-13 activity, a fact that was known by Dr. Zurawski and Sanofi but not mentioned in the Petition, again revealing their hindsight bias. IMX2132, 31:9-

36:12. IMX2185, ¶51. For example, "inhibition of both interleukin-4-induced and interleukin-13-induced responses could be obtained by monoclonal antibody X2/45 raised against interleukin-4R_{EX}, the extracellular domain of the interleukin-4 receptor α subunit." EX1019, 659. In 1994, Renard et al. demonstrated that the "S460" anti-IL-4R antibody blocked both IL-4 and IL-13 activity. IMX2178, 2255. Similarly, Dr. Zurawski published a paper in 1994 with an anti-IL-4R antibody in which he noted that "the anti-IL-4R used in our experiments inhibits the effects of both IL-4 and IL-13." IMX2161, 402. And at least two of the anti-IL-4R antibodies disclosed in Schering-Plough were known to block both IL-4 and IL-13 activity. EX1010, 13874-13875 (disclosing that s456, and s103 block both IL-4 and IL-13 activity); EX1007; IMX2185, ¶51.

Nor were anti-IL-4R antibodies unique in their ability to block both IL-4 and IL-13 activity. IMX2185, ¶52. For example, Dr. Zurawski demonstrated that IL-4 muteins that could block both IL-4 and IL-13 activity. *See, e.g.*, IMX2128, 2213 (showing that "that a mutant form of human IL-4 . . . specifically blocks IL-4 and IL-13-induced proliferation"); EX1011, 412; EX1019, 659; IMX2185, ¶52. Downstream effectors such as STAT-6 also were recognized as potential targets for antagonizing the activity of both IL-4 and IL-13. EX1011, 415; IMX2185, ¶52.

And treatment with TH_1 cytokines (e.g., IFN-γ) was also known to downregulate the activity of both IL-4 and IL-13. EX1011, 403; IMX2179; IMX2180; IMX2181; IMX2182; IMX2185, ¶52.

As discussed above in Section III.C.1, a POSA would not have been motivated to pursue a therapeutic that could block both IL-4 and IL-13 activity due to concerns with increased risk of parasitic infection, the development of inflammatory disorder and cancer. However, given other methods and molecules for targeting both IL-4 and IL-13, only impermissible hindsight permits Sanofi to point to MAb230 while ignoring other approaches.

3. MAb230's Affinity for IL-4R Would Not Have Been a Reason for Modifying MAb230 to Develop a Therapeutic

Sanofi also alleges that a POSA would have selected MAb230 because it has "a 50% neutralization constant ('ND_{50}') of 0.003-0.006 μg/mL," a value higher than the therapeutic candidates in Schering-Plough. Pet., at 44 (citing EX1400, ¶¶49, 148). While Sanofi asserts that the ability to bind tightly is desirable or a characteristic of a good therapeutic candidate, this assertion is based entirely on a conclusory expert statement *without any citations to the prior art*. *Id.* Sanofi has not demonstrated that a POSA would have been seeking an antibody with

MAb230's affinity, or even that MAb230's affinity would be a positive characteristic that would prompt developing MAb230 into a candidate therapeutic. IMX2185, ¶¶54-56.

As Dr. Finkelman explains, affinity alone does not indicate whether an antibody would make a good therapeutic because the effects of affinity depend on what the antibody does when bound to its antigen. IMX2185, ¶¶54-56. The discussion in §III.C.1 above lays out why a person of ordinary skill in the art would have been concerned about potential toxicities associated with blocking IL-4 and IL-13 activity, including increased risk of parasitic infection, predisposition to inflammatory disorders, and increased risk of developing cancer. A person of ordinary skill in the art would have been concerned that, because the toxicity operates by the same mechanism as the potential benefit (*i.e.*, by blocking IL-4 and IL-13 activity), a high affinity antibody would amplify the toxicities as much or more than the beneficial effect. Accordingly, an antibody's affinity is not enough to identify it as a therapeutic candidate. In searching for a candidate, other factors would have been considered much more important, *e.g.*, useful biological characteristics. And as discussed above, MAb230 did not possess such characteristics.

D. Sanofi has failed to show that a POSA would have had a reasonable expectation of success in modifying MAb230 to generate a therapeutic antibody

In both grounds in the Petition, the *sole* motivation Sanofi argues to combine the cited art is to develop a therapeutic antibody. For example, Sanofi's Petition argues that "Schering-Plough expressly motivates a POSITA to humanize murine anti-hIL-4R blocking antibodies *to derive potential therapeutics*." Pet., at 43 (emphasis added). Sanofi's expert, Dr. Zurawski, explains, "[o]ne humanizes a mouse antibody to decrease the likelihood that the antibody triggers [an immune] reaction *when injected into a human*." EX1400, ¶214 (emphasis added). Indeed, the Petition repeatedly relies on the human therapeutic applicability of anti-IL-4R antibodies, and devotes an entire section to the "Need for Therapeutic Antibodies that Block IL-4 and IL-13 Signaling." *See, e.g.*, Pet., at 2-3, 11, 23-24, 25, 36, 42-45, 47-48, 57-58. Certainly, the Petition does not assert any non-clinical reasons to combine the cited art.

While Sanofi's sole reason to combine the cited art is to create a therapeutically effective monoclonal antibody, Sanofi fails to show that a POSA would have had a reasonable expectation of success in so doing. As the Federal Circuit has explained, when the sole alleged reason to combine the prior art is to

develop a potential therapeutic, a demonstration of obviousness requires that "a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective." *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) (quoting *In re Cyclobenzaprine Hydrochloride*, 676 F.3d 1063, 1070 (Fed. Cir. 2012)); *see also, Phigenix, Inc. v. Immunogen, Inc.*, IPR2014-00676, Paper 39, at 21 (Oct. 27, 2015) (holding that "Petitioner's rationale . . . was to make an immunoconjugate useful in treating tumors in human patients . . . [and] Petitioner does not persuade us that a preponderance of the evidence establishes that a skilled artisan would have had a reasonable expectation of success . . . in the treatment of breast tumors in humans").

Here, Sanofi's Petition fails to demonstrate that a POSA would have reasonably expected to succeed in treating allergic disease with a modified MAb230. Sanofi's reasonable expectation of success arguments fail because, instead of providing evidence regarding the expectation of success in producing a therapeutically effective antibody, Sanofi merely argued that a POSA could have successfully performed the *process* of altering MAb230 to "isolat[e] at least one species of the '487 Patent's claimed genus of antibodies." Pet., at 45. Accordingly,

Sanofi has not demonstrated that a POSA would have had a reasonable expectation of success in modifying Mab230 in accordance with the sole alleged motivation to combine the art.

And a full consideration of the prior art reveals that a POSA would not have had a reasonable expectation of producing a therapeutically effective antibody by modifying MAb230 as Sanofi suggests. By May 1, 2001, the prior art had not demonstrated the feasibility of targeting IL-4 or IL-13, either individually or in combination, to treat allergic disorders, much less the feasibility of doing so with antibodies against IL-4R. Dr. Zurawski admitted that he was unaware of whether "any anti-IL-4 receptor antibodies [had] been tested in clinical trials." *See, e.g.*, IMX2132, 37:16-18. The most investigated strategy by that point in time was administration of sIL-4R, which had just commenced clinical trials. EX1011, 409. Accordingly, such therapies had no track record of success that would have led a POSA to have a reasonable expectation of success in developing a therapeutic.

As discussed above, a POSA also would have had significant safety concerns in using a therapeutic that blocked both IL-4 and IL-13 activity. *See* §III.C.1; IMX2185, ¶¶43-49. Findings in the art "raise[d] the specter that such [cytokine-blocking] therapies will increase the risk of nematode infections, as well

as the likelihood of development of T_H1 cytokine–related inflammatory disorders, such as type 1 diabetes mellitus, multiple sclerosis, Crohn's disease, rheumatoid arthritis, and sarcoidosis." IMX2159, 777. These potentially serious side-effects provide another reason why a POSA would not have had a reasonable expectation of success in developing a therapeutic by humanizing MAb230. IMX2185, ¶¶43-49. Sanofi's Petition and Dr. Zurawski, who is not licensed to treat patients, completely ignore such real-world risks in attempting to develop a therapeutically effective antibody. Sanofi cannot be said to have established a reasonable expectation of success when it turns a blind eye to such risk factors.

* * *

Given the above, Sanofi has failed to present a prima facie case of obviousness in Ground 1.

IV. Ground 2 fails to establish obviousness

For multiple reasons, the Board should find the challenged claims not unpatentable because Sanofi has failed to meet its burden of persuasion. Like Ground 1, Ground 2 is fatally rooted in impermissible hindsight. *See* §IV.A below. Additionally, Ground 2 fails because a POSA also would not have had reason to use Hoogenboom's EIS methodology because it was known to diminish or

eliminate the very properties Sanofi alleges would have made a POSA select MAb230. *See* §IV.B below. And finally, Sanofi has not demonstrated that a POSA would have had a reasonable expectation of success in converting Mab230 into a therapeutic antibody using Hoogenboom's EIS method because that method had not been demonstrated to be reliable. *See* §IV.C below.

A. Sanofi's obviousness arguments in Ground 2 are based on impermissible hindsight

Ground 2, like Ground 1, involves the alleged motivation to generate a therapeutic that retains MAb230's properties. The Board should find the challenged claims not unpatentable under Ground 2 for the same reasons as described in Sections III.B-III.D above. Just as Ground 1 presents a hindsight-driven reconstruction of the invention by selecting MAb230 to alter with Schering-Plough's humanization method, Ground 2 presents a hindsight-driven reconstruction of the invention by selecting MAb230 to alter with a combination of Schering-Plough's and Hoogenboom's methods. *See* §§III.B-III.D. The hindsight underlying Ground 2 is further seen in the narrowly-framed instructions for Dr. Zurawski to "provide an opinion whether Hart and Schering-Plough combined with Hoogenboom renders the '487 Patent claims obvious," which ignores the art

as a whole. EX1400, ¶210. And the purported favorable properties of MAb230 would not have provided a reason to combine Hart, Schering-Plough, and Hoogenboom any more than they would have provided a reason to combine Hart and Schering-Plough alone. Therefore, a POSA would not have had reason to select MAb230 in view of the wide range of other strategies for treating allergic disorders.

B. A POSA would not have had reason to use Hoogenboom's method when seeking to retain MAb230's characteristics

A POSA would not have had reason to use Hoogenboom's EIS method to generate a fully human antibody based on MAb230 because EIS would have had a high chance of diminishing or eliminating the very properties Sanofi alleges would have made MAb230 a candidate for converting into a potential therapeutic. IMX2141, ¶¶34-37. As discussed below, a POSA would have known that EIS leads to altered epitope binding and decreased affinity. IMX2141, ¶¶34-37. Therefore, even if a POSA were interested in high affinity, EIS would have been unappealing because an altered antibody may not bind to the same epitope and/or have the same biological activities, and an altered specificity or lowered affinity would directly erode any advantage that MAb230's properties allegedly would

have provided. IMX2141, ¶¶34-37.

Sanofi improperly ignores evidence that EIS may change an antibody's binding characteristics, thus negating an alleged reason to choose Mab230 in the first place. IMX2141, ¶34. EIS, also referred to as guided selection, requires replacing all of the antigen-interacting portions of the antibody with new amino acid sequences. IMX2141, ¶35. Practical experience with EIS revealed that "human antibodies derived by guided selection unlike CDR-grafted antibodies, may retain only some of the original key elements of the binding site chemistry." IMX2162, 833; IMX2141, ¶¶36. Such differences in binding site chemistry were thought to be the cause of the observation that using EIS to generate a fully human interferon receptor antibody resulted in an antibody that "differed in epitope specificity from the parental hybridoma." IMX2163, 259; IMX2141, ¶36. And a POSA would have understood that these shifts in epitope binding could result in changes in the biological effects of antibodies. IMX2141, ¶36. As Beiboer explained, and as Dr. Marasco confirmed, "[d]ue to the different chemistry of the human antibody-antigen interaction, it can be envisaged that in some cases *guided selection may alter the antibody-mediated triggering or signal transduction of the starting rodent antibody*" IMX2162, 841 (emphasis added); IMX2141, ¶36. Dr.

Zurawski completely ignored such evidence in the art, undermining his obviousness arguments.

Sanofi also improperly ignores evidence that EIS may diminish an antibody's binding affinity, again negating the alleged reason to select Mab230. A POSA would have understood that the changes in binding site chemistry during EIS repeatedly decreased the affinity of newly generated human antibodies relative to the original murine antibody. *See, e.g.*, IMX2163, 259; EX1404, 995; IMX2164, 181; IMX2141, ¶37. For example, Klimka et al. demonstrated that "[e]xpression of the human anti-CD30 scFv hAK30 as soluble fragment revealed a 10-fold lower apparent Kd" relative to the original murine scFv." IMX2163, 259; IMX2141, ¶37. Similarly, Figini et al. noted that a human Fab fragment generated with EIS had a binding affinity "approximately fivefold weaker than that of the murine [reference Fab fragment]." EX1404, 995; IMX2141, ¶37. Wang *et al.* tested two human Fab fragments' affinity relative to the parental Fab fragment and found that the "results showed that the affinity of the human Fab are lower than that of the parental Z8 Fab." IMX2164, 181; IMX2141, ¶37. Accordingly, a person of ordinary skill in the art would not have expected new antibodies generated by Hoogenboom's method to maintain their affinity, contradicting Sanofi's alleged reason to use EIS on

MAb230. IMX2141, ¶37.

Sanofi identified two features of MAb230—the ability to block both IL-4 and IL-13 activity and its affinity—as the purported positive characteristics of MAb230 that would have led a POSA to modify MAb230. If this were the case (despite Sanofi's lack of supporting evidence), then a POSA would have been concerned with maintaining those characteristics as part of generating a human antibody. But, as described above, EIS had been repeatedly demonstrated to alter those very same properties that Sanofi alleges to be valuable. IMX2141, ¶¶34-37. Dr. Zurawski—who has never carried out EIS, never published a paper on EIS, and did not search the literature for publications on EIS—failed to recognize these limitations of EIS, let alone establish a reason to combine the art in view of these limitations of EIS. IMX2132, 21:22-22:3, 16:8-18:4. Accordingly, Sanofi's obviousness argument fails.

C. A POSA would not have had a reasonable expectation of success in using Hoogenboom's method to convert Mab230 into a fully human antibody

A full consideration of the prior art reveals that a POSA would not have had a reasonable expectation of success in applying Hoogenboom's EIS methodology to convert Mab230 into a therapeutic. IMX2141, ¶¶38-41. By 2000, "very few

successful humanizations by guided selection [had] been reported" IMX2164, 172; IMX2141, ¶39. Even by 2012, a review reported that "very few human mAbs by this [guided selection] approach have been reported." IMX2165, 55; IMX2141, ¶39. The Hoogenboom reference itself only discloses performing EIS on a single antibody (MAB32). EX1402, Example 1; IMX2132, 85:10-21. With such little success, a POSA would not have had a reasonable expectation of success in using EIS to convert Mab230 into a therapeutic antibody. IMX2141, ¶39.

As Dr. Marasco explains, the art reveals a number of reasons for failures in using EIS to develop acceptable new antibodies, all of which undermine Sanofi's arguments that a POSA would have had a reasonable expectation of success. IMX2141, ¶¶40-41. One difficulty in performing EIS is that there is a "great difficulty of finding a suitable heavy chain using a light chain guide . . . [because] heavy chains which fortuitously coordinate with an affinity-matured light chain from another species to bind the same epitope in the same orientation with comparable affinity must be exceedingly rare in human heavy chain repertoire libraries." IMX2166, ¶[0008]; IMX2162, 838 (stating that "[i]n contrast to the rapid and successful chain shuffling of the light chain, the shuffling of the heavy chain was more difficult"); IMX2141, ¶40. Further, "even if suitable heavy chain

partners for the guiding light chains exist in the repertoire they are likely to be lost in the process of generating the phage-displayed library." IMX2166, ¶[0008]; IMX2141, ¶40. Some researchers noted that, rather than producing the desired antibodies, EIS had a "troublesome" tendency for nonspecific antibodies to arise from the selection process. IMX2164, 183; IMX2141, ¶40. For example, Wang stated that "[a] troublesome and intriguing phenomenon in this [EIS] process was the emergence of, sometimes dominant, non-specific binding clones." *Id.*; IMX2141, ¶40.

Another particular difficulty identified in performing EIS was its difficulty in identifying and selecting a new heavy chain CDR3 region while maintaining the same binding characteristics. IMX2141, ¶41. It has been found in the art that finding a replacement for the CDR3 region has proved to be difficult in EIS. IMX2141, ¶41. Therefore, some researchers recommended performing alternative methods in which the murine heavy chain CDR3 was retained, rather than using EIS to generate a fully human antibody. IMX2141, ¶41. For example, Mersmann *et al.* noted that, "[i]n order to avoid an epitope shift during humanization of VH by guided selection as previously reported, the parental HCDR3 of the murine MAb [to be used] was retained for subsequent selections." IMX2168, 243; *see also*,

IMX2169, 1736-1737; IMX2141, ¶41. And Hoogenboom noted that "[i]t may be advantageous to apply the polycombinatorial approach to humanising by a chain-shuffling process in which the VHCDR3 sequence of the rodent antibody is imprinted upon the human VH segments." EX1402, 30:25-28; IMX2141, ¶41. Performing this alternative methodology in which CDR3 is retained would not have led to a human antibody, under the proper construction of that term, because it would result in a humanized antibody, not a human antibody. IMX2141, ¶41

Even if a POSA were to generate an antibody using EIS, a POSA would not have had reason to expect success in producing a therapeutic antibody. Just as Ground 1 does not demonstrate that a POSA would have had a reasonable expectation of success in generating a therapeutic antibody by altering MAb230, Ground 2 also does not demonstrate an expectation of therapeutic success. *See* §III.D. Ground 2 discusses only whether antibodies can be "successfully transformed" into human antibodies using Hoogenboom's method, and completely ignores whether a POSA would have had an expectation of success in producing a therapeutic antibody. Pet., at 58-59. Moreover, a POSA would have doubted that antibodies blocking both IL-4 and IL-13 activity would be successful because of a lack of previous success, an increased risk of pathogenic infection, and an

increased risk of developing inflammatory diseases. *See* §III.D. Further doubt would have been provided by the fact that antibodies developed with Hoogenboom's method "tend to have a significant number of amino acid differences from the closest germ-line sequence . . . [and] antibodies with numerous differences from germ-line sequences may be expected to be immunogenic when used therapeutically in humans." IMX2170, ¶[0008]. Therefore, as Dr. Marasco explains, a POSA would not have had a reasonable expectation of successfully using EIS to achieve the asserted goal of reducing immunogenicity and making a therapeutic antibody. IMX2141, ¶¶38-41.

* * *

Given the above, Sanofi has failed to present a prima facie case of obviousness in Ground 2.

V. This *Inter Partes* Review Is Unconstitutional.

In *Oil States Energy Services LLC v. Greene's Energy Group, LLC*, the Supreme Court explicitly limited its decision to the constitutional challenge raised by Oil States:

> We emphasize the narrowness of our holding. We address the constitutionality of inter partes review only…

> Moreover, we address only the precise constitutional challenges that Oil States raised here. Oil States does not challenge the retroactive application of inter partes review, even though that procedure was not in place when its patent issued. Nor has Oil States raised a due process challenge. Finally, our decision should not be misconstrued as suggesting that patents are not property for the purpose of the Due Process Clause or the Takings Clause.

Oil States Energy Services, LLC v. Greene's Energy Group, LLC, 584 U. S. ____ (2018), at 16–17.

Immunex respectfully objects to this tribunal's exercise of jurisdiction to adjudicate the patentability of the '487 patent because it would violate Immunex's rights under the Takings clause of the Fifth Amendment. The retroactive nature of IPRs—these proceedings were not in place when the application leading to the '487 patent was filed—underscores the unconstitutionality of this process.

VI. Conclusion

Sanofi fails to meet its burden of persuasion in this proceeding. The Board should reject the Petition and find all of the challenged claims not unpatentable.

Respectfully submitted,
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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), I certify that the above-captioned **IMMUNEX CORPORATION'S PATENT OWNER RESPONSE UNDER 37 C.F.R. §42.120** contains 13,994 words as counted by the word-processing program used to generate this reply. This total does not include the table of contents, the table of authorities, appendix of exhibits, certificate of service, or this certificate of word count.

Respectfully submitted,
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CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

The undersigned hereby certifies that the above-captioned the above-captioned **IMMUNEX CORPORATION'S PATENT OWNER RESPONSE UNDER 37 C.F.R. §42.120** was served in its entirety on May 17, 2018, upon the following parties via electronic mail:

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