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UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA, WESTERN DIVISION

IMMUNEX CORPORATION,

Plaintiff,

v.

SANOFI; SANOFI-AVENTIS U.S. LLC; GENZYME CORPORATION; AVENTISUB LLC; and REGENERON PHARMACEUTICALS, INC.,

Defendants.

Case No. 2:17-cv-02613-SJO (PLA)

DEFENDANTS' COMBINED OPENING CLAIM CONSTRUCTION BRIEF AND MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT

Judge: Hon. S. James Otero

Hearing: March 12, 2018

Time: 10:00 a.m.

Place: Courtroom 10C

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SANOFI-AVENTIS U.S. LLC; GENZYME CORPORATION; and REGENERON PHARMACEUTICALS, INC.,

Counterclaim-Plaintiffs,

v.

IMMUNEX CORPORATION and AMGEN INC.,

Counterclaim-Defendants.

Discovery Cut-off: August 17, 2018

Pretrial Conference: March 4, 2019

Trial: March 19, 2019

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TABLE OF EXHIBITS

Exhibit[1]	Description
1	U.S. Patent No. 8,679,487
2	U.S. Patent Application No. 14/175,943, Non-Final Rejection (January 12, 2016)
3	Deposition Transcript of Michael J. Taussig, Ph.D. (January 11, 2018)
4	U.S. Patent No. 5,710,023
5	Immunex Laboratory Notebook No. 8844, IMNX00003943-4000
6	European Patent No. EP 2292665
7	U.S. Patent No. 7,605,237

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[1] Exhibits are attached to the Declaration of John F. Garvish, II, filed concurrently herewith.

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TABLE OF ABBREVIATIONS

Abbreviation	Name
'035 Publication	U.S. Patent Publication No. 2008/0160035
'237 Patent	U.S. Patent No. 7,605,237
'371 Patent	U.S. Patent No. 8,357,371
'487 Patent	The patent-in-suit, U.S. Patent No. 8,679,487
'702 Application	U.S. Application No. 12/291,702, Dkt. 153-13
Defendants	Regeneron and/or Sanofi
EPO	European Patent Office
GenPharm Patent	U.S. Patent No. 5,770,429, Dkt. 155-7
IL-4	Interleukin-4
IL-4R	Interleukin-4 Receptor
Immunex	Immunex Corp. and/or Amgen Inc.
Krummenacher	Claude Krummenacher et al., "Localization of a binding site for herpes simplex virus glycoprotein D on herpesvirus entry mediator C by using antireceptor monoclonal antibodies," J. Virol. 2000 Dec; 74(23):10863-72, Dkt. 155-9
Nice	Edouard Nice et al., "Mapping of the antibody- and receptor-binding domains of granulocyte colony-stimulating factor using an optical biosensor," J. Chromatopgr., 1993, 646:159-168, Dkt. 155-5
Perez	Perez de la Lastra et al., *Epitope Mapping of 10 monoclonal antibodies against the pig analogue of human membrane cofactor protein (MCP)*, Immunology 1999, 96:663-670, Dkt. 153-23
PTAB	Patent Trial and Appeal Board of the PTO
PTO	U.S. Patent and Trademark Office
Regeneron	Regeneron Pharmaceuticals, Inc.
Robinson Decl.	Robinson Declaration, Dkt. 153
Sanofi	Sanofi, Sanofi-Aventis U.S. LLC, Genzyme Corporation and/or Aventisub LLC
Schering Patent	U.S. Patent No. 5,865,537, Dkt. 155-4
SUF	Statement of Undisputed Facts
Taussig Decl.	Taussig Declaration, Dkt. 155
Van Der Geld	Y.M. Van Der Geld et al., "Characterization of monoclonal antibodies to proteinase 3 (PR3) as candidate tools for epitope mapping of human anti-PR3 autoantibodies," Clin. Exp. Immunol., 1999, 118:487-496, Dkt. 155-13

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I. INTRODUCTION

In the late 2000s, Immunex's anti-IL-4R antibody, AMG-317, failed in clinical trials. Instead of continuing its own search for a therapeutic, Immunex sought to stake a claim to all anti-IL-4R antibodies Immunex's competitors were developing. Relying on a vague specification drafted in connection with the failed AMG-317 project and claims written after Immunex had studied Defendants' own patent filings describing their independently-created anti-IL-4R antibodies, Immunex now asserts a monopoly over virtually any anti-IL-4R antibody, including the accused Dupixent®, a "game-changer" in the fight against atopic dermatitis and other incurable diseases.

The '487 Patent embodies the very type of unconscionable overreach and obstacle to innovation the Supreme Court and Federal Circuit's recent 35 U.S.C. § 112 jurisprudence has sought to curb. While it teaches no actual therapeutics or novel methods of developing them, Immunex's patent nevertheless purports to cover all antibodies that **"compete[]"** with an anti-IL-4R "reference antibody" (an AMG-317 precursor) that has never been shown to treat any disease.

The '487 Patent is invalid for indefiniteness because its claims do not "particularly point[] out and distinctly claim[] the subject matter which the inventor . . . regards as the invention." 35 U.S.C. § 112, ¶ 2. In its rush to obtain vague, overbroad claims that might someday read on products developed by its competitors, Immunex failed to provide any guidance on how skilled artisans ought to ascertain the boundaries of the claims—that is, whether "compet[ition]" actually exists between the "reference antibody" and the claimed antibodies. This is a fatal flaw under the Supreme Court's *Nautilus* decision and the Federal Circuit's recent *Teva* and *Dow* decisions implementing the *Nautilus* standard. This is not a close question. Indeed, in an office action issued in a related application after *Nautilus*, **the same PTO examiner who allowed the '487 Patent** rejected nearly identical claims to antibodies that "compete[] with a reference antibody" on related § 112 grounds. Judgment of invalidity is thus appropriate.

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II. RELEVANT UNDISPUTED FACTS

While the science behind Defendants' 11-year long efforts to develop Dupixent® is complex, the facts that are determinative here are straightforward.[2]

An antibody is a Y-shaped protein comprised of chains of amino acids. SUF ¶¶ 6-9. Antibodies are used by the immune system to neutralize pathogens by binding to them. SUF ¶¶ 3-4, 12. Each tip of the "Y" of an antibody contains a "paratope" (analogous to a lock) that is specific for one particular "epitope" (analogous to a key) of a target antigen, allowing the two structures to bind to each other. SUF ¶¶ 11-12.

The sole independent claim of the '487 Patent claims an entire genus of antibodies entirely by their function: "An isolated human antibody **that competes with a reference antibody** for binding to human [IL-4R], wherein" the light and heavy chains of the "reference antibody"—not the claimed "isolated human antibod[ies]"—include the amino acid sequences found in "SEQ ID NO:10" and "SEQ ID NO:12." Ex. 1, cl. 1 (emphasis added). While Claim 1 recites portions of the amino acid sequence of the **reference antibody's** light and heavy chains, the '487 Patent contains no teaching whatsoever with respect to the amino acid sequence of the alleged **invention**, *i.e.*, the claimed "isolated human antibod[ies]." Ex. 1. Instead, Immunex purports to broadly claim any anti-IL-4R antibody based on undescribed and undisclosed attributes that enable it to "compete[]" with a "reference antibody" for binding to IL-4R.

As counsel for Immunex argued during the August 3, 2017 conference, competition between antibodies is loosely analogous to a game of "musical chairs with only one chair left and two contestants. . . . So if there's an antibody bound to the IL-4R receptor already and another antibody comes in and is competing to bind with that receptor," the second antibody is deemed to compete for binding. SUF ¶ 41. But unlike in a game of "musical chairs," a determination of whether two antibodies

[2] For a complete statement of relevant facts, Defendants respectfully refer the Court to the Statement of Undisputed Facts ("SUF").

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"compete[]" for binding must be made **experimentally**, through a number of measurements. SUF ¶¶ 33-35. As counsel also acknowledged, "there's various assays that can be done to test that and **measure the extent of that competition**." SUF ¶ 42 (emphasis added). But at the time of the alleged invention (and even today), there were numerous accepted methods of measuring "antibody" competition involving numerous variables, including:

- different assay types (*e.g.*, flow cytometry, surface plasmon resonance ("SPR"), enzyme-linked immunosorbent assay ("ELISA") or radioimmunoassay ("RIA")),
- different assay conditions (*e.g.*, temperature, concentration, format, pH, duration), and
- different measurement thresholds (*e.g.*, 20%, 50%, 80%).

SUF ¶¶ 33-34, 37-38, 59-65, 71-76. It was known in the prior art that different assays, conditions, or thresholds may lead to different conclusions as to the presence or absence of competition. SUF ¶¶ 40, 49-52, 66-70, 77.

The '487 Patent issued shortly before the seminal *Nautilus* decision. SUF ¶ 2. Immunex since continued to prosecute claims directed to "a genus of antibodies that are **described only by their function of competing with a reference**." Ex. 2 at 5. The same PTO examiner who allowed the '487 Patent rejected Immunex's efforts to obtain such claims, noting that Immunex may not claim "what one has not conceived." *See* Ex. 2 at 7, 8; SUF ¶¶ 25-31.[3]

Recently, the EPO's Opposition Division revoked the European counterpart to the '487 Patent . SUF ¶¶ 44-45. In so doing, the EPO Opposition Division determined that:

[3] While the examiner's rejection was based on written description, rather than indefiniteness, it is well established that "definiteness and written description requirements are related [concepts that] . . . approach a similar problem from different directions." *Korszun v. Pub. Techs. Multimedia, Inc.*, No. 3-00-cv-327, 2002 U.S. Dist. LEXIS 18855, at *7 (D. Conn. Aug. 30, 2002) (quoting *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1561 (Fed. Cir. 1991)).

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> the expression "reference" is not found in conjunction with a competition assay in the (parent) application, **in fact the (parent) application does not comprise any teaching on how to perform the competition assay, or <u>which standards to apply to arrive at any conclusions</u>**.

SUF ¶ 45 (emphasis added).

III. ARGUMENT

All of the asserted claims are invalid for two distinct reasons: (1) the claim limitation "competes" fails the *Nautilus* test; and (2) Immunex drafted independent Claim 1 with broad functional language, while failing to recite a corresponding structure for the claimed "isolated human antibod[ies]." Additionally, two of the asserted claims are invalid because they recite a limitation—"binding affinity (K_a)"—that similarly does not pass muster under *Nautilus*.

To the extent the Court deems it necessary to engage in claim construction, it should (1) construe the term "isolated human antibody" pursuant to § 112(6) and limit its scope based on the structures disclosed in the specification; and (2) construe the term "human" as encompassing both "fully **or** partially human."

A. The "Competes" Limitation Is Indefinite and Renders All of the Asserted Claims Invalid

Nautilus held that, under § 112, a patent claim is definite only if "viewed in light of the specification and prosecution history, [it] inform[s] those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014). Claims must be precise enough to give clear notice to "the public of what is still open to them," and eliminate any "zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims." *Id*. (citations omitted).[4]

[4] While *Nautilus* articulated a new standard for indefiniteness, even before *Nautilus* "[a] claim [wa]s indefinite if its legal scope [wa]s not clear enough that a person of ordinary skill in the art could determine whether a particular [product] infringes or not." *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1384 (Fed. Circ. 2003).

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The *Nautilus* standard is particularly stringent in cases involving claim limitations that require measurements. In *Teva Pharms. USA Inc. v. Sandoz, Inc*., for instance, the Federal Circuit considered a claim covering a polypeptide product, which included a limitation on the "molecular weight" of the substance. 789 F.3d 1335 (Fed. Cir. 2015). The Court explained that "molecular weight" could be determined by three different types of measurements recognized in the art, each of which is calculated in a different manner and would yield different values. *Id*. at 1338. The claims and specification provided no insight into what type of measurement was actually intended. The Federal Circuit affirmed a finding of invalidity based on indefiniteness, holding that the patentee had failed to inform with reasonable certainty those skilled in the art about the scope of the invention. *Id*. at 1345.

Similarly, in *Dow Chem. Co. v. Nova Chems. Corp.*, 803 F.3d 620, 630 (Fed. Cir. 2015), the Federal Circuit considered a patent whose claims recited a limitation—"slope"—that could be measured using at least four known methods. The Federal Circuit held that "[p]articularly . . . where different approaches to measurement are involved," *Nautilus* requires that "[t]he claims, when read in light of the specification and the prosecution history, must provide objective boundaries for those of skill in the art." *Id*. at 630 (internal quotations omitted). "The existence of **multiple methods leading to different results** without guidance in the patent or the prosecution history as to which method should be used renders the claims indefinite." *Id*. at 634 (emphasis added). Applying these principles, the Federal Circuit held the patent-in-suit indefinite because "each of [the] four [known] methods may produce different results," and "[n]either the patent claims nor the specification . . . discusse[d] the four methods or provide[d] any guidance as to which method should be used." *Id*. at 633-34.

The '487 Patent is indefinite under controlling case law because (1) it fails to teach any particular technique for measuring antibody "compet[ition]"; (2) the multiple recognized methods of measuring "compet[ition]" (using multiple different variables) lead to different, outcome-determinative results; and (3) Immunex does not

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proffer any evidence, scientific or otherwise, to overcome these fatal flaws.

1. The '487 Patent Fails to Teach Any Technique for Measuring Competition

The '487 Patent fails to teach a skilled artisan how to measure "compet[ition]" between antibodies. Turning first to the claim language, "competes" is recited only once in Claim 1, without any guidance as to how the presence or absence of "compet[ition]" is to be determined. Thus, "the claim on its face offers no guidance on which measure of ['competes'] the claims cover.'" *Teva*, 789 F.3d at 1341.

The remainder of the '487 Patent disclosure fares no better. "[C]ompetes" is recited six times in the specification. But every recitation is identical, generic, and circular—"a [monoclonal antibody] that **competes** with 12B5 [or 6-2, 27A1, 5A1, 63, or 1B7] for binding to a cell that express human IL-4R." Ex. 1, 21:19-20; 22:7-8; 22:66-67; 23:47-48; 24:28-29; 25:9-10. These six instances say nothing about how a skilled artisan would know **whether** an antibody "competes," let alone **how** to measure the extent of "compet[ition]" between antibodies. *See Dow*, 803 F.3d at 634 ("Neither the patent claims nor the specification here discusses the four methods or provides any guidance as to which method should be used or even whether the possible universe of methods is limited to these four methods.").

Under at least *Nautilus*, *Teva*, and *Dow*, the '487 Patent's failure to teach any particular way to ascertain or measure "compet[ition]" is fatal. By design, the '487 Patent covers every "isolated human antibody" that "competes" with a "reference antibody" for binding to human IL-4R, and thus plainly embraces the full breadth of assays, assay conditions, and thresholds that were known and accepted in the prior art for determining competition. But the '487 Patent fails to provide any guidance as to the type of assay, assay conditions, and assay thresholds that the skilled artisan ought to apply to ascertain the scope of the claims. SUF ¶¶ 35-36; Robinson Decl. ¶¶ 79-81. Under these circumstances, the '487 Patent is indefinite as a matter of law. *See Teva*, 789 F.3d at 1344-45 ("'[M]olecular weight' or average molecular weight can be

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ascertained by any of three possible measures: M_p, M_n, and M_w. The claims do not indicate which measure to use. The specification never defines molecular weight or even mentions M_p, M_w, or M_n. And the term 'average molecular weight' does not have a plain meaning to one of skill in the art.").

2. Prior-Art Techniques of Measuring "Compet[ition]" Require Judgment Calls and Yield Discordant Results

It is undisputed that "[s]everal **different** techniques for assessing competition" were known in the prior art. Taussig Decl. ¶ 55 (emphasis added); Robinson Decl. ¶¶ 39, 59; SUF ¶¶ 33-35, 38. Furthermore, the known techniques to measure competition require the skilled artisan to make numerous judgment calls. SUF ¶¶ 33-35, 38-39, 59-65, 71-76.

- **First**, skilled artisans must select an assay **type**. At the time of the invention, as today, there were at least **four different competition assays** recognized by skilled artisans: flow-cytometry, SPR, ELISA and RIA. SUF ¶¶ 33-35, 39; Taussig Decl. ¶¶ 55-61; Robinson Decl. ¶¶ 66-68.

- **Second**, skilled artisans must specify the **numerous conditions** required for the selected assay. Those conditions include at least temperature, antibody concentration, pH, antibody order (*e.g.*, sequential or concurrent), assay format (*e.g.*, sandwich or in tandem), and experimental duration. SUF ¶¶ 59-65; Ex. 3 at 167:9-168:13, 172:19-173:2, 185:1-23, 186:17-187:2.

- **Third**, skilled artisans must select the **threshold for analyzing the assay results** to determine whether the tested antibodies compete. SUF ¶¶ 71, 79. Although the prior art teaches that a competition threshold of some magnitude must be selected to distinguish competitive from non-competitive results, there is not a consensus among skilled artisans as to the appropriate threshold to select. SUF ¶ 71.[5] Any number from 1% to 100% could be selected as the threshold depending on the objectives of the assay. SUF ¶¶ 72-76.[6]

[5] *See also* Robinson Decl. ¶¶ 69-74, 112-14; Dkt. 155-5 at IMNX00013628 ("[A]n arbitrary level of inhibition had to be chosen for the delineation of positive versus negative effects."); *compare* Dkt. 153-23 at DEFS1568224 (using a 50% threshold) *with* Dkt. 155-13 at IMNX00013585 (using a 90% threshold) *and* Dkt. 155-9 at IMNX00013668 (using a 40% threshold).

[6] For example, skilled artisans often used a parameter called "percentage of inhibition" or "PI" to decide whether a pair of antibodies compete. Robinson Decl. ¶¶ 69-74. Using this method, a skilled artisan compares the PI measured during a

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Yet the '487 Patent offers no guidance to the skilled artisan in making these selections. SUF ¶¶ 36-37. Rather than teach the boundaries of Immunex's purported inventions, the '487 Patent leaves the skilled artisan guessing as to how to implement its teaching and where the boundaries of Immunex's claims may in fact lie.

And, to be sure, the boundaries of the asserted claims are akin to shifting sands. For instance, during proceedings concerning the now revoked European counterpart to the '487 Patent, Immunex took the position that a prior art reference by Perez taught methods for determining competition between antibodies. SUF ¶¶ 43-46. Immunex expressly asserted that a "skilled person could therefore use a method disclosed in [Perez] D24 to identify competition between a test antibody and a reference antibody." SUF ¶ 48; Dkt No. 153-41, ¶ 6.20. Immunex also asserted that "[Perez] provides methods for determining competition between antibodies **and competition was identified successfully using those methods**." SUF ¶ 47; Dkt No. 153-41, ¶ 6.20 (emphasis added).

But, as Immunex admitted, it is a "fact" that "[Perez] discloses two methods for assessing competition which give different results." SUF ¶¶ 49-54; Robinson Decl. ¶¶ 59, 89-97. One method disclosed by Perez uses a flow cytometry assay design. SUF ¶ 51. A second method disclosed by Perez uses an SPR assay design. SUF ¶ 52. Critically, Perez found that multiple pairs of antibodies compete for binding under the flow cytometry assay design but not under the SPR assay design. SUF ¶ 53. Likewise, Perez found that multiple pairs of antibodies compete for binding under the SPR assay design but not under the flow cytometry assay design. SUF ¶ 54.

The table below summarizes the results from Perez using the two assay types to measure competition between nine antibodies, which are identified in each column and row, respectively. Robinson Decl. ¶ 93. An "F" at the intersection of any two

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competition assay with a predetermined threshold. *Id.* If the measured PI exceeds the predetermined threshold, the antibodies are deemed to compete. But if the measured PI falls below the predetermined threshold, the antibodies are deemed not to compete. *Id.*; Dkt. 153-23 at DEFS1568224 (using, *e.g.*, "50% or higher . . . as a cut-off . . . to place the mAbs into four groups of mutually competitive antibodies").

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antibodies indicates that they were found to compete by flow cytometry, while an "S" indicates that they were found to compete by SPR.

Comparison of competition data in Perez		First mAb								
		INIA2C11	INIA6D8	JM5C3	JM2G11	JM4C8	JM6C5	JM6C11	JM7A11	INIA1C5
2nd mAb	INIA2C11	F S	F S	F	F S					F
	INIA6D8	F S	F S	F	F S				S	S
	JM5C3	S	F S	F S	F S	S			S	
	JM2G11	F S	F S	F S	F S		S			
	JM4C8	S		S	S	F S	F S	F	F S	
	JM6C5	S	S	S	S	F S	F S	F	F	
	JM6C11			S	S	F S	F S	F S	F	S
	JM7A11	S	F S	S	F S	F S	F S	F S	F S	S
	INIA1C5									F S

As shown by the red-highlighted cells, Perez observed 26 pairs of antibodies that "compete[d]" when measured by one assay (either flow cytometry or SPR) but not the other. Robinson Decl. ¶¶ 92-94 (using the 50% competition threshold described in Perez to classify competitive vs. non-competitive antibodies). Moreover, Perez found that the results of one assay may diametrically oppose the results of the other. Robinson Decl. ¶ 95. Indeed, for one pair of antibodies Perez observed 0% inhibition using flow cytometry and 100% inhibition using SPR. *Id.* Immunex's own reference therefore shows that SPR and flow cytometry can **lead to different results**—even though both assays are intended to measure "compet[ition]" between antibodies.

Having admitted that Perez discloses the types of "competition assays" a skilled artisan would use to evaluate the scope of the '487 Patent, having stated that "competition was identified successfully using [Perez's] methods," and having admitted that it is a "fact" that "[Perez] discloses two methods for assessing competition which give different results," Immunex cannot now avoid Perez's ultimate conclusion that different competition assays yield different results. SUF ¶¶ 47-49; *see Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1374 (Fed. Cir. 2005) ("This blatant admission by this same defendant before the EPO clearly supports this court's holding that those skilled in the art would construe the claims of the '777 patent to encompass razors with more than three blades."). Accordingly, the

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undisputed record shows "the existence of multiple methods leading to different results without guidance in the patent or the prosecution history as to which method should be used," rendering the '487 Patent indefinite. *Dow*, 803 F.3d at 634.[7]

This conclusion is corroborated by experiments Defendants' expert, Dr. William H. Robinson, performed to assess competition between one of Regeneron's anti-IL-4R antibodies, 16F3, and the '487 Patent's 12B5 "reference antibody." Dr. Robinson's experiments replicated Perez's teachings and confirmed that the assay design was outcome determinative. SUF ¶¶ 55-58; Robinson Decl. ¶¶ 98-111. Using Perez's flow cytometry assay, Dr. Robinson measured **99% inhibition**. Robinson Decl. ¶¶ 98-108. In contrast, using Perez's SPR assay, Dr. Robinson measured **0% inhibition for these same antibodies**. *Id*. In other words, Dr. Robinson found that whether 16F3 competes with 12B5 depends on which assay is used, thus confirming Perez with respect to IL-4R antibodies.

Dr. Robinson's conclusion that "compet[ition]" is a nebulous concept is confirmed by Immunex's statements in the parallel *inter partes* review proceedings involving the '487 Patent. Before the PTAB, Immunex took the position that two assays described in two prior art patents (the GenPharm Patent and the Schering Patent) are "examples of competition assays" that could be used to assess "compet[ition]." Dkt. 153-9 at 32-33.[8] These prior art patents, however, demonstrate that a "compet[ition]" determination turns on numerous assay conditions. For example, the GenPharm Patent teaches that competition is affected by antibody **concentration**. Dkt 155-7 at 132:29-30; Ex. 3 at 185:5-23. The Schering Patent similarly teaches that competition is affected by **temperature**. Dkt. 155-4 at

[7] *See also Forest Labs., Inc. v. Teva Pharms. USA, Inc.*, No. 2016-2550, 2017 WL 6311688, at *5 (Fed. Cir. Dec. 11, 2017) ("[P]recedents . . . hold claims indefinite in particular circumstances where the claims require measured quantities (absolute or relative), different techniques for such measurements are known in the art and some produce infringing results and others not, the intrinsic evidence does not adequately specify the technique or techniques to use, and extrinsic evidence does not show that a relevant skilled artisan would know what technique . . . to use.").

[8] *See Aylus Networks, Inc. v. Apple Inc.*, 856 F.3d 1353, 1360 (Fed. Cir. 2017) ("[T]he prosecution disclaimer doctrine [extends] to IPR proceedings" before the PTAB).

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32:58-33:4; Ex. 3 at 188:24-189:24; Robinson Decl. ¶¶ 122-23. But the '487 Patent and its prosecution history provide no guidance as to what concentration or temperature a skilled artisan should utilize when measuring competition.

3. There Is No Genuine Dispute Between Experts That Precludes Summary Judgment

Immunex appears to argue that, notwithstanding the lack of guidance Immunex has provided in the '487 Patent, a skilled artisan can nonetheless determine which art-recognized technique is most appropriate to assess the '487 Patent's "competes" limitation. Immunex's expert, Dr. Michael J. Taussig, opines—without citation to any intrinsic or extrinsic evidence—that "a person of ordinary skill at the priority date would have understood how to set up each assay, perform routine optimisation of assay conditions, and interpret the results to reliably determine whether two antibodies compete with each other for binding to an antigen." Taussig Decl. ¶¶ 55, 87. Tellingly, however, Dr. Taussig never identifies (either in his declaration or in his seven plus-hour deposition testimony) all the different variables—which particular assay type, which particular assay conditions, and which particular threshold—a skilled artisan would select to determine whether an antibody satisfies the "competes" limitation.[9]

Moreover, Dr. Taussig's conclusory opinion that a skilled artisan could simply figure out the appropriate competition assay, conditions, and threshold runs counter to *Nautilus* and its progeny and flies in the face of the Immunex-sanctioned Perez reference. *Dow*, 803 F.3d at 635 (holding immaterial "that someone skilled in the art could determine which method was the most appropriate") (citing *Teva*, 789 F.3d at 1338, 41). As the Federal Circuit has made clear, while "[b]efore *Nautilus*, a claim was not indefinite if someone skilled in the art could arrive at a method and practice

[9] Even if Dr. Taussig had identified all the particular variables, Dr. Taussig's unsupported, *post hoc* selections would still be insufficient to save Immunex's defective claims. *See, e.g.*, *Butamax™ Advanced Biofuels LLC v. Gevo, Inc.*, 117 F. Supp. 3d 632, 641-42 (D. Del. 2015) ("Based on the broad and ambiguous language of the specification, the court does not find commonsensible [patentee's expert's] conclusory assertion that a person of ordinary skill would be directed by the specification to use the [specific method of measurement].").

that method," "[u]nder *Nautilus* this is no longer sufficient." *Id.* at 634. Indeed, Dr. Taussig fails to identify anything in the intrinsic record that supports his opinion because, as he admits, "the patent doesn't teach competition assay parameters." SUF ¶ 36; Ex. 3 at 192:2-193:3. Accordingly, the Court should reject Dr. Taussig's unsubstantiated opinion, which is directly at odds with Immunex's position before the EPO and amounts to nothing more than a *post hoc* rationalization. *See, e.g.*, *Nautilus*, 134 S. Ct. at 2130 ("It cannot be sufficient that a court can ascribe *some* meaning to a patent's claims; the definiteness inquiry trains on the understanding of a skilled artisan at the time of the patent application, not that of a court viewing matters *post hoc*.").[10]

B. Claim 1 Should Be Construed Pursuant to § 112(6) and the '487 Patent's Failure to Recite a Corresponding Structure Renders the Claim Indefinite

Even if the term "competes" were not indefinite, Immunex's decision to write independent Claim 1 in functional language requires all of the asserted claims to be construed pursuant to 35 U.S.C. § 112(6). The validity of these claims thus turns on whether the specification adequately describes the claimed antibodies' actual structure. It does not, and Immunex's decision to overreach dooms its patent.

A patentee may express an element of a claim "as a means or step for performing a specified function . . . and such claim shall be construed to cover the corresponding structure . . . described in the specification and equivalents thereof." 35 U.S.C. § 112(6). Construing a § 112(6) term "is a two-step process. The court must first identify the claimed function. Then, the court must determine what structure, if any, disclosed in the specification corresponds to the claimed function." *Williamson v. Citrix Online, LLC*, 792 F.3d 1339, 1351 (Fed. Cir. 2015) (internal citations omitted). Such structure "must be clearly linked or associated with the claimed function." *Ergo*

[10] Dr. Taussig also argues that certain extrinsic evidence—Regeneron's '371 and '237 Patents—filed after the '487 Patent's claimed priority date, demonstrates that "Regeneron was aware of how to . . . determine [antibody competition]." Taussig Decl. ¶¶ 80, 87. Not so. "[T]he indefiniteness inquiry focuses upon whether the relevant ['487] patent record discloses **a single meaning** among multiple possibilities, not whether an unrelated patent contained such disclosures." *Otsuka Pharm. Co. v. Torrent Pharms. Ltd.*, 151 F. Supp. 3d 525, 545 n. 36 (D.N.J. 2015) (emphasis added).

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Licensing v. CareFusion 303, Inc., 673 F.3d 1361, 1363 (Fed. Cir. 2012). "The inquiry is whether one of skill in the art would understand the specification itself to disclose a structure, not simply whether that person would be capable of implementing a structure." *Biomedino, LLC v. Waters Techs. Corp.*, 490 F.3d 946, 953 (Fed. Cir. 2007). "Failure to specify the corresponding structure in the specification amounts to impermissible pure functional claiming." *Ergo*, 673 F.3d at 1363. "If the patentee fails to disclose adequate corresponding structure, the claim is indefinite." *Williamson*, 792 F.3d at 1352.

The term "isolated human antibody that competes with a reference antibody for binding to human IL-4 interleukin-4 [IL-4] receptor" should be construed pursuant to § 112(6). This is because the claimed "isolated human antibod[ies]" are defined only by their function. While it is true that there is a presumption that § 112(6) does not apply when a claim term lacks the word "means," the law is clear that a patentee may not avoid § 112(6) through artful claim drafting. Thus, the presumption against § 112(6) is overcome where the claim term "fails to recite sufficiently definite structure or else recites function without reciting sufficient structure for performing that function." *Williamson*, 792 F.3d at 1350 (internal quotations omitted).

Claim 1 falls within § 112(6) because "isolated human antibody" is insufficient structure for performing the claimed "compet[ing]" function. As the parties' experts agree, the term "antibody" is generic for a diverse group of molecules that may bind to a diverse group of targets. SUF ¶¶ 3, 5, 23-24; Ex. 3 at 85:16-86:1, 188:24-189:8; Robinson Decl. ¶¶ 174-76. Antibodies are defined by their amino acid sequence, which determines their structure and, ultimately, the target to which the antibodies bind. SUF ¶¶ 7, 16-22; Ex. 3 at 90:4-7 ("[P]roteins are made of amino acids, and . . . the sequence of the amino acids . . . determines the structure of a protein."); Robinson Decl. ¶¶ 175-76.

Rather than set forth a particular amino acid sequence for the claimed "isolated human antibod[ies]," the '487 Patent instead claims the antibodies only by what they

do: their "compet[ition] with a reference antibody for binding to human IL-4 interleukin-4 (IL-4) receptor." Ex. 1, claim 1. Thus, Immunex has plainly written a means-plus-function claim limitation. Claim 1 merely replaces "means" with this general purpose "isolated human antibody" and recites a function performed by the "isolated human antibody." Without describing the amino acid sequence, the claim language recites the biological equivalent of a black box computer. *See, e.g.*, *Aristocrat Techs. Austl. Pty Ltd. v. Int'l Game Tech.*, 521 F.3d 1328, 1333 (Fed. Cir. 2008) ("Because general purpose computers can be programmed to perform very different tasks in very different ways, simply disclosing a computer as the structure designated to perform a particular function does not limit the scope of the claim . . . as required by section 112 paragraph 6."); *Zeroclick LLC v. Apple, Inc.*, No. 15-cv-04417-JST, 2016 WL 5477115, at *4 (N.D. Cal. Aug. 16, 2016) (holding that a functionally-defined "program" was subject to § 112(6)).

It is undisputed that not all isolated human antibodies will bind to the IL-4 receptor, let alone "compete[] for binding" with the recited reference antibody. SUF ¶ 111; Robinson Decl. ¶ 176. Instead, only **particular** antibodies having **particular amino acid sequences** will perform this specialized function. Indeed, the parties agree that even a single amino acid change can alter an antibody's function. SUF ¶¶ 20-21. Because "isolated human antibody" does not convey the amino acid sequence(s)—*i.e.*, the structure(s)—that enable performance of the "compet[ition]" function, Claim 1 should be construed pursuant to § 112(6). *Williamson*, 792 F.3d at 1350.

The specification, however, **never describes** an antibody that would qualify as a claimed "isolated human antibody," nor does it give any indication of the structure of antibodies that "compete[]" with 12B5 (or any other "reference antibody"). SUF ¶¶ 25-31; Robinson Decl. ¶¶ 178-181. Instead, the specification states only that the invention encompasses "a MAb that competes with 12B5 for binding to a cell that expresses human IL-4R." Ex. 1 at 22:7-8. This conclusory description is not an adequate corresponding structure, and thus Claim 1 and all the claims that depend

from it are indefinite. *Blackboard, Inc. v. Desire2Learn Inc.*, 574 F.3d 1371, 1385 (Fed. Cir. 2009) ("That ordinarily skilled artisans could carry out the recited function in a variety of ways is precisely why claims written in 'means-plus-function' form must disclose the particular structure that is used to perform the recited function."); *Core Wireless Licensing S.A.R.L. v. Apple Inc.*, No. 15-cv-05008-PSG, 2016 WL 3124614, at *15 (N.D. Cal. June 3, 2016) (finding a claim reciting an "inserter" subject to § 112(6) where the patentee failed to disclose the structure, and noting that patentees "cannot rely on the knowledge of one skilled in the art to fill in the gaps").

C. Claims 8 and 9 Are Independently Indefinite Because the '487 Patent Fails to Define the Limitation "[B]inding [A]ffinity (K_a)"

While the indefiniteness of Claim 1 dooms the '487 Patent in its entirety, the limitation "binding affinity (K_a)," which appears in dependent Claims 8 and 9, renders these claims indefinite for a similar but independent reason. Like the "competes" limitation, the '487 Patent does not indicate how a skilled artisan should measure the "binding affinity (K_a)" of the claimed isolated human antibodies, nor does it specify the type of binding affinity assay, the assay conditions, or the type of IL-4R to be used in the assessment. Claims 8 and 9 are therefore indefinite.

1. The '487 Patent Fails to Teach Any Technique for Measuring Binding Affinity

The '487 Patent lacks any guidance as to how a skilled artisan should measure an antibody's "binding affinity (K_a)." Claims 8 and 9 require that the claimed "isolated human antibody binds to human IL-4 receptor with a binding affinity (K_a) of at least [1×10^8 or 1×10^9]," but offer no guidance as to how to measure whether an antibody possesses the requisite level of binding affinity. *See Teva*, 789 F.3d at 1341. The remainder of the '487 Patent—which includes only generic references to "binding affinity"—similarly fails to provide any guidance. The specification states, "In particular embodiments, antibodies raised against IL-4R have a binding affinity (K_a) for IL-4R of at least 1×10^8. In other embodiments, the antibodies exhibit a K_a of at

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least 1×10^{9} or at least 1×10^{10}." Ex. 1 at 26:42–45. The specification also states, "[i]n one embodiment, the antibody has a binding affinity for human IL-4R that is substantially equivalent to the binding affinity of 12B5 [or 6-2, 27A1, 5A1, 63 or 1B7] for human IL-4R." *Id.* at 21:22-24 (6-2), 22:10-13 (12B5), 23:2-5 (27A1), 23:50-53 (5A1), 24:31-34 (63), 25:12-14 (1B7). These references provide no guidance as to how a skilled artisan should measure an antibody's binding affinity (K_a) or which form of IL-4R should be used to determine whether the binding affinity meets the claimed thresholds of "1×10^{8}" or "1×10^{9}." Robinson Decl. ¶¶ 155, 162; *see Dow*, 803 F.3d at 634.

2. The Prior Art Teaches Different Methods for Assessing Binding Affinity Which Lead to Discordant Results

It is undisputed that the prior art "describe[s numerous] methods for measuring binding affinity" to IL-4R and that "the assay conditions used to measure affinity have some effect on the measured K_a." SUF ¶¶ 85-91, 101-103. Taussig Decl. ¶ 107; Ex 3 at 129:23-132:4; Robinson Decl. ¶¶ 147-154. It is also undisputed that Claims 8 and 9 require an assessment of binding affinity "to human IL-4 receptor," and that multiple forms of human IL-4R were known in the art and included within the scope of the claims. SUF ¶ 100; Ex. 1 at 12:10-15, 16:29-37; *see also* Ex. 3 at 194:4-196:5 (agreeing that IL-4R as defined in the '487 Patent encompasses the monomeric and dimeric forms of IL-4R). Thus, because the different assays, different conditions, and different forms of IL-4R used to measure binding affinity yield different, outcome-determinative results, Claims 8 and 9 are indefinite.

[redacted]

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[redacted]

Similarly, Regeneron's own research performed years before this litigation confirms that the type of IL-4R used to assess binding affinity drastically affects the results. Regeneron's '035 Publication includes results of binding affinity experiments performed by Regeneron scientists on Regeneron's own IL-4R antibodies, and these results demonstrate that the binding affinity (K_a) can change more than 200-fold—from less than 1×10^8 to more than 1×10^9—depending on whether the monomeric or dimeric form of IL-4R is used to perform the binding affinity assay.[11] SUF ¶¶ 93-99; Robinson Decl. ¶¶ 161-166; Dkt. 153-20 at Table 1 (showing a change in K_a from 2.9×10^7 to 7.2×10^9 for one IL-4R antibody (VAB1H1-2) and from 8.8×10^7 to 1.9×10^{10} for another IL-4R antibody (VAB10G8-19), when K_D is converted to K_a). Because Claims 8 and 9 require a binding affinity of at least 1×10^8 or 1×10^9, the form of IL-4R used to perform the binding affinity assay is outcome determinative.

Immunex appears to contend that because the term "binding affinity (K_a)" could be interpreted to mean "strength of the binding between the antibody and antigen, expressed in terms of the association constant K_a," it is not indefinite. Taussig Decl. ¶¶ 105-108. But after *Nautilus*, the fact that a skilled artisan could attribute **some** meaning to the term is legally irrelevant. *Dow*, 803 F.3d at 630 ("In *Nautilus*, the

[11] While an unrelated, later-filed patent cannot supply the disclosures missing from the patent-in-suit, *see Otsuka Pharm.*, 151 F. Supp. 3d at 545 n. 36, a later-filed patent can be evidence of failures as of the priority date. *See Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003) (turning to post-filing date reports to demonstrate failure on or before the filing date). Here, Regeneron's later-filed patent publication demonstrates that different methods known in the art as of the priority date failed to yield a single result.

Supreme Court expressly rejected the 'insolubly ambiguous' or 'amenable to construction' standard."). Under *Nautilus* and its progeny, because there are multiple different methods for assessing binding affinity (K_a) and the '487 Patent does not identify the method a skilled artisan should use, the scope of Claims 8 and 9 is not reasonably ascertainable by a skilled artisan and these claims are indefinite.

D. If, Notwithstanding the '487 Patent's Invalidity, the Court Wishes to Resolve the Parties' Claim Construction Disputes, the Court Should Endorse Defendants' Proposed Constructions

1. Claim 1 Should Be Limited to the Class of "[I]solated [H]uman [A]ntibod[ies]" That Are Disclosed in the Specification

Should the Court determine that Claim 1 is not invalid for indefiniteness, it should limit the term "isolated human antibody" to the six sets of sequences actually disclosed in the specification. As explained above, this limitation is subject to § 112(6) because it defines the claimed antibodies solely by their function. The only structures disclosed in the patent specification—albeit **not** as examples of the antibodies Immunex sought to claim—are the six partial amino acid sequences for antibodies called 6-2, 12B5, 27A1, 5A1, 63, and 1B7. Ex. 1 at 21:39-44 (6-2); 22:36-41 (12B5); 23:17-22 (27A1); 23:65-24:3 (5A1); 24:46-51 (63); 25:30-36 (1B7). The patent specification describes these antibodies as binding to IL-4R and as capable of inhibiting activity of both IL-4 and IL-13. *Id*. at 21:14-15.

These antibodies are the **only** structures disclosed in the specification. If the '487 Patent does disclose a corresponding structure to satisfy § 112(6), it must be one of these six structures, and the term "isolated human antibody" should be so limited. *See Toshiba Tec Corp. v. Katun Corp.*, No. 15-01979 SJO, 2016 WL 8861713, at *17 (C.D. Cal. Dec. 1, 2016) (Otero, J.) (finding "optical penetration member" subject to § 112(6), and limiting it to the cylindrical structure disclosed in the patent specification); *Broadcom Corp. v. Amazon.com Inc.*, No. 16-01774 JVS, 2017 WL 5151356, at *6 (C.D. Cal. Sept. 1, 2017) (finding "converter" subject to § 112(6), and limiting its construction based on the three disclosed algorithms).

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2. The Term "[H]uman" Should Be Construed as "Fully or Partially Human"

The term "human" is used consistently in both the claims and the specification of the '487 Patent to include "fully **or** partially human," as Defendants have proposed. Ex. 1 at 12:4-18:31, 19:41-44, 18:32-27:36, Claims (reciting an "isolated human antibody," "human IL-4 receptor," "human IL-4," and "human IL-13"); Robinson Decl. ¶¶ 167-170.

The specification expressly notes that Immunex's purported invention encompasses both fully human and partially human antibodies. Ex. 1 at 19:41-44 ("Procedures have been developed for generating human antibodies in non-human animals. The antibodies may be **partially** human, or preferably completely human."); 20:57-60 ("Antibodies of the invention include . . . **partially** human (preferably fully human) monoclonal antibodies . . . ."); 21:1-2 ("The desired antibodies are at **least partially** human, and preferably fully human."). In fact, one of the disclosed embodiments includes "chimeric antibodies, e.g., humanized versions of murine monoclonal antibodies." *Id.* at 19:21-22.

Similarly, the specification indicates that IL-4 receptor includes partially human forms of IL-4R, such as "soluble fragments, fusion proteins, oligomers, and other variants." Ex. 1 at 12:10-15. For example, the '487 Patent describes a heterodimer of IL-4R comprising a soluble **human** IL-4R and a soluble IL-13R, and refers to the IL-13R polypeptide disclosed in U.S. Patent No. 5,710,023 ("'023 Patent"). *Id.* at 17:41-53. The '023 Patent's IL-13R polypeptide, however, is **derived from a murine (*i.e.*, mouse) IL-13R chain**, and thus the resulting IL-4R heterodimer would be only **partially human**. *See* Ex. 4 at 1:4-8; 1:53-56; 4:4-10; Example 1.

Immunex's position during the prosecution of an application in the '487 Patent's priority chain, the '702 Application—which shares the specification of the '487 Patent—confirms that "human" encompasses more than "fully human." For example, Claim 1 of the '702 Application recited a "**fully human** control antibody."

Dkt. 153-13 at IMNX00008714. Immunex thus clearly appreciated the difference between "human" and "**fully human**."

Because the intrinsic evidence expressly describes human as both fully and partially human, Defendants' construction should be adopted. *See Oatey Co. v. IPS Corp.*, 514 F.3d 1271, 1276 (Fed. Cir. 2008) (refusing to adopt a construction that would exclude disclosed embodiments); *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1308 (Fed. Cir. 2007) (finding features described as part of the "present invention" determine the scope of invention).

In contrast, Immunex's proposed construction—which would have the Court construe "human" as "consistent with amino acid sequences produced by the human immune system"—should be rejected. Immunex's proposed construction is wordy, confusing, and unmoored to the intrinsic disclosure. Furthermore, the intrinsic record lacks any explanation, guidance, or methodology for determining whether an antibody's amino acid sequence is "consistent" with other amino acid sequences, nor is it clear what Immunex means by "consistent." Because Immunex's construction only serves to confuse, it should be rejected. *See Meds. Co. v. Mylan, Inc.*, 853 F.3d 1296, 1303 (Fed. Cir. 2017) (rejecting patentee's proposed construction because it "cannot provide 'reasonable certainty' regarding the scope of the asserted claims"). Defendants' construction, which mirrors the language of the specification, should instead be adopted.

IV. CONCLUSION

For the foregoing reasons, the Court should grant Defendants' motion for summary judgment and declare the claims of the '487 Patent invalid as indefinite. Alternatively, if the '487 Patent is not declared invalid, the Court should adopt Defendants' proposed constructions.

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Dated: January 25, 2018

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CERTIFICATE OF SERVICE

Pursuant to Rule 5-3 of the Local Civil Rules of the United States District Court for the Central District of California, I hereby certify under penalty of perjury under the laws of the United States of America that on January 25, 2018, a true copy of the above document was filed through the Court's Electronic Case Filing system and served by that system upon all counsel of record registered for the system and deemed to have consented to electronic service in the above-captioned case.

Dated: January 25, 2018

/s/ John F. Garvish, II
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