Paper No. 1

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.

***Inter Partes* Review No. IPR2017-01129**

Patent No. 8,679,487

PETITION FOR *INTER PARTES* REVIEW UNDER 35 U.S.C. § 312

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Petitioners' Exhibit List

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1003	Excerpts from the File History of U.S. Patent Application No. 14/175,943 ("'943 Application"), which is a continuation of U.S. Patent No. 8,679,487
1004	Declaration of Gerard Zurawski, Ph.D.
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1006	U.S. Patent Publication No. 2008/0160035 ("Stevens" or "'035 Publication")
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1008	U.S. Patent Application No. 09/847,816 ("'816 Application")
1009	PCT International Publication No. WO 96/33735 ("Kucherlapati")
1010	Zurawski et al., *The Primary Binding Subunit of the Human Interleukin-4 Receptor is Also a Component of the Interleukin-13 Receptor*, Journal of Biological Chemistry (June 9, 1995) ("Zurawski")
1011	Agosti et al., *Novel Therapeutic Approaches for Allergic Rhinitis*, 20 Immunology and Allergy Clinics of North America 2000, 401–423 ("Agosti")
1012	Declaration of William H. Robinson, Ph.D., M.D.
1013	*Curriculum Vitae* of William H. Robinson, Ph.D., M.D.

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1014	Hage et al., *Crystal Structure of the Interleukin-4/Receptor α Chain Complex Reveals a Mosaic Binding Interface*, 97 Cell 1999, 271–281 ("Hage")
1015	Whitty et al., *Interaction Affinity Between Cytokine Receptor Components on the Cell surface*, 95 Proc. Natl. Acad. Sci. USA, Oct. 1998, 13165–13170 ("Whitty")
1016	United States Patent Application Pub. No. 2002/0002132 ("Pluenneke" or "'132 Publication")
1017	Harlow & Lane, *Antibodies, A Laboratory Manual* (1988)
1018	Keegan, *Interleukin 4 Receptor, in Encyclopedia of Immunology* 1453 (Peter Delves and Ivan Roitt eds., 1998) ("Keegan")
1019	Tony et al., *Design of human interleukin-4 antagonists inhibiting interleukin-4-dependent and interleukin-13-dependent responses in T-cells and B-cells with high efficiency*, 225 Eur. J. Biochem. 1994, 659-665
1020	*L.A. Biomedical Research Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, 2017 U.S. App. LEXIS 3582 (Fed. Cir. Feb. 28, 2017)
1021	Borrebaeck, *Antibody Engineering*, Second Ed. (1995)
1022	Kussie et al., *A single engineered amino acid substitution changes antibody fine specificity*, J. Immunol. 1994, 152:146-152
1023	Winkler et al., *Changing the Antigen Binding Specificity by Single Point Mutations of an Anti-p24 (HIV-1) Antibody*, J. Immunol. 2000, 165:4505-4514
1024	Vasudevan et al., *A single amino acid change in the binding pocket alters specificity of an anti-integrin antibody AP7.4 as revealed by its crystal structure,* Blood Cells, Molecules, and Diseases 32, 2004, 176-181
1025	Zola, *Monoclonal Antibodies A Manual of Techniques*, CRC Press, 1987

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1026	Perez et al., *Epitope Mapping of 10 monoclonal antibodies against the pig analogue of human membrane cofactor protein (MCP)*, Immunology 1999, 96:663-670
1027	Alberts B. et al., *Molecular Biology of the Cell*, 4th ed. 2002, Garland Science, New York
1028	U.S. Patent Application No. 10/324,493 ("'493 Application")
1029	U.S. Patent No. 7,186,809 ("'809 Patent")
1030	U.S. Patent Application No. 11/588,696 ("'696 Application")
1031	U.S. Patent No. 7,465,450 ("'450 Patent")
1032	U.S. Patent Application No. 12/291,702 ("'702 Application")
1033	Cooper et al., *Role of heavy chain constant domains in antibody-antigen interaction. Apparent specificity differences among streptococcal IgG antibodies expressing identical variable domains*, J. Immunol. 1993, 150:2231-2242
1034	McLean et al., *Isotype Can Affect the Fine Specificity of an Antibody for a Polysaccharide Antigen*, J. Immunol. 2002, 169:1379-1386
1035	Walter et al., *Analysis of human antibody sequences in Antibody Engineering, A Practical Approach* (1996)
1036	Berman & Alt, *Human heavy chain variable region gene diversity, organization and expression*, International Review Immunology 1990, 5:203-214
1037	Alberts B. et al., *Molecular Biology of the Cell*, 3d ed. 1994, Garland Science, New York
1038	U.S. Patent No. 5,599,905 ("'905 Patent")
1039	U.S. Patent No. 9,587,026 ("'026 Patent")

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1040	Brüggemann et al., *Human Antibody Production in Transgenic Animals*, Arch. Immunol. Ther. Exp. 2015, 63:101–108
1041	Nicholson et al., *Antibody Repertoires of Four- and Five-Feature Translocus Mice Carrying Human Immonuglobulin Heavy Chain and κ and λ Light Chain Yeast Artificial Chromosomes*, J. Immunol. 1999, 163:6898-6906
1042	King D., *Applications and Engineering of Monoclonal Antibodies*, Chapter 1, (1998)
1043	Minton et al., *Microbiota: A 'natural' vaccine adjuvant*, Nature Reviews Immunology 2014, 14:650-651
1044	Lee et al., *Complete humanization of the mouse immunoglobulin loci enables efficient therapeutic antibody discovery*, Nature Biotechnology 2016, 32:356–363
1045	Lefranc, *Nomenclature of the Human Immunoglobulin Heavy (IGH) Genes*, Exp Clin Immunogenet 2001;18:100–116
1046	Lefranc, *Nomenclature of the Human Immunoglobulin Kappa (IGK) Genes*, Exp Clin Immunogenet 2001;18:161–174
1047	Lefranc, *Nomenclature of the Human Immunoglobulin Lambda (IGL) Genes*, Exp Clin Immunogenet 2001;18:242–254
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Pursuant to 35 U.S.C. § 312 and 37 C.F.R. § 42.100, Sanofi-Aventis U.S. LLC and Genzyme Corp. ("Sanofi"), and Regeneron Pharmaceuticals, Inc. ("Regeneron") (collectively, "Petitioners"), request *inter partes* review of U.S. Patent No. 8,679,487 (Ex. 1001), which issued March 25, 2014. As explained herein, there is a reasonable likelihood that Petitioners will prevail in establishing that the '487 Patent is unpatentable as anticipated.

I. INTRODUCTION

The '487 Patent is one member of an extended patent family sharing a specification that dates back to May 1, 2001. This original specification discloses six monoclonal antibodies ("MAbs") that interact with the human interleukin-4 ("IL-4") receptor ("IL-4R"). The initial patents in this family claimed the various MAbs disclosed in the specification. But toward the end of 2008, Patent Owner changed tactics. Rather than claiming the antibodies described in the original specification, Patent Owner began to file new continuing applications attempting to claim an expansive universe of antibodies by their functional relationship to a disclosed antibody—that is, attempting to claim any antibody that competes with one of the MAbs disclosed in the specification. Among the fundamental problems with this strategy is that Patent Owner did not invent this expansive universe of antibodies or describe them in the original specification. To the contrary, some of

these antibodies had already been independently developed by Petitioners, and disclosed in the "Stevens" application published earlier in 2008.

Beginning in 2008, *seven years* after filing its first application in the family, Patent Owner filed three applications attempting to broadly claim all IL-4R antibodies not by their sequence, but by their purported ability to compete with the MAbs disclosed in the specification. The first was abandoned early on. The third was properly found by the Examiner to lack written description support. As the Examiner explained, "[t]he specification"—the same as the original specification—"fails to disclose and there is no art-recognized correlation between the structure of the genus of yet to be discovered antibodies and the function of competing for binding to human IL-4 receptor with specific reference antibodies." Ex. 1003 at 0086-0087 (emphasis in original). This finding came shortly after the Federal Circuit clarified the law on written description of functional antibody claims in *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014). The second application—addressed by the same Examiner before the rules were clarified in *AbbVie*—slipped through the cracks, and issued as the '487 Patent. This attempt to ensnare antibodies that Patent Owner did not invent or describe in its original specification is inconsistent with the law and the PTO's application of the law post-*AbbVie*. The Board now has the opportunity to make things right.

The ’487 Patent lacks both written description and enablement support in the original specification. It is therefore not entitled to claim priority to any earlier application in its patent family. And without a claim of priority to any earlier application, the ’487 Patent is anticipated, and rendered wholly invalid, by the very Stevens application that its competing claims sought to cover.

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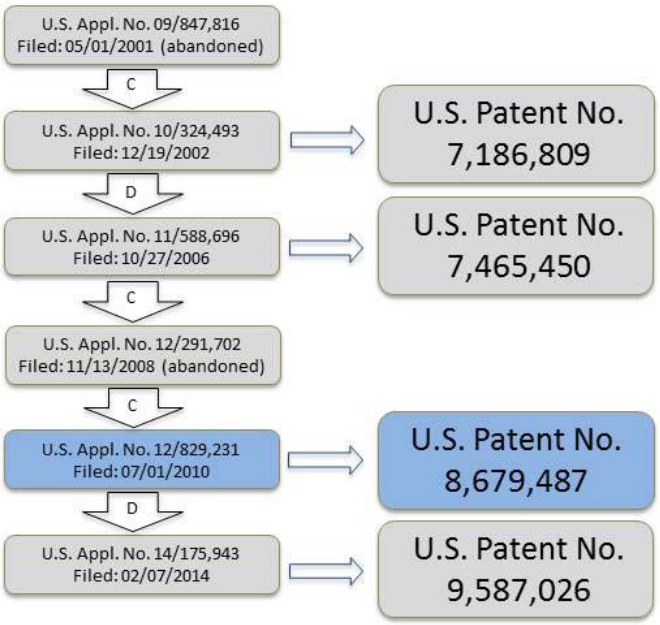
The ’487 Patent is titled “Anti-Interleukin-4 Receptor Antibodies.” It includes one independent claim and sixteen dependent claims directed to “isolated human antibod[ies] that compete[] with a reference antibody for binding to human [] interleukin-4 (IL-4) receptor.” Ex. 1001, Claim 1. The ’487 Patent issued from the ’231 Application, the fifth application in the family, filed July 1, 2010, and it claims a 2001 priority date through a series of continuation and divisional applications beginning with the ’816 Application, filed May 1, 2001. Ex. 1001, Cover. Patent Owner also filed subsequent continuing applications claiming the benefit of the ’816 Application, including the ’943 Application. Ex. 1003 at 0131-0212. These applications and issued patents are related as shown below:



Ex. 1012 ¶73. Each of these applications shares an original specification,[1] which fails to describe a single antibody that competes with a reference antibody for binding to human IL-4R ("hIL-4R"), as claimed in the '487 Patent. Ex. 1012 ¶94. The specification discloses only six antibodies and their corresponding variable region amino acid sequences—MAbs 12B5, 6-2, 27A1, 5A1, 63, and 1B7—but these antibodies are neither disclosed nor described to compete with any antibody, let alone a reference antibody as claimed in the '487 Patent. *Id.* ¶¶94-96; Ex. 1008

[1] The specifications for these applications are substantially the same as the specification for the '816 Application, referred to herein as the "original specification." The minor differences between these specifications (*e.g.*, the cross-references to related applications) do not impact the analyses herein.

at 0028:10-0034:21. Indeed, the specification is devoid of *any* examples showing antibody competition experiments. Ex. 1012 ¶64.

During prosecution of the earlier applications in the '487 Patent family, Patent Owner sought claims directed to the antibodies it developed and disclosed in its original specification. The first patent to issue—the '809 Patent—includes claims directed to MAb 12B5. Ex. 1029, Claim 1; Ex. 1012 ¶76. The claims generally cover combinations of antibodies and antibody derivatives comprising a light chain variable region sequence of SEQ ID NO:10 and/or heavy chain variable region sequence of SEQ ID NO:12, which correspond to MAb 12B5. The second patent to issue—the '450 Patent—also relates to MAb 12B5 and generally covers methods of treating septic arthritis with an antibody comprising the variable regions found in MAb 12B5. Ex. 1031, Claim 1; Ex. 1012 ¶77. The application for the '809 Patent, as originally filed, additionally claimed antibodies comprising light and/or heavy chain sequences corresponding to the five other disclosed MAbs. Ex. 1028, Claims 1-3, 7-17; Ex. 1012 ¶76.

Petitioners are pioneers in antibody discovery and development, and have also filed applications and been awarded patents directed to antibodies to hIL-4R. One such application—Petitioner Regeneron's Stevens application—published on July 3, 2008. Ex. 1006. Stevens is directed to high affinity antibodies to hIL-4R and includes claims to antibodies having specific heavy chain and light chain

variable sequences. *Id.*, Claims 3-13. Stevens also includes data demonstrating that at least certain of its antibodies compete for binding to IL-4R with Patent Owner's MAb 12B5 (referred to in Stevens as the "control antibody"), inhibit IL-4 binding to IL-4R, inhibit the biological effects of IL-4 and interleukin-13 ("IL-13") in cells, and have binding affinity constants higher than 1×10^{10}. *Id.*, Figs. 1A-1C, Claim 1, Examples 2-5, Tables 1, 3-5; Ex. 1004 ¶¶68, 91.

On November 13, 2008—four months after Petitioner's Stevens application published—Patent Owner filed the '702 Application, which sought to cover antibodies disclosed in Stevens. Ex. 1032. Not surprisingly, the amino acid sequences for Petitioner's antibodies disclosed in Stevens, which Petitioner invented using its own patented transgenic mice technology, are different from Patent Owner's 12B5 antibodies claimed in the '809 and '450 Patents. *Compare* Ex. 1006 *with* Ex. 1029 *and* Ex. 1031. As a result, Patent Owner's '702 Application sought to cover a genus of antibodies significantly broader than 12B5, using functional claims that mimic the disclosure in Stevens. For example, Stevens' Figures 1A-1C show that certain of Petitioner's antibodies compete with Patent Owner's 12B5 "control antibody" for binding to IL-4R. Ex. 1006. Mimicking this terminology, Patent Owner's '702 Application sought claims generally directed to all "isolated antibod[ies] that compete[] for binding to human IL-4 receptor with a fully human **control antibody** comprising the light chain

variable region sequence (SEQ ID NO:10) and the heavy chain variable region sequence (SEQ ID NO:12) of antibody 12B5." Ex. 1032, Claim 1 (emphasis added). Having defined the scope of the covered antibodies broadly to include all antibodies that compete with a 12B5 control antibody, Patent Owner further sought dependent claims that directly track the claims and disclosure in Stevens. For example, claims 4–7 were directed to IL-4 and IL-13 binding and signaling inhibition, and claim 10 was directed to antibodies having binding affinities of at least 1×10^{10}. Ex. 1032, Claims 4-7, 10.

Ultimately, Patent Owner abandoned the claims of the '702 Application. But before doing so, Patent Owner filed the '231 Application—which ultimately issued as the '487 Patent—continuing its strategy of pursing broad claims intended to cover antibodies beyond its own disclosed antibodies using language that tracks Stevens' disclosure. Ex. 1002 at 0180-0255. The '231 Application included claims similar to the '702 Application, including the claim that issued as independent Claim 1 of the '487 Patent. That claim seeks to cover all isolated human antibodies that compete with a reference antibody containing SEQ ID NOS: 10 and 12 (such as MAb 12B5) for binding to hIL-4R. Ex. 1001, Claim 1.

By seeking broad, functionally-defined claims covering antibodies that Patent Owner did not invent or describe, but that competitors invented, Patent Owner obtained claims that are anticipated by the prior art. Indeed, Stevens

anticipates the claims of the ’487 Patent. This is not surprising: the claims of the ’487 Patent use terminology mimicking the disclosure in Stevens. In doing so, however, Patent Owner obtained claims that do not have 35 U.S.C. § 120 support in earlier applications, including the ’816 Application. Ex. 1012 ¶¶90-92. Specifically, the claims of the ’487 Patent lack 35 U.S.C. § 112 written description support because the ’816 Application does not describe a single antibody that competes with any other antibody, including MAb 12B5. Nor does the ’816 Application identify any particular structure that an antibody must possess in order to compete with a reference antibody. Ex. 1012 ¶¶93-120. The claims of the ’487 Patent also lack Section 112 enablement support in the ’816 Application because the full scope of Patent Owner’s functionally-defined claims cannot be practiced without undue experimentation. Ex. 1012 ¶¶121-152. One of skill in the art would be required to make an enormous number of candidate antibodies and test each of those candidate antibodies for competition against the reference antibodies, to see whether they fall within the ’487 Patent claims. This is an extraordinarily time consuming process that may still not yield the entire scope of claimed antibodies, even after many years of experimentation. Ex. 1012 ¶¶142-148. Accordingly, the ’816 Application fails to adequately describe and enable the claims, and the ’487 Patent is not entitled to Section 120 priority from any earlier application in its patent family. Stevens, which published after the purported priority date of the

'487 Patent, but before the '231 Application was filed, is therefore prior art and renders the '487 Patent's broad functional claims unpatentable as anticipated. Ex. 1004 ¶¶68-107.

II. MANDATORY NOTICES

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

Sanofi-Aventis U.S. LLC, Genzyme Corp. and Regeneron Pharmaceuticals, Inc. are the real parties-in-interest.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

On March 20, 2017, Petitioners filed a complaint against Amgen Inc. and Immunex Corporation in the United States District Court for the District of Massachusetts, Case No. 17-cv-10465, seeking a declaration that Petitioners' development, manufacturing, sale, promotion and related activities for their product Dupixent® (dupilumab) do not directly or indirectly infringe the '487 Patent.

C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

Lead counsel: John B. Campbell (Reg. No. 54,665) of McKool Smith P.C.

Back-up counsel: Mike McKool (*pro hac vice* pending) and John F. Garvish (*pro hac vice* pending), of McKool Smith P.C.

D. Service Information (37 C.F.R. § 42.8(b)(4))

Email: RS-IPR@McKoolSmith.com

Post: John B. Campbell, McKool Smith P.C., 300 W. 6th Street, Suite 1700, Austin, Texas 78701

Telephone: (512) 692-8700

Fax: (512) 692-8744

Petitioners consent to electronic service.

III. GROUNDS FOR STANDING

Petitioners certify that the '487 Patent is available for *inter partes* review, and that Petitioners are not barred or estopped from requesting an *inter partes* review challenging the claims on the grounds identified in this Petition. The '487 Patent has not been subject to a previous estoppel-based proceeding of the AIA.

IV. STATEMENT OF PRECISE RELIEF REQUESTED FOR EACH CLAIM CHALLENGED

A. Claims for Which Review Is Requested (37 C.F.R. § 42.104(b)(1))

Petitioners request the review and cancellation of claims 1–17 (the "Challenged Claims") of the '487 Patent.

B. Statutory Grounds of Challenge (37 C.F.R. § 42.104(b)(2))

The Challenged Claims should be canceled for the following reason:

Ground 1: Claims 1–17 are unpatentable under 35 U.S.C. §§ 102(a) and 102(b) based on Stevens (Ex. 1006). Stevens was published July 3, 2008 and is prior art under §§ 102(a) and 102(b) because, as explained *infra*, the application

that matured into the '487 Patent was filed July 1, 2010 and is not entitled to earlier priority under 35 U.S.C. § 120.

V. FIELD OF TECHNOLOGY

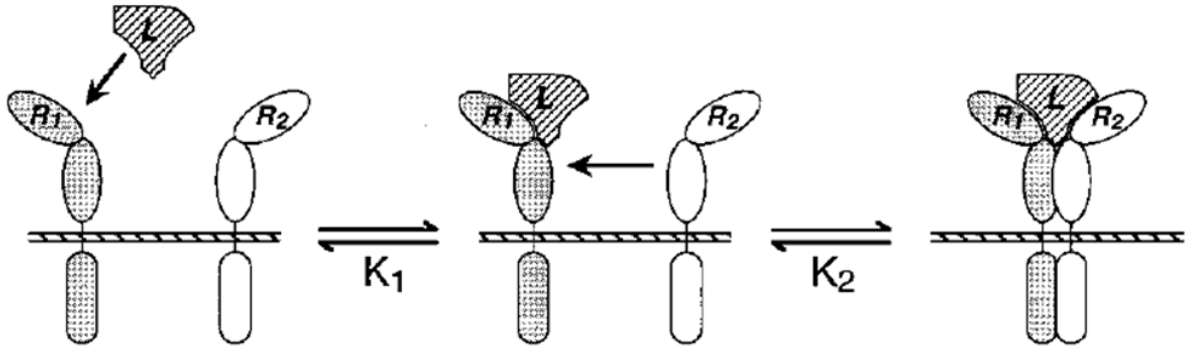
The '487 Patent is directed to antibodies that block hIL-4R and accordingly inhibit IL-4 and IL-13 induced signaling. Ex. 1001 at 0001(Title, Abstract), 0016(18:32)-0017(19:5).

A. IL-4 and IL-13

IL-4 and IL-13 are small signaling proteins (called cytokines) that regulate the adaptive immune system. Ex. 1004 ¶¶26-28. Before May 1, 2001, IL-4 and IL-13 were understood to play a pivotal role in the development of several hyperactive allergic disorders (*e.g.*, eczema, hay fever, and some types of asthma). *Id.* In particular, it was known that IL-4 induced signaling mediates a wide variety of immunogenic responses, which ultimately culminate in the body releasing cytotoxic chemicals that cause many of the symptoms associated with allergies (*e.g.*, inflammation, flushing). Ex. 1004 ¶¶26-28; Ex. 1011 at 405-409; Ex. 1007 at 2:1-14. It was also known that IL-13 mediates many of the same immunogenic responses as IL-4. Ex. 1004 ¶27.

Prior to May 1, 2001, skilled artisans discovered that IL-4 and IL-13 induce overlapping physiological effects because they share a common receptor subunit, termed IL-4 receptor alpha ("IL-4Rα"). Ex. 1004 ¶28; Ex. 1010 at 13869. As

illustrated below, IL-4 signaling through IL-4R occurs in a two-step process. First, IL-4 ("L") binds to IL-4Rα ("R_1") to form an IL-4/IL-4Rα complex. Second, the IL-4/IL-4Rα complex associates with one of two other subunits ("R_2") to form a ternary (three-member) signaling complex. Ex. 1004 ¶30.



Ex. 1015 at 13166. The two potential subunits with which the IL-4/IL-4Rα complex may associate are called common gamma chain ("γc") and IL-13 receptor alpha 1 ("IL-13Rα1"). Ex. 1004 ¶¶29-32. When the IL-4/IL-4Rα complex associates with the γc subunit, it is termed a "Type 1" receptor complex, and when it associates with the IL-13Rα1 subunit, it is termed a "Type 2" receptor complex. Ex. 1004 ¶¶29-32.

IL-13 induced signaling utilizes the same receptor subunits that comprise the Type 2 receptor, but the interaction begins with IL-13Rα1. Ex. 1004 ¶¶31-32; Ex. 1014 at 271. First, IL-13 binds to IL-13Rα1. Second, the IL-13/IL-13Rα1 complex associates with IL-4Rα to form a ternary signaling complex. Ex. 1004

¶32. The binding site between IL-4Rα and the IL-13/IL-13Rα1 complex coincides with the binding site between IL-4Rα and IL-4 ("IL-4Rα's active site"). Ex. 1004 ¶¶28-32; Ex. 1014 at 279.

Because IL-4Rα's active site is integral to IL-4 and IL-13 induced signaling, skilled artisans understood that a therapeutic agent that blocks IL-4Rα's active site would simultaneously inhibit both IL-4 and IL-13 induced signaling. Ex. 1004 ¶33; Ex. 1011 at 412; Ex. 1014 at 279. Accordingly, IL-4Rα's active site became a target for therapeutics directed toward mitigating the effects of hyperactive allergic disorders well before May 1, 2001. Ex. 1004 ¶33; Ex. 1011 at 410-412; Ex. 1007 at 2:19-23. In particular, monoclonal antibodies that block the active site of IL-4Rα ("anti-hIL-4R blocking antibodies") were known as "especially interesting" therapeutics because "[s]uch agents may be expected to inhibit the signaling induced by the binding of both IL-4 and IL-13 because of shared receptor subunits [*i.e.*, IL-4Rα]." Ex. 1011 at 412; Ex. 1007 at 2:19-20; Ex. 1004 ¶33.

B. Monoclonal Antibodies

Many prior art anti-hIL-4R blocking antibodies were derived from mice. *E.g.*, Ex. 1007; Ex. 1004 ¶37. It was widely understood in the prior art that the first step for isolating anti-hIL-4R antibodies from mice is to isolate the extracellular domain of hIL-4Rα for use as the target antigen—a molecule that causes the immune system to produce antibodies against it. Ex. 1007 at 6:56-57 (teaching

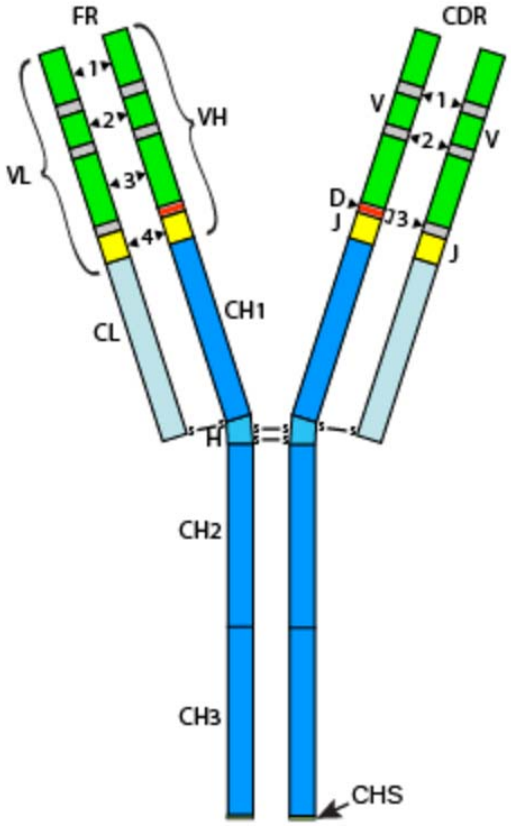
using as the antigen the "the extracellular domain of the human 130 kDa IL-4R," which is hIL-4Rα). Subsequently, the mice are immunized with hIL-4Rα once every few weeks until significant evidence of anti-hIL-4R antibody production is detected. Ex. 1007 at 4:9-41, 7:40-54. Next, the mice are sacrificed and the B-cells in their spleens (which produce antibodies) are harvested. Ex. 1007 at 4:9-11. The harvested B-cells are fused to cancerous B-cells, called myelomas, to form immortal B-cells, called hybridomas. Ex. 1007 at 3:57-4:14; Ex. 1004 ¶39.

Because each hybridoma expresses antibodies with identical structure, the hybridomas can be isolated and allowed to proliferate *in vitro* such that each isolated culture produces many copies of the same antibody—called monoclonal antibodies (MAbs). Ex. 1012 ¶¶40, 143-144. Subsequently, the MAbs can be screened by the appropriate functional assays for desirable features (*e.g.*, blocking IL-4R). Ex. 1012 ¶¶43, 61; Ex. 1007 at 4:14-21, Examples 2-4, 7. Each of these steps was described in the prior art.

As shown in the figure below,[2] antibodies are generally understood as "Y-shaped proteins." Ex. 1004 ¶34; Ex. 1012 ¶¶29-32. They are composed of two identical heavy chains and two identical light chains, which are bound together by disulfide bonds. Ex. 1004 ¶34. These chains are further subdivided into variable

[2] http://www.imgt.org/IMGTeducation/Tutorials/index.php?article=IGandBcells&chapter=Properties&lang=UK&nbr=3.

regions (VH, VL) and constant regions (CH1-CH3, CL). Ex. 1004 ¶34. An antibody's binding characteristics (*e.g.*, specificity and affinity) are primarily determined by the sequence of amino acids within its variable regions, while the constant regions mediate how the immune system responds to an antibody/antigen complex and whether the antibody forms a polymer. Ex. 1012 ¶33; Ex. 1004 ¶36. The variable region for each heavy and light chain is subdivided into four framework regions (FRs) and three complementarity determining regions (CDRs). Ex. 1004 ¶35. The CDRs fold together to form the antibody's antigen binding site. Ex. 1004 ¶35; Ex. 1012 ¶¶34-35. The specific part of an antigen to which the antibody binds is called the epitope. Ex. 1004 ¶35; Ex. 1012 ¶ 36.



C. Isolating Human Antibodies

Although "human" and "murine" (mouse) antibodies are composed of the same 20 amino acid building blocks, the amino acid sequences that compose an antibody correlate to the DNA of the host species from which the antibody was derived. Ex. 1004 ¶38. Thus, the sequence of amino acids in a "human" antibody can differ from a "murine" antibody, and the human immune system is capable of identifying and targeting characteristically murine antibodies as foreign invaders (*e.g.*, as it would for a pathogen). Ex. 1004 ¶38. Accordingly, humans who have been systemically injected with fully murine antibodies often develop an undesirable human anti-mouse antibody ("HAMA") reaction. Ex. 1004 ¶38. To mitigate the risk of an HAMA reaction, by May 1, 2001, skilled artisans had devoted considerable research toward developing techniques for making antibodies with characteristically human amino acid sequences. *E.g.*, Ex. 1004 ¶38; Ex. 1007; Ex. 1009.

One such prior art technique for making human antibodies, described in the '487 Patent's original specification, involves use of transgenic mice. Ex. 1008 at 0057(Abstract) ("Particular antibodies provided herein include human monoclonal antibodies generated by procedures involving immunization of transgenic mice."), 0027:3-4 ("Examples of techniques for production and use of [] transgenic animals are described in U.S. Patents 5,814,318, 5,569,825, and 5,545,806 . . . ."); Ex. 1012

¶¶39-45. Transgenic mice are mice that have been genetically modified with foreign (*e.g.*, human) genes to express, for example, human antibodies instead of murine antibodies when exposed to a foreign antigen (such as hIL-4Rα). *See* Ex. 1008 at 0026:31-35; Ex. 1012 ¶42. Human antibodies generated using transgenic mice are expected to "have utilities similar to those ascribable to nonhuman antibodies directed against the same antigen." Ex. 1009 at 13:29-32.

To make human antibodies to IL-4R using this technique, a transgenic mouse is "immuniz[ed] . . . with an IL-4R polypeptide" so that "antibodies directed against the IL-4R polypeptide are generated in said [mouse]." Ex. 1008 at 0026:27-29. The antibodies are then isolated "by conventional procedures, e.g., by immortalizing spleen cells harvested from the transgenic [mouse] after completion of the immunization schedule" and fusing the spleen cells "with myeloma cells to produce hybridomas, by conventional procedures." Ex. 1008 at 0027:14-23; Ex. 1012 ¶¶60-61. The hybridomas in turn produce human IL-4R monoclonal antibodies, which can be "purified by conventional techniques." Ex. 1008 at 0027:23-24. The hybridomas may be screened to "identify[] a hybridoma cell line that produces a monoclonal antibody that binds an IL-4R polypeptide." Ex. 1008 at 0027:18-21. These "[h]ybridomas or MAbs may be further screened to identify MAbs with particular properties, such as the ability to block an IL-4-induced activity, and to block an IL-13-induced activity." Ex. 1008 at 0027:24-26.

D. Competition Assays

After antibodies have been isolated, they may be further tested to determine their characteristics. One type of test that may be performed is a competition assay to determine whether the antibodies compete with other antibodies for binding to an antigen. Ex. 1012 ¶46.

Determining whether two antibodies compete for binding to an antigen is not a black and white inquiry. At a conceptual level, one antibody can be said to compete with a second antibody for binding to an antigen if the antibodies bind to a similar place on the antigen (*e.g.*, on overlapping epitopes). Ex. 1012 ¶46. In practice, however, a determination of whether two antibodies compete depends on the experimental protocol with which one measures competition. Ex. 1004 ¶46; Ex. 1012 ¶¶47-55. The prior art demonstrates that for a pair of antibodies, the results of one competition assay (*e.g.*, Surface Plasmon Resonance ("SPR")) may signify competition, while the results of another assay (*e.g.*, Flow Cytometry) may not. *See* Ex. 1026 at 667-69; Ex. 1004 ¶46; Ex. 1012 ¶¶54-55.

VI. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art ("POSITA") relevant to the '487 Patent and the earlier applications in its family would have had at least a Ph.D. or an M.D., with research experience in immunology, biochemistry, cell biology, molecular biology, or a related field or at least 2-3 years of professional experience

in one or more of those fields. Furthermore, a POSITA would have had an understanding of how one generates antibodies to a chosen antigen from animals (*e.g.*, mice), and how one isolates human antibodies by generating human antibodies directly from transgenic animals or transforming animal antibodies into human antibodies. *See* Ex. 1004 ¶21; Ex. 1012 ¶26.

For purposes of this Petition, the 35 U.S.C. § 120 priority analysis is performed from the perspective of a POSITA as of the '487 Patent's claimed May 1, 2001 priority date,[3] and the 35 U.S.C. § 102 anticipation analysis is performed from the perspective of a POSITA as of the '487 Patent's July 1, 2010 actual filing date. Ex. 1012 ¶¶25-28; Ex. 1004 ¶¶20-21.

VII. THE '487 PATENT

A. Admitted Prior Art and Alleged Improvement

Patent Owner admits that anti-hIL-4R blocking antibodies were readily isolatable by skilled artisans before May 1, 2001. Ex. 1008 at 0026:6-7. ("Antibodies specific for IL-4 or IL-4R may be prepared by well known procedures."). Patent Owner also admits that human anti-hIL-4R blocking

[3] The priority analysis would be the same even if the '487 Patent claimed priority as late as November 13, 2008 and the analysis considered a POSITA as of that date. Ex. 1012 ¶¶25-28.

antibodies could be isolated from transgenic animals by "conventional procedures." Ex. 1008 at 0027:3-17.

Using the "conventional" methods for generating and isolating human anti-hIL-4R blocking antibodies from transgenic mice, Patent Owner obtained the amino acid sequences for the heavy and light chain variable regions of six human anti-hIL-4R blocking antibodies: MAbs 6-2, 12B5, 27A1, 5A1, 63, and 1B7 (the "Six MAbs"). Ex. 1008 at 0028:10-0034:21.[4] However, the '487 Patent does not claim the sequence of any of the Six MAbs or their derivatives—earlier patents in the family claimed them. *Compare* Ex. 1001 *with* Ex. 1029 *and* Ex. 1031. The '487 Patent represents a radical extension beyond its original specification. Claim 1, the only independent claim, claims a generic "antibody" on purely functional terms: "[a]n isolated human antibody that competes with a reference antibody for binding to human IL-4 [] receptor." Ex. 1001. It further recites that the reference antibody—not the claimed antibody—"comprises" SEQ ID NOS: 10 and 12, which are the variable light and heavy chain amino acid sequences for MAb 12B5. *Id.* Notwithstanding that the claims hinge on antibody competition, the concept of competition between two antibodies is not sufficiently described in the original specification. *See* Ex. 1008 at 0028:10-0034:21; Ex. 1012 ¶¶63-64.

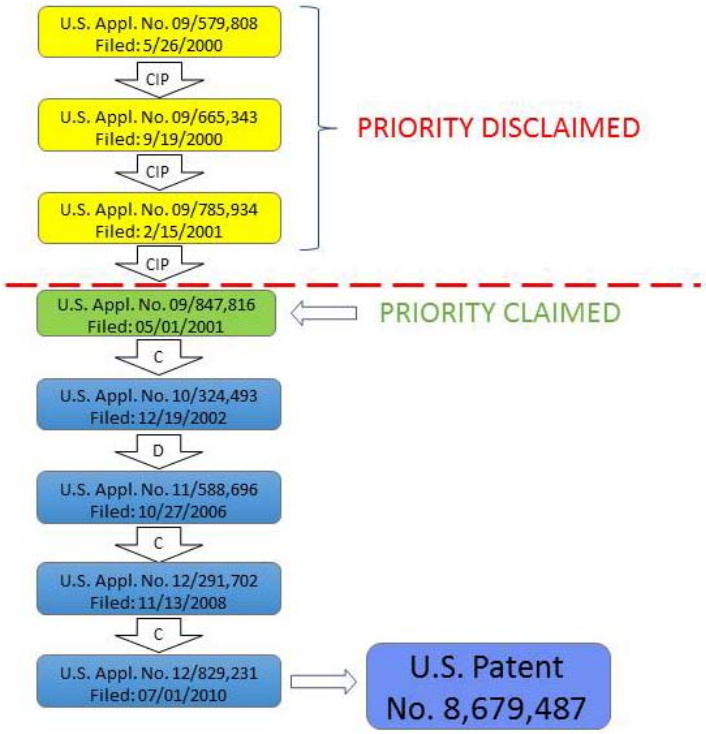
[4] The encoding nucleotides and amino acid sequences for the Six MAbs are disclosed in SEQ ID NOS: 5-26. Ex. 1008 at 0051:13-30, 0053:11-0055:11.

The dependent claims do not meaningfully limit Claim 1. Ex. 1001; Ex. 1012 ¶¶65-72. Claims 2–10 recite functional limitations linked with the "compet[ing]" function recited in Claim 1 (cross-blocking the reference antibody, inhibiting IL-4 and IL-13, and tightly binding to IL-4R). Claims 11–15 are directed to types of antibodies (full-length antibodies, isotypes, antibody fragments, fusion proteins, and single chain antibodies) which were "conventional" in the prior art. Ex. 1001 at 0015(15:39-62), 0017(19:13-20), 0018(22:29-31), 0020(26:12-28). Claims 16–17 are directed to combining the claimed antibody with a pharmaceutically acceptable solvent or "kit."

B. Prosecution History of the '487 Patent

Patent Owner filed the '231 Application on July 1, 2010. The '231 Application originally named Richard J. Armitage, Jose Carlos Escobar, Arvia E. Morris, and John D. Pluenneke as inventors. Ex. 1002 at 0164. On September 20, 2010, Patent Owner submitted declarations supporting the deletion of John D. Pluenneke as a named inventor. Ex. 1002 at 0144-0150. Patent Owner also expressly disclaimed priority to the three earliest applications in the family chain

(shown below),[5] and asserted that priority of the '231 Application was claimed only to the May 1, 2001 filing date of the '816 Application. Ex. 1002 at 0145.



Although the functionally claimed genus of antibodies "that compete[]" is not described in the original specification, it was the central distinguishing factor that Patent Owner relied upon to overcome prior art asserted by the Examiner during prosecution. The Examiner first rejected the claims as anticipated by U.S. Patent No. 5,717,072 ("Mosley"), which teaches "an isolated human antibody that

[5] The disclaimed US. Applications are Nos. 09/579,808, filed May 26, 2000, 09/665,343, filed September 19, 2000, and 09/785,934, filed February 15, 2001. Ex. 1002 at 0145.

binds to human IL-4 receptor . . . and inhibits IL-4 mediated activities." Ex. 1002 at 0119-0120. Although Patent Owner acknowledged that Mosley provides a "method for generating . . . anti-human IL-4 receptor antibodies," Patent Owner argued that the Examiner "only *assumes* that 'the antibody' of Mosley . . . competes for binding against the antibodies in the rejected claims" and that the Examiner's "assertion must be proved in order to support the rejection." Ex. 1002 at 0101 (emphasis in original).

In a series of subsequent rejections and responses, Patent Owner repeatedly argued that the Examiner had to *prove* that a prior art antibody competes with the '487 Patent's reference antibody to maintain the rejection. *See* Ex. 1002 at 0075-0076 (requesting "documentary evidence" that Mosley's antibodies compete because "it cannot be concluded that an antibody made according to Mosley would *necessarily* compete for binding with the reference antibody of the rejected claims") (emphasis in original), 0061 ("If it is a fact that any two antibodies that bind to the same 207 amino acid polypeptide [*i.e.*, extracellular portion of IL-4Rα] must *necessarily* compete for binding to the polypeptide, then let the evidence show it.") (emphasis in original), 0040. Ultimately, unable to produce evidence that prior art antibodies compete with the '487 Patent's reference antibody, the Examiner relented and issued a notice of allowance and the '487 Patent issued on March 25, 2014. Ex. 1002 at 0001, 0021.

C. Claim Construction

In an *inter partes* review, a claim is given its "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b). Petitioners therefore request that the claim terms be given their broadest reasonable interpretation (BRI), as understood by a POSITA and consistent with the specification.[6]

1. "human" (Claim 1)

The BRI of "human" is "partially or fully human." As the Federal Circuit has explained, "[w]hen a patent thus describes the features of the 'present invention' as a whole, this description limits the scope of the invention." *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1308 (Fed. Cir. 2007). Like the patent in *Verizon*, the '487 Patent explains that "[a]ntibodies of **the invention include**, but are not limited to, **partially human** (preferably fully human) monoclonal antibodies that inhibit a biological activity of IL-4 and also inhibit a biological activity of IL-13." Ex. 1001 at 0017(20:57-60) (emphasis added). And the specification consistently describes "human antibodies" as including partially human antibodies. *See* Ex. 1001 at 0017(19:41-44) ("Procedures

[6] District courts apply different standards of proof and claim interpretation. Any construction or application (implicit or explicit) of the claims in this Petition is specific to the BRI standard.

have been developed for generating **human antibodies** in non human animals. The antibodies may be **partially human**, or preferably completely human.") (emphasis added), 0018(21:1-2). Because the '487 Patent defines the "[a]ntibodies of the invention" to include partially human antibodies, the BRI of "human" is partially or fully human.

Petitioners anticipate that Patent Owner will assert that the term "human" means "fully human" (or the like). Construing "human" in a way that excludes partially human antibodies would be inappropriate not only because it is contrary to Patent Owner's express definition of its "invention," but also because it would exclude disclosed embodiments. The '487 Patent explains that "**embodiments include** chimeric antibodies, e.g., humanized versions of murine monoclonal antibodies." Ex. 1001 at 0017(19:21-22) (emphasis added). "Chimeric antibodies" are partially human antibodies. Ex. 1004 ¶67. As noted by this Board, and well established in the case law, "a general principle of claim construction counsels against interpreting claim terms in a way that excludes embodiments disclosed in the specification." *Nissan N. Am., Inc. v. Norman IP Holdings, LLC*, IPR2014-00564, Paper 36 at 7 (PTAB Aug. 26, 2015) (citing *Oatey Co. v. IPS Corp.*, 514 F.3d 1271, 1276-77 (Fed. Cir. 2008)). Accordingly, any argument that "human" means "fully human" (or the like) should be rejected.

D. The Challenged Claims Are Not Entitled to Priority Earlier Than July 1, 2010.

Patent Owner claimed that priority for the '487 Patent "begins with" the '816 Application, filed May 1, 2001. Ex. 1002 at 0145. However, the '487 Patent is not entitled to a May 1, 2001 priority date because the '816 Application fails to provide adequate written description and enablement support for the Challenged Claims, as required by 35 U.S.C. § 120. At best, the '487 Patent is entitled to a priority date of July 1, 2010—the actual filing date of the application that issued as the '487 Patent. Ex. 1012 ¶¶90-92; Ex. 1001, Cover. Stevens, which published July 3, 2008, is therefore prior art to the '487 Patent under at least 35 U.S.C. §§ 102(a) and 102(b), and anticipates the Challenged Claims.

Determining whether the '487 Patent is entitled to its claimed priority date is an appropriate inquiry for the Board. *See, e.g.*, *Rackspace US, Inc. v. PersonalWeb Technologies, LLC*, IPR2014-00058, Paper 10 at 13-21 (PTAB Apr. 15, 2014) (instituting IPR after determining that intervening "printed publication that was published before the actual filing date of the application that issued as the [challenged] patent" was prior art, because the challenged patent was not entitled to claim § 120 priority to the earliest filed application in a chain of continuations and divisions); *Daiichi Sankyo Co. v. Alethia Biotherapeutics, Inc.*, IPR2015-00291, Paper 75 at 6-20 (PTAB Jun. 14, 2016) (finding claimed genus of antibodies with desired functional properties was not entitled to priority to parent

application); *Samsung Elecs. Co. v. Affinity Labs of Texas, LLC*, IPR2014-01181, Paper 16 at 49 (PTAB Jan. 28, 2016) ("In analogous reexamination proceedings—which are likewise limited to grounds of unpatentability based on prior art patents and publications—the Federal Circuit has determined that a priority analysis is not only permissible but a 'critical legal tool.'") (quoting *In re NTP, Inc.*, 654 F.3d 1268, 1277 (Fed. Cir. 2011)).

"[A] patent's claims are not entitled to an earlier priority date merely because the patentee claims priority. Rather, for a patent's claims to be entitled to an earlier priority date, the patentee must demonstrate that the claims meet the requirements of 35 U.S.C. § 120." *In re NTP*, 654 F.3d at 1276. Section 120 requires, among other things, that the claimed invention be disclosed in the parent application in the manner provided by 35 U.S.C. § 112, first paragraph. 35 U.S.C. § 120. Thus, the parent application must satisfy Section 112's written description and enablement requirements for the claimed invention, and failure to satisfy either requirement destroys priority. 35 U.S.C. § 112; *Hyatt v. Boone*, 146 F.3d 1348, 1352 (Fed. Cir. 1998) ("The earlier application must contain a written description of the subject matter of the [invention], and must meet the enablement requirement" to confer priority).

Because the '816 Application does not adequately describe or enable the Challenged Claims of the '487 Patent, the Challenged Claims are not entitled to the

benefit of priority to the '816 Application or other earlier applications in the '487 Patent family chain: *i.e.*, the '702 Application (filed November 13, 2008), the '696 Application (filed October 27, 2006), and the '493 Application (filed December 19, 2002). Ex. 1028; Ex. 1030; Ex. 1032. These continuation and divisional applications share the original specification of the '816 Application and all similarly fail to adequately describe and enable the Challenged Claims for the same reasons—which apply when viewed from the perspective of a POSITA as of any possibly relevant filing date. *See In re NTP*, 654 F.3d at 1277 ("[I]f the later filed application claims priority through the heredity of a chain of applications, each application in the chain must satisfy § 112."); Ex. 1012 ¶¶25-27.

Accordingly, the Challenged Claims are entitled to a priority date no earlier than July 1, 2010—the '487 Patent's actual filing date.

1. The Challenged Claims Cover an Overly Broad Genus of Functionally-Defined Antibodies.

Claim 1 of the '487 Patent, from which all other Challenged Claims depend, recites:

> An isolated human antibody that **competes with a reference antibody** for binding to human IL-4 interleukin-4 (IL-4) receptor, wherein the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:10 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:12.

Ex. 1001, Claim 1 (emphasis added). The Challenged Claims cover a genus of isolated human antibodies defined solely by their function of "compet[ing]" with a reference antibody "for binding to human IL-4 [] receptor." *Id.* The claimed genus is incredibly broad for several reasons. Ex. 1012 ¶¶101-102.

First, the Challenged Claims include untold numbers of potential "isolated human antibod[ies]" (claimed antibodies) because they do not limit the claimed antibody to any particular structure. Ex. 1012 ¶103. In fact, the claimed antibody is not tied or limited to any particular amino acid sequence. Ex. 1012 ¶¶63, 103. The claimed antibody also is not limited in length and can be a full-length antibody, fragment, fusion protein, or a single chain antibody. Ex. 1001, Claims 11, 13-15; Ex. 1012 ¶104. In addition, the claimed antibody is not limited to a particular light chain type (kappa, lambda) or heavy chain type (IgA, IgD, IgE, IgG, IgM), or a particular light chain family ($V_\kappa1$–$V_\kappa7$, $V_\lambda1$–$V_\lambda11$) or heavy chain family (V_H1–V_H7). Ex. 1001, Claim 12; Ex. 1012 ¶¶38, 105-108. The claimed antibody is also not limited to any particular CDR length or structure. Ex. 1012 ¶109. Thus, the claimed antibody could be comprised of virtually any amino acid sequence. Ex. 1012 ¶110. As of May 1, 2001, it was known that the total number of potential fully human, full-length antibodies of diverse amino acid sequences was at least 10^{12} antibodies—*i.e.*, trillions of antibodies—based on which sequences could theoretically result from somatic recombination. *Id.* And that number does not

account for partially human antibodies,[7] fragments, fusion proteins or single chain antibodies. Ex. 1012 ¶111. Critically, the Challenged Claims provide no structural limitations regarding the claimed antibodies, and thus no guidance regarding which of the 10^{12} to 10^{14} (or more) potential antibodies could fall within the scope of the claims. Ex. 1012 ¶110.

Second, the Challenged Claims include multiple reference antibodies with which the claimed antibodies could "compete[]."Ex. 1012 ¶112. The claims specify that the reference antibody's light chain comprises SEQ ID NO:10 and its heavy chain comprises SEQ ID NO:12. But the claims do not require that the specified amino acid sequences comprise the variable regions of the light and heavy chains. *Id.* However, even assuming that the specified sequences must comprise the variable regions, the claims do not limit the reference antibody to any particular isotype. Ex. 1012 ¶113.

Third, the Challenged Claims provide no limitation regarding the claimed antibodies' function of "compet[ing] with a reference antibody for binding to human IL-4 [] receptor." Ex. 1001, Claim 1; Ex. 1012 ¶114. The Challenged

[7] The written description and enablement analyses herein do not depend on the claims including partially human antibodies. Thus, even if "human" is construed to include only fully human antibodies (which it should not be), the Challenged Claims are not entitled to an earlier priority date.

Claims do not specify a method of testing competition (*e.g.*, a particular assay), any parameters of testing (*e.g.*, order, concentration), or degree of competition required (*e.g.*, 1%, 50%, 99.9%). Ex. 1012 ¶ 114. The Challenged Claims also do not specify a particular epitope of IL-4R to which the claimed antibodies must compete for binding. Ex. 1012 ¶136.

For at least these reasons, the Challenged Claims encompass an overly-broad genus of claimed antibodies, including antibodies that were not discovered as of May 2001 and others still yet to be discovered. Ex. 1012 ¶124.

2. The '816 Application Does Not Satisfy the Written Description Requirement for the Challenged Claims.

As outlined above, the Challenged Claims cover a broad genus of isolated human antibodies defined solely by their function of competing with a reference antibody for binding to hIL-4R. The '816 Application, however, fails to describe a single isolated human antibody species that falls within that genus, let alone common structural features that would allow a POSITA to visualize or recognize all covered species. Ex. 1012 ¶¶93, 120. Put another way, the Challenged Claims recite a desired result (competing with a reference antibody), but the '816 Application fails to describe the means for achieving that result. The '816 Application therefore fails to provide written description support for the Challenged Claims and, for this reason alone, the Challenged Claims cannot

benefit from priority to the '816 Application (or any other earlier application). Ex. 1012 ¶99.

a. The Law of Written Description.

The test for sufficient written description is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). "[T]he purpose of the written description requirement is to 'ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification.'" *Id*. at 1353-54 (quoting *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920 (Fed. Cir. 2004)). "[R]equiring a written description of the invention plays a vital role in curtailing claims . . . that have not been invented, and thus cannot be described." *Id.* at 1352.

A genus may only be claimed when the specification proves that the patentee "has truly invented the genus, *i.e.*, that [the patentee] has conceived and described sufficient representative species encompassing the breadth of the genus. Otherwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus." *AbbVie*, 759 F.3d at 1300. Thus, written description requires "a precise definition" of the claimed genus, "such as by

structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials." *Ariad*, 598 F.3d at 1350. This "precise definition" additionally "requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Id.*

Furthermore, "[w]hen a patent claims a genus using functional language to define a desired result, 'the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.'" *AbbVie*, 759 F.3d at 1299 (quoting *Ariad*, 598 F.3d at 1349). As the Federal Circuit recently acknowledged in addressing written description for patents claiming a genus of antibodies defined solely by their function, "[f]unctionally defined genus claims can be inherently vulnerable to . . . challenge for lack of written description support," *AbbVie*, 759 F.3d at 1301, because "the functional claim may simply claim a desired result . . . without describing species that achieve that result"—an impermissible "attempt to preempt the future before it has arrived." *Ariad*, 598 F.3d at 1349, 1353.

In *AbbVie*, the patents claimed a genus of fully human antibodies defined by their desired function of binding to human interleukin-12 ("IL-12"). *Id*. at 1299. The Federal Circuit found that substantial evidence supported the jury's verdict that the claimed genus lacked written description support, because the patents "only describe[d] one type of structurally similar anti-bodies [sic] and [] those antibodies [were] not representative of the full variety or scope of the genus." *Id.* at 1300. Although the specification disclosed over 300 antibodies and thus the number of described species was "high quantitatively, the described species [were] all of the similar type and d[id] not qualitatively represent other types of antibodies encompassed by the genus." *Id.* at 1291, 1300. In addition, the patents did "not describe any common structural features of the claimed antibodies." *Id.* at 1301. "The asserted claims attempt[ed] to claim every fully human IL-12 antibody that would achieve a desired result, *i.e.*, high binding affinity and neutralizing activity . . . whereas the patents d[id] not describe representative examples to support the full scope of the claims." *Id.*

b. The '816 Application Does Not Describe Sufficient Species or Common Structural Features for the Challenged Claims' Functionally-Defined Genus.

The Challenged Claims cover a genus of any isolated human antibody that "competes with" a reference antibody for binding to hIL-4R. The '816 Application

does not support these incredibly broad claims because it fails to describe a single species of antibody that falls within their scope.

The Challenged Claims require the claimed "isolated human antibody" to compete with a "reference antibody" comprising SEQ ID NOS: 10 and 12 in its light and heavy chains. The '816 Application discloses the partial sequence of one antibody that could qualify as a "reference antibody" within the scope of the Challenged Claims: MAb 12B5. Ex. 1012 ¶¶62, 93; Ex. 1008 at 0029:36-0030:3. The '816 Application teaches that for MAb 12B5, the amino acid sequence "encoding the variable region of the light chain . . . is presented in SEQ ID NO:10" and the amino acid sequence "encoding the variable region of the heavy chain . . . is presented in SEQ ID NO:12." Ex. 1008 at 0029:16-0030:13. The '816 Application also teaches that MAb 12B5's light chain CDRs 1-3 are "believed to correspond" respectively to amino acids 24-35, 51-57, and 90-99 of SEQ ID NO: 10, and its heavy chain CDRs 1-3 are "believed to correspond" respectively to amino acids 31-35, 50-65, and 98-104 of SEQ ID NO: 12. Ex. 1008 at 0053:37-0054:7. The '816 Application further teaches that "12B5 was determined to be an IgG1 antibody" and that "[a]ntibodies of other subclasses, such as IgG4 or IgM monoclonal antibodies, may be derived from 12B5." Ex. 1008 at 0053:31-36.

The '816 Application, however, fails to describe a single antibody that competes with a "reference antibody" or MAb 12B5. Ex. 1012 ¶93. That is, the

’816 Application fails to describe even one antibody species that falls within the claimed genus. While the ’816 Application discloses partial amino acid sequences for the Six MAbs (12B5, 6-2, 27A1, 5A1, 63 and 1B7), it never explains that any of those six antibodies “competes” with a “reference antibody” or MAb 12B5. Ex. 1012 ¶¶57, 94-98; Ex. 1008 at 0028:10-0034:21. Not only does the ’816 Application fail to state that any of the Six MAbs “competes” with a “reference antibody” or MAb 12B5, but it also fails to include any description of any assay performed on the Six MAbs to prove that they compete with a “reference antibody” or MAb 12B5. Ex. 1012 ¶¶64, 98. Simply put, a POSITA would not conclude from reading the ’816 Application that the Six MAbs “compete” with a “reference antibody.” Ex. 1012 ¶96.

In fact, the phrase “reference antibody” is found nowhere in the ’816 Application, while the word “competes” is used only six times, each time in the same *pro forma* sentence for each of the Six MAbs: “Particular monoclonal antibodies of the invention are selected from the group consisting of . . . a MAb that competes with [6-2/12B5/27A1/5A1/63/1B7] for binding to a cell that expresses human IL-4R . . . .” Ex. 1008 at 0028:22-23, 0029:18, 0030:16, 0031:7-8, 0031:38-39; Ex. 1012 ¶¶62, 95. The ’816 Application never describes how, or how to determine whether, an antibody “competes” with a “reference antibody.” Ex. 1012 ¶¶96-98.

At most, the '816 Application discloses that the Six MAbs are IL-4 and IL-13 antagonists, rather than antagonists of the reference antibody in the claims. Ex. 1012 ¶96. This is by no means the "precise definition" required to demonstrate to a POSITA that the inventors possessed a genus of antibodies that "compete[]" with a "reference antibody," such as MAb 12B5, for binding to IL-4R. *See Ariad*, 598 F.3d at 1350. Indeed, the Board has held that a priority application, like the '816 Application, lacks "adequate written description support for a genus of antibodies having the desired functional properties" where the application "fails to disclose any species of antibody that" possesses the desired function and "also fails to provide any specific structural or physical information so as to define a genus of antibodies having the desired" function. *Daiichi*, Paper 75 at 16-18.

The '816 Application's failure to state and prove that any specific antibody (including the Six MAbs) competes with a reference antibody is particularly devastating in light of Patent Owner's own argument. During prosecution, Patent Owner repeatedly argued that an antibody that binds to IL-4R does not necessarily compete with a reference antibody, and only testing would prove competition. Ex. 1002 at 0061 ("If it is a fact that any two antibodies that bind to the same [portion of hIL-4R] must *necessarily* compete for binding . . . then let the evidence show it.") (emphasis in original), 0040 (arguing that "it is legal error" and "a factual error as well" for the Examiner to assume that "antibodies that bind to the

same small target" (*i.e.*, hIL-4R) compete with each other, without testing them). However, the '816 Application fails to include any such proof, and thus—by Patent Owner's own admission—it fails to adequately describe the Challenged Claims.

To the extent Patent Owner argues that a POSITA would be able to perform experiments to determine that the Six MAbs compete with 12B5 for binding to IL-4R and thus fall within the scope of the claims, that is still insufficient to satisfy written description. *See L.A. Biomedical Research Inst. v. Eli Lilly & Co.*, 2017 U.S. App. LEXIS 3582, *15-18 (Fed. Cir. Feb. 28, 2017) (Ex. 1020) (finding claims lacked written description support in priority application that failed to disclose claim limitation, and rejecting patent owner's argument that limitation was supported because it could be determined by a POSITA). "It is not sufficient for purposes of [] written description . . . that the disclosure, when combined with knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). "[I]f the claimed invention does not appear in the specification . . . the claim . . . fails regardless whether one of skill in the art could make or use the claimed invention." *Ariad*, 598 F.3d at 1348.

Moreover, for the sake of argument, even if the '816 Application disclosed that the Six MAbs compete with 12B5 for binding to hIL-4R—and thus are within

the claims—the disclosure of the partial amino acid sequences for those six species would still not be enough to adequately describe the claimed genus. Ex. 1012 ¶¶100, 116-119. As in *AbbVie*, "[t]he asserted claims attempt to claim every [isolated human antibody] that would achieve a desired result"—here, competing with a reference antibody for binding to hIL-4R—"whereas the ['816 Application does] not describe representative examples to support the full scope of the claims." 759 F.3d at 1301.

Even if the Six MAbs are assumed to be within the scope of the claims, the '816 Application fails to adequately describe their binding characteristics. The '816 Application states generally that "[p]articular monoclonal antibodies of the invention are selected from the group consisting of [the Six MAbs]; a MAb that is cross-reactive with [the Six MAbs]; a MAb that binds to the same epitope as [the Six MAbs]; . . . [and an] antibody [that] has a binding affinity for human IL-4R that is substantially equivalent to the binding affinity of [the Six MAbs] for human IL-4R." Ex. 1008 at 0028:21-29, 0029:16-24, 0030:14-22, 0031:6-14, 0031:37-0032:6. However, the '816 Application fails to actually describe the Six MAbs' cross-reactivity, epitope, or binding affinity. Ex. 1012 ¶¶57-59, 95-96.

Additionally, the Six MAbs are not representative of the diversity of the claimed genus because they are all structurally similar. Ex. 1012 ¶¶116-119. The Six MAbs all have the same heavy chain family (V_H3), the same light chain type

(Kappa), one of two light chain families (V_K1 or V_K3), similar CDR lengths, and share 85-100% sequence similarity in the variable regions when compared to 12B5. Ex. 1012 ¶¶117-118.

	Six MAbs
Sequence Similarity (compared to MAb 12B5)	85-100%
CDR Length	Similar
V_H Family	V_H3
Light Chain Type	Kappa
V_L Family	V_K1 or V_K3

The Challenged Claims, however, provide no limitations on these structural characteristics, and thus include MAbs with different heavy chain families (*e.g.*, V_H1, V_H7), different light chain types (*e.g.*, Lambda), different light chain families (*e.g.*, V_K2, V_K4, V_K1–V_K11), different CDR lengths, and different sequence similarities (*e.g.*, less than 85%). Ex. 1012 ¶118. But the '816 Application does not describe any examples of antibodies having these different characteristics. Ex. 1012 ¶118. The '816 Application's disclosure of the Six MAbs therefore does not provide sufficient support for the broad universe of structurally diverse antibodies within the scope of the Challenged Claims. Ex. 1012 ¶119.

The Federal Circuit's *AbbVie* decision demonstrates the deficiencies in the '816 Application's disclosure. In *AbbVie*, the specification at issue disclosed 300 antibodies falling within the scope of the claims, which had 90% sequence

similarity in the variable regions, identical CDR lengths, same epitope binding site, same heavy chain family, and same light chain type. *AbbVie*, 759 F.3d at 1291, 1293, 1300. The Federal Circuit found that the disclosure of these structurally similar antibodies was insufficient to support the challenged claims, which also encompassed antibodies that "differ[ed] considerably" from the disclosed antibodies. *Id.* at 1300. As a proxy to demonstrate the breadth of the claims, the Federal Circuit compared disclosed antibodies J695 and Joe-9 to the accused product Stelara—which the parties agreed infringed and was included in the claimed genus—and found that Stelara had only 50% sequence similarity, different CDR length, different epitope binding site, different heavy chain family, and different light chain type. *Id.*

	Stelara	J695	Joe-9
Sequence Similarity	50%	90%	90%
CDR Length	Different	Identical	Identical
Epitope Binding Site	Side Binder	Bottom Binder	Bottom Binder
V_H Family	V_H5	V_H3	V_H3
Light Chain Type	Kappa	Lambda	Lambda

Id. at 1293. The Federal Circuit thus found that "the claimed genus covers structurally diverse antibodies," but the specifications at issue "only describe species of structurally similar antibodies" and therefore do not provide adequate written description for the claimed genus. *Id.* at 1300-1301.

In *AbbVie*, disclosure of 300 structurally similar IL-12 antibodies was insufficient to provide adequate written description for the claimed genus of structurally diverse IL-12 antibodies. Here, the '816 Application's disclosure of a mere 6 structurally similar IL-4R antibodies can hardly be sufficient to provide adequate written description for the Challenged Claims' genus of structurally diverse IL-4R antibodies. Ex. 1012 ¶¶116-119. The Challenged Claims are a prime example of "functional claim[s] [that] simply claim a desired result . . . without [the '816 Application] describing species that achieve that result." *Ariad*, 598 F.3d at 1349.

To the extent Patent Owner argues otherwise, the written description requirement cannot be satisfied merely because the Challenged Claims define the claimed antibodies by their desired characteristic of competing with a reference antibody for binding to hIL-4R. "It is undisputed that the structure of the antibody determines its antigen binding characteristic. In order to demonstrate that [Patent Owner] has invented what is claimed [in the Challenged Claims], [the '816 Application] must adequately describe representative antibodies to reflect the structural diversity of the claimed genus." *AbbVie*, 759 F.3d at 1301; Ex. 1012 ¶36 ("[A]n antibody's binding properties . . . are dependent on [its] amino acid sequence."). The '816 Application at best describes six structurally similar

antibodies, which are not representative of the structural diversity of the extremely broad genus of the Challenged Claims.

Because the '816 Application does not provide adequate written description for the Challenged Claims, the Challenged Claims are not entitled to the benefit of priority to the '816 Application. Nor are the Challenged Claims entitled to priority to other earlier applications, because those applications share the specification of the '816 Application, and their claims provide no further written description support. While the claims of the '702 Application recite "[a]n isolated antibody that competes for binding to human IL-4 receptor with a fully human control antibody comprising the light [and heavy] chain variable region sequence[s] . . . of antibody 12B5," Ex. 1032 at 69-72, that general language does not fill the disclosure gaps in the specification. But even if the Challenged Claims were entitled to the benefit of the '702 Application's November 13, 2008 filing date (which they are not), Stevens would still be prior art under § 102(a) because it was published on July 3, 2008.

c. The Examiner Agreed that Substantively Identical Claims in Patent Owner's Later Application Lacked Written Description Support.

The prosecution history of a later divisional application in the '487 Patent family—the '943 Application, which shares the original specification of the '816 Application—further supports these arguments. In an Office Action issued after the

Federal Circuit's *AbbVie* decision, the Examiner rejected "competes with a reference antibody" claims substantively identical to the Challenged Claims for failure to comply with the written description requirement. Ex. 1003. The Examiner's reasoning—and Patent Owner's subsequent cancellation of those claims—demonstrates that the '816 Application fails to provide written description support for the Challenged Claims. *See* Ex. 1012 ¶¶82-89.

The '943 Application originally included the following independent claim (the "'943 Claim"):

> 1. An isolated antibody that **competes with a reference antibody** for binding to human IL-4 receptor, wherein: [] the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:14 [or 18 or 22] and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:16 [or 20 or 24].

Ex. 1003 at 0201 (emphasis added). Like the Challenged Claims, the '943 Claim covers a broad genus of antibodies that "compete[] with a reference antibody for binding to human IL-4 receptor," wherein the reference antibody's light and heavy chains comprise specified amino acid sequences (*i.e.*, those of the variable regions of MAb 27A1, 5A1, or 63). *Id.* at 0171:26-0174:22.

On January 12, 2016, after the *AbbVie* decision issued on July 1, 2014, the same Examiner for the '487 Patent rejected the '943 Claim for failure to comply with the written description requirement. Ex. 1003 at 0090-0099. The Examiner

explained that the '943 Claim "encompass[es] a genus of antibodies that are described only by their function of competing with a reference for binding to a specific target. However, there is no identification of any particular sequence or structure of the antibody that must be conserved in order to provide the required function of competing with the recited antibodies for binding to the human IL-4 receptor." Ex. 1003 at 0095 (emphasis in original). The Examiner noted that the '943 Claim "encompass[es] antibodies that are yet to be discovered." *Id.* Indeed, the Examiner observed that—like the '816 Application—the '943 Application discloses the Six MAbs, but "does not disclose antibodies *that compete with the recited antibodies*." *Id.* (emphasis added). Even for the Six MAbs, the Examiner noted that the specification failed to teach to which epitopes those antibodies bind, or that they "compete for the same epitope." *Id.*

The Examiner further explained:

> To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. . . . The specification . . . fails to disclose and there is no art-recognized correlation between the structure of the genus of yet to be discovered antibodies and the function of competing for binding to human IL-4 receptor with specific reference antibodies. **In other words, the specification does not teach the structure which results in an antibody that competes with a reference antibody for binding to human IL-4 receptor.**

> Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Ex. 1003 at 0096-0097 (underlined emphasis in original, bolded emphasis added). Patent Owner was therefore "not in possession of the encompassed antibodies that compete with a reference antibody for binding to human IL-4 receptor . . . at the time of filing the current application." *Id.* at 0098 (emphasis in original).

Just as the Examiner concluded that Patent Owner was not in possession of the '943 Claim at the time of filing, Patent Owner was also not in possession of the Challenged Claims at the time of filing the '816 Application. This conclusion is bolstered by Patent Owner's subsequent cancellation of the '943 Claim. Ex. 1003 at 0070-0079 (noting that Examiner's written description rejection was "rendered moot by the instant amendments to the claims"). After the Examiner's rejection, Patent Owner abandoned its functional "antibody that competes" claims in favor of narrower claims limited to an antibody with specified variable region CDR sequences from MAb 27A1, 5A1 or 63. Ex. 1003 at 0073-0074(Claim 17). These claims are markedly narrower than the Challenged Claims and the rejected '943 Claim because they specify the structure of the claimed antibodies as opposed to function of the claimed antibodies or structure of reference antibodies. These claims ultimately issued in the '026 Patent on March 7, 2017. Ex. 1039, Claim 1.

3. The '816 Application Does Not Satisfy the Enablement Requirement for the Challenged Claims.

The '816 Application does not enable a POSITA to make and use the full scope of antibodies within the Challenged Claims' broad genus without undue experimentation. The '816 Application therefore fails to enable the Challenged Claims, and for this reason alone the Challenged Claims cannot benefit from priority to the '816 Application (or any other earlier application). Ex. 1012 ¶¶92, 121-152.

a. The Law of Enablement.

Written description and enablement are separate and distinct requirements. *Ariad*, 598 F.3d at 1351. To satisfy the enablement requirement, the specification must provide "such full, clear, concise, and exact terms as to enable any person skilled in the art" to make and use the claimed invention. 35 U.S.C. § 112 ¶ 1. "Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their *full scope* without undue experimentation." *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013) (emphasis added). While a specification may be enabling "even if a 'reasonable' amount of routine experimentation is required in order to practice a claimed invention . . . such experimentation must not be 'undue.'" *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999). In determining

whether experimentation would be undue, the following *Wands* factors may be considered:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors "are illustrative, not mandatory," and which factors are "relevant depends on the facts." *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

While the specification need not disclose "minor details" that are well known in the art, *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997), a patentee "cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification." *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010). "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." *Genentech*, 108 F.3d at 1366.

"A patentee who chooses broad claim language must make sure the broad claims are fully enabled." *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 999 (Fed. Cir. 2008). In other words, "[t]he scope of the claims must be less than or equal to

the scope of the enablement to ensure that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims." *Id.*

b. The '816 Application Fails to Enable a POSITA to Practice the Full Scope of the Broad Challenged Claims Without Undue Experimentation.

The '816 Application does not provide sufficient guidance for a POSITA to practice the full scope of the Challenged Claims without undue experimentation. Ex. 1012 ¶¶121-152. Rather, at the time of the '816 Application, a POSITA would have been required to engage in a labor-intensive, time-consuming, iterative, trial-and-error process to generate, screen and sequence hIL-4R antibodies, and then test each antibody for competition against a reference antibody to determine whether each antibody falls within the scope of the claims. The '816 Application "discloses only a starting point for further iterative research in an unpredictable . . . field," and thus fails to enable the Challenged Claims. *Wyeth*, 720 F.3d at 1386.

The '816 Application's teachings are not commensurate with the staggeringly broad scope of the Challenged Claims. The Challenged Claims include untold numbers of antibodies comprising virtually any amino acid sequence or structure, as well as multiple reference antibodies. The Challenged Claims also provide no limitation regarding the required functionality of competing with a reference antibody for binding to IL-4R. Ex. 1012 ¶¶123-127.

The '816 Application fails to provide enabling disclosure for these broad claims because practicing the full scope of claimed antibodies would require undue experimentation. Ex. 1012 ¶142. First, a POSITA would have to generate all of the potential antibodies that could fall within the scope of the claims. Ex. 1012 ¶143. This could be done following the prior art procedures described in the '816 Application: (1) generating soluble hIL-4R "using well known techniques," Ex. 1008 at 0024:29-0025:15; (2) serially immunizing transgenic animals (*e.g.*, mice) with soluble hIL-4R "by conventional procedures," which generally involves "boost[ing]" the animals "every 4 weeks [] with the IL-4R immunogen" for a total of "2 to 5 months," Ex. 1008 at 0049:28-33; (3) sacrificing the animals, harvesting their spleen cells and fusing the spleen cells with myeloma cells "by conventional procedures" to produce hybridomas, separating the individual hybridomas, and then allowing the hybridomas to proliferate to produce individual hybridoma colonies that produce antibodies, Ex. 1008 at 0027:18-21, 0049:34-0050:4; and (4) screening the individual hybridoma colonies to identify which produce antibodies that bind to IL-4R, Ex. 1008 at 0027:18-21; Ex. 1012 ¶143. This process alone could take between 3 to 14 months to complete for one round of hybridoma generation and screening, with each round expected to generate hundreds to thousands of diverse antibodies, only some of which will bind to IL-4R. Ex. 1012 ¶145.

Each individual hybridoma colony generally produces a set of identical antibodies (MAbs), and different hybridoma colonies generally produce different sets of MAbs. Ex. 1012 ¶144. A POSITA would therefore need to determine the amino acid sequence of an MAb from each hybridoma colony identified to produce MAbs that bind to IL-4R to track which potential claimed antibodies have been generated. Ex. 1012 ¶¶144. A POSITA would be required to repeat this generation, screening and sequencing process over and over to generate all potential claimed antibodies—for example, using different transgenic animals or different antibody generation methods—until the POSITA was satisfied that diverse antibodies were no longer being generated. Ex. 1012 ¶¶44-45, 145. The '816 Application, however, provides no guidance regarding when this process would be complete (if ever), because it provides no guidance regarding how many of the more than trillions of possible antibodies (as discussed in Section VII.D.1) could be generated from IL-4R, much less actually bind to IL-4R or compete with a reference antibody for binding to IL-4R. Ex. 1012 ¶110.

Nonetheless, for each of the unknown number of diverse antibodies generated through the above process and identified to bind to IL-4R, a POSITA would need to perform even further experimentation. That is, a POSITA would be required to perform a competition assay between each antibody and each MAb 12B5 reference antibody (*e.g.*, the IgG1, IgG4 and IgM 12B5 antibodies disclosed

in the ’816 Application), and analyze the results to determine whether there is competition and thus whether the identified antibody is in fact a claimed antibody within the scope of the Challenged Claims. Ex. 1012 ¶146. Performing all of these steps would be an extraordinarily time-consuming and labor-intensive multi-step process that, even after many years of experimentation, may not yield the entire genus of claimed antibodies. Ex. 1012 ¶¶142, 147. This is a clear case of undue experimentation.

The Federal Circuit has found that analogous experimentation is undue. In *Wyeth*, the claims also covered a genus of compounds that required certain functionality, but the specification disclosed only one claimed compound species. 720 F.3d at 1382. “The scope of the claims at issue [wa]s broad” and included “at least tens of thousands of candidates.” *Id.* at 1385. The Court found that practicing the full scope of the claims would require “a complicated and lengthy series of experiments” involving “synthesizing and screening *each* of at least tens of thousands of compounds.” *Id.* at 1385-86 (emphasis in original). The Court held that this “constitutes undue experimentation,” even though the specification described assays for screening the candidate compounds to determine whether they exhibited the required functionality, and even though the Court “accept[ed] as true” that using the disclosed assays was “routine[].” *Id.* at 1385. The Court also noted that the specification was “silent about how to structurally modify” the only

disclosed species, "let alone in a way that would preserve the recited" functionality. *Id.* The Court thus concluded that the claims were not enabled, because "practicing the full scope of the claims, measured at the time of filing, would require excessive experimentation." *Id.*

The '816 Application is even less enabling, and the Challenged Claims are far broader, than the specification and claims in *Wyeth*. *See* Ex. 1012 ¶¶149-151. While in *Wyeth* a POSITA knew that tens of thousands of compounds were potentially within the claimed genus, the '816 Application provides no guidance regarding the number of at least trillions of possible antibodies that are IL-4R antibodies potentially within the claimed genus. Ex. 1012 ¶151. Thus, to practice the full scope of the Challenged Claims, a POSITA would need to undertake "a complicated and lengthy series of experiments" involving "synthesizing and screening *each* of" an unknown number of candidate claimed antibodies. *Wyeth*, 720 F.3d at 1385-86 (emphasis in original). Even if this process were "routine[]," it would still constitute excessive and undue experimentation. *Id.* at 1385.[8]

Moreover, while the *Wyeth* specification disclosed one claimed compound with the required functionality, the '816 Application fails to describe even one

[8] While the experimentation required to make one or a few claimed antibodies may be routine, the experimentation required to practice the "full scope" of claimed antibodies—as required for enablement—is undue. *Wyeth*, 720 F.3d at 1384.

claimed antibody with the required functionality. And even if the '816 Application explained that the Six MAbs possessed the required functionality, it still fails to provide any "guidance or predictions about particular substitutions" of amino acids on these MAbs that would preserve the required functionality of competing with the Challenged Claims' reference antibody. *Wyeth*, 720 F.3d at 1386; Ex. 1012 ¶139. As the Federal Circuit has acknowledged, "[i]t is undisputed that the structure of [an] antibody determines its antigen binding characteristic[s]." *AbbVie*, 759 F.3d at 1301. Indeed, changing even a single amino acid on an antibody can alter its binding characteristics and its ability to compete with a reference antibody. Ex. 1012 ¶139.

In addition, while the *Wyeth* specification disclosed an assay for determining whether candidate compounds exhibited the required functionality, the '816 Application fails to describe any assay for determining whether candidate antibodies exhibit the required functionality of competing with a reference antibody. Ex. 1012 ¶140. While the '816 Application discloses certain assays (*e.g.*, an assay in Example 5 for "Assessing Blocking Activity" (CD23) and an assay in Example 7 for "Measuring Loss of Barrier Function"), it does not describe using any assays to determine competition between two antibodies. Ex. 1012 ¶140.

Although several competition assays were known in the prior art, a determination of whether two antibodies compete is highly dependent on the

experimental protocol used. The results of one competition assay may signify competition between two antibodies, while the results of another competition assay may signify no competition between those same two antibodies. Ex. 1012 ¶¶54-55, 141; Ex. 1004 ¶46; Ex. 1026 at 667-669. The '816 Application provides no guidance regarding which competition assay should be used or what threshold constitutes competition. Ex. 1012 ¶¶114, 140-141. Knowledge of prior art competition assays is therefore "not a substitute" for an enabling disclosure. *ALZA*, 603 F.3d at 941.

The Board has also found a priority application similar to the '816 Application to be non-enabling. In *Daiichi*, the Board found that practicing claims of anti-Siglec-15 "antibodies having [a] desired function . . . would have required excessive experimentation, even if routine," because a POSITA would have to "generate anti-Siglec-15 antibodies" and "engage in a complicated and lengthy screening process to practice the invention." Paper 75 at 14-15. And the priority application, like the '816 Application, "offer[ed] no credible guidance . . . that would have been useful for generating antibodies having the required functional properties." *Id.* at 15.

The *Wands* factors further support the conclusion that the '816 Application fails to enable the Challenged Claims. As demonstrated above, an excessive quantity of experimentation would be necessary to practice the full scope of the

Challenged Claims (factor 1), even though the state of the prior art was well-developed (factor 5) and the level of skill in the art was relatively high (factor 6); the '816 Application fails to provide any direction or guidance or describe any examples of a specific antibody within the scope of the claims (factors 2, 3); the '816 Application fails to provide any direction or guidance for determining whether a candidate antibody "competes" with a reference antibody (factor 2); the predictability of practicing the full scope of the claims based on the disclosure in the '816 Application is low (factor 7); and the claims are staggeringly broad (factor 8).[9] *See Wands*, 858 F.2d at 737; Ex. 1012 ¶¶121-152. Accordingly, the Challenged Claims are not entitled to the benefit of priority to the '816 Application.

[9] While the dependent Challenged Claims are arguably somewhat narrower than independent claim 1, they are still overbroad genus claims that require undue experimentation—in some cases even further experimentation. For example, determining the full scope of claims 6–7 and 8–10 would require a POSITA to further test each claimed antibody to determine, respectively, whether it inhibits human IL-4 and IL-13 signaling through hIL-4R and binds to hIL-4R with the recited binding affinity. Ex. 1012 ¶¶69, 148.

VIII. REASONS FOR THE RELIEF REQUESTED UNDER 37 C.F.R. §§ 42.22(A)(2) AND 42.104(B)(4)

A. Ground 1: The Challenged Claims Are Anticipated by Stevens

Petitioner's Stevens application is titled "High Affinity Human Antibodies to Human IL-4 Receptor" and was published on July 3, 2008. Ex. 1006. Stevens is prior art to the '487 Patent under 35 U.S.C. §§ 102(a) and 102(b) because, as set forth above, the Challenged Claims are entitled to priority no earlier than July 1, 2010. Stevens anticipates each of the Challenged Claims. *See* Ex. 1004 at 51-71.

Like the Challenged Claims, Stevens teaches "[a]n isolated human antibody or antibody fragment thereof which binds to human interleukin-4 receptor alpha (hIL-4Rα) with an affinity constant (K_D) of less than 200 pM." Ex. 1006, Abstract. Stevens teaches 23 isolated human antibodies that were selected for their ability to block IL-4 binding to IL-4R, inhibit IL-4 and IL-13 induced signal transduction, and tightly bind to IL-4R. Ex. 1006 ¶¶0006, 0032, 0063. Stevens further teaches that each of the 23 disclosed antibodies competes with MAb 12B5, the only potential reference antibody disclosed to be within the Challenged Claims. Ex. 1006, Fig. 1A, ¶0065; Ex. 1004 ¶68; Ex 1012 ¶62.

1. Claim 1: "An isolated human antibody that competes with a reference antibody for binding to human IL-4 interleukin-4 (IL-4) receptor, wherein the light chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:10 and the heavy chain of said reference antibody comprises the amino acid sequence of SEQ ID NO:12."

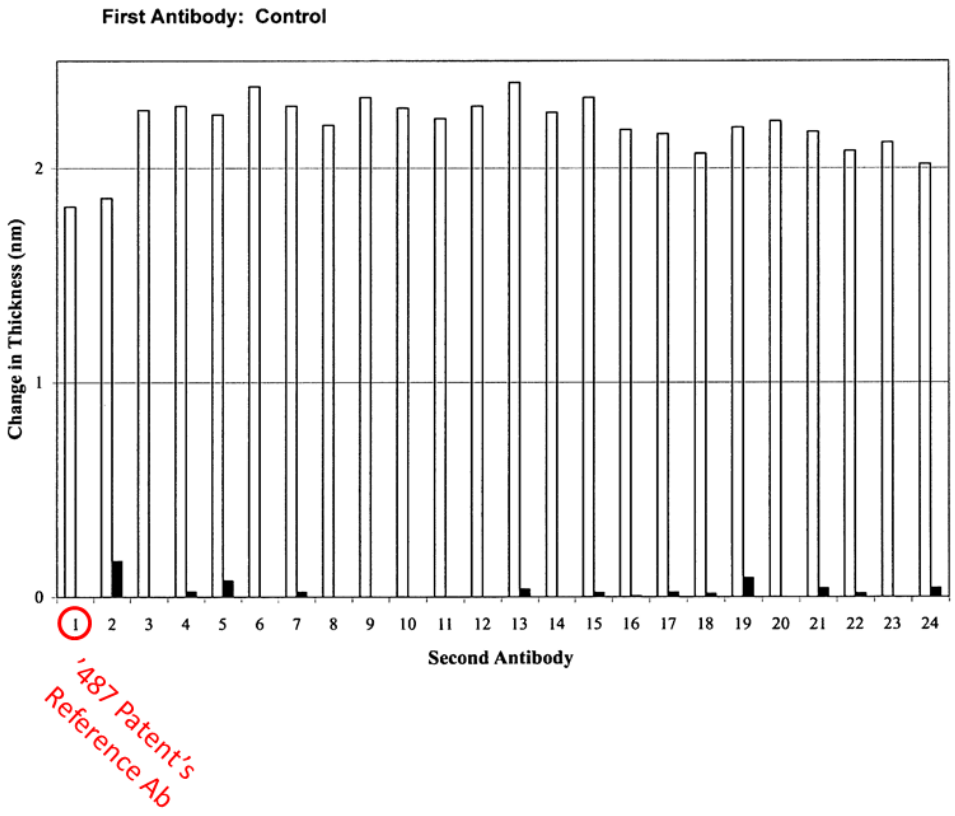
Stevens teaches isolated human antibodies that compete with MAb 12B5 (*i.e.*, an IgG1 reference antibody) for binding to hIL-4R. Ex. 1006 ¶¶0007, 0063-0065, Figs. 1A-1C; Ex. 1004 ¶¶70-75. In particular, Stevens discloses 23 isolated human antibodies that neutralize IL-4 and IL-13 activity by binding to hIL-4Rα. Ex. 1006, Abstract (teaching "[a]n isolated human antibody or antibody fragment thereof which binds to human interleukin-4 receptor alpha"), ¶0006. These anti-hIL-4R blocking antibodies were isolated from VelocImmune® mice, which is Petitioner's patented transgenic mouse technology by which one initially derives antibodies that contain fully human variable regions and mouse constant regions. Ex. 1006 ¶0046. Subsequently, "[t]he mouse constant regions are replaced with desired human constant regions to generate the fully human antibodies of the invention." Ex. 1006 ¶0052.[10]

Figures 1A–C disclose the results from a series of competition assays, including between Stevens' antibodies and a MAb that has the same heavy and

[10] Because Stevens teaches "fully human antibodies," Claim 1 is anticipated even if "human" is construed to include only fully human antibodies.

light chain sequences as MAb 12B5 from the '487 Patent (*i.e.*, with SEQ ID NOS:10 and 12). Ex. 1006 ¶0065; Ex. 1004 at 51. In the first series of assays (Figure 1A), hIL-4R was pre-incubated with MAb 12B5 and then exposed to one of 23 human anti-hIL-4R blocking antibodies that were isolated from VelocImmune® mice. Ex. 1006 ¶0074. Column number 1 on the x-axis of Figure 1A is MAb 12B5, while column numbers 2–24 designate each of Stevens' 23 isolated human antibodies. Ex. 1006 ¶0032.

Fig. 1A

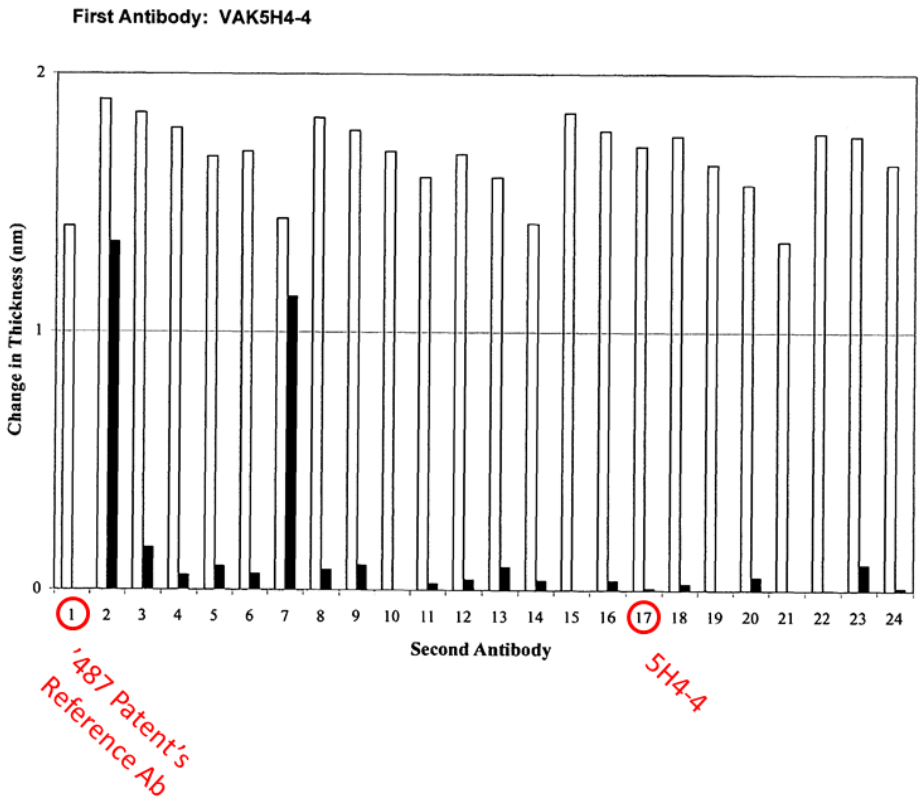


Ex. 1006, Fig. 1A. The first clear bar shows the level of binding of MAb 12B5 to hIL-4R, while the second, dark bar shows the level of binding from each of

Stevens' antibodies. Ex. 1006 ¶0074. As shown by the small-to-nonexistent black bars above each of numbers 2–24, MAb 12B5 blocks binding of every one of the 23 antibodies taught in Stevens. This demonstrates that MAb 12B5 competes with each of Stevens' antibodies. Ex. 1004 ¶73.

In addition, Stevens discloses a second series of competition assays that were conducted in the reverse order from that depicted in Figure 1A. Ex. 1006 ¶0074. For example, Figure 1C shows results of an analogous competition assay to Figure 1A, except that MAb 5H4-4 was used as the first, pre-incubated antibody, while MAb 12B5 and the other 22 antibodies disclosed in Stevens were added as the second antibody. Ex. 1006 ¶0032.

Fig. 1C



Ex. 1006, Fig. 1C. As shown in Figure 1C, there is no discernable black bar above MAb 12B5 (*i.e.*, column number 1), which shows that MAb 5H4-4 competes with MAb 12B5 for binding to hIL-4R. Ex. 1004 ¶74. Thus, the combination of Figures 1A and 1C of Stevens disclose that MAb 5H4-4 cross-competes with MAb 12B5. Stevens therefore anticipates Claim 1. Ex. 1004 ¶75.

2. Claim 2: "The isolated human antibody of claim 1, wherein when said reference antibody is bound to human IL-4 receptor, binding of said isolated antibody to said human IL-4 receptor is inhibited."

Figure 1A, above, discloses that each of the isolated human antibodies disclosed in Stevens is blocked from binding to hIL-4R by MAb 12B5. Ex. 1004 ¶¶76-77. Thus, Stevens anticipates Claim 2.

3. Claim 3: "The isolated human antibody of claim 1, wherein when said isolated human antibody is bound to human IL-4 receptor, binding of said reference antibody to said human IL-4 receptor is inhibited."

Figure 1C, above, discloses that MAb 5H4-4 blocks MAb 12B5 from binding to hIL-4R. Ex. 1004 ¶¶78-79. Thus, Stevens anticipates Claim 3.

4. Claim 4: "The isolated human antibody of claim 1, wherein said isolated human antibody inhibits the binding of human IL-4 to human IL-4 receptor."

Stevens teaches isolated human antibodies that compete with MAb 12B5 and also inhibit IL-4 from binding to IL-4R. Ex. 1006 ¶¶0006, 0066-0069. As shown in Table 3, for example, Stevens discloses that MAb 5H4-4 is a highly potent inhibitor of IL-4 binding (*i.e.*, 96% inhibition). Ex. 1004 ¶¶80-81.

TABLE 3

Antibody	% Inhibition (BIAcore ™)	IC_{50} (ELISA pM)
VX 4E7-9	79	118
VX 3F7-6	86	274
VAB 8G10-1	74	244
VAB 7B9-3	96	59
VAB 6C10-14	79	441
VAB 5C5-11	96	24
VAB 4D5-3	82	240
VAB 3B4-10	72	322
VAB 1H1-2	78	146
VAB 16G1-1	92	18
VAB 16F3-1	97	19
VAB 15C8-17	97	29
VAB 11G8-1	77	240
VAB 10G8-19	85	18
VAB 10C1-5	93	34
VAK 5H4-4	96	33
VAK 7G8-5	95	27
VAK 8G11-13	95	26
VAK 9C6-11	96	67
VAK 10G6-7	95	37
VAK 11D4-1	95	35
VAK 12B11-9	96	99
VAK 10G12-5	94	59

Ex. 1006, Table 3. Stevens teaches that each of its isolated human antibodies inhibits IL-4 binding to some degree. Thus, Stevens anticipates Claim 4.

5. Claim 5: "The isolated human antibody of claim 1, wherein said isolated human antibody inhibits the binding of human IL-13 interleukin-13 (IL-13) to human IL-4 receptor."

Stevens discloses isolated human antibodies that compete with MAb 12B5 and also inhibit formation of the ternary IL-13 signaling complex by "block[ing] hIL-13/hIL-13R1 complex binding to hIL-4R." Ex. 1006 ¶¶0029, 0073. Thus, Stevens teaches antibodies that inhibit the binding of human IL-13 to IL-4R—as recited in Claim 5—to the extent that any antibody can block IL-13 from binding to IL-4R. Thus, Stevens anticipates Claim 5. Ex. 1004 ¶¶49, 82-83.

6. Claim 6: "The isolated human antibody of claim 1, wherein said isolated human antibody inhibits human IL-4 signaling through human IL-4 receptor."

In addition to competing with MAb 12B5, Stevens' isolated human antibodies "are characterized by binding to hIL-4R with high affinity and by the ability to neutralize hIL-4R activity." Ex. 1006 ¶0006. Stevens provides experimental data to demonstrate that its isolated human antibodies inhibit IL-4 signaling through IL-4R. Ex. 1006 ¶¶0070-0072; Ex. 1004 ¶¶84-85. Thus, Stevens anticipates Claim 6.

7. Claim 7: "The isolated human antibody of claim 1, wherein said isolated human antibody inhibits human IL-13 signaling through human IL-4 receptor."

Stevens teaches antibodies that compete with MAb 12B5 and also inhibit IL-13 signaling through hIL-4R. Ex. 1006 ¶¶0006, 0029. Stevens provides experimental data to demonstrate that its isolated human antibodies inhibit IL-13 signaling through IL-4R. Ex. 1006 ¶0073; Ex. 1004 ¶¶86-87. Thus, Stevens anticipates Claim 7.

8. Claims 8–10: "The isolated human antibody of claim 1, wherein said isolated human antibody binds to human IL-4 receptor with a binding affinity (Ka) of at least [1×10^{8}/1×10^{9}/1×10^{10}]."

Stevens discloses several isolated human antibodies that compete with MAb 12B5 and exhibit a binding affinity constant in excess of 1×10^{10}. Ex. 1006 ¶¶0051, 0065, Table 1. For example, Table 1 of Stevens shows that MAb 5H4-4 has a

dissociation constant (K_d) of 0.02 nM for monomeric IL-4R and 4 pM for dimeric IL-4R. A POSITA would have known that these dissociation constants equate to association constants (K_a) of approximately 5×10^{10} for monomeric IL-4R and 2.5×10^{11} for dimeric IL-4R because dissociation and association constants are inversely related—*i.e.*, $K_a = 1/K_d$. Ex. 1004 ¶92. Because 1×10^{10} is the highest affinity threshold recited in Claims 8–10, and Stevens discloses antibodies with affinities in excess of 1×10^{10}, Stevens anticipates Claims 8–10. Ex. 1004 ¶¶88-92.

9. Claim 11: "The isolated human antibody of claim 1, wherein said isolated human antibody is a full-length antibody."

In addition to competing with MAb 12B5, Stevens teaches that the isolated human antibodies "can be full-length" antibodies. *See* Ex. 1006 ¶0006; Ex. 1004 ¶¶93-94. Stevens anticipates Claim 11.

10. Claim 12: "The isolated human antibody of claim 1, wherein said isolated human antibody is an IgA antibody, an IgD antibody, an IgE antibody, IgG antibody, an IgG1 antibody, an IgG2 antibody, an IgG3, antibody, an IgG4 antibody, or an IgM antibody."

Stevens teaches that in addition to competing with MAb 12B5, the isolated human antibody may be of any isotype, including, "for example, an IgG1 or IgG4 antibody." Ex. 1006 ¶¶0006, 0047-0049, 0052; Ex. 1004 ¶¶95-96. Stevens anticipates Claim 12.

11. Claim 13: "The isolated human antibody of claim 1, wherein said isolated human antibody is a fragment of an antibody."

In addition to competing with MAb 12B5, Stevens teaches isolated human antibodies that are fragments, "for example, a Fab, $F(ab')_2$ or scFv fragment." Ex. 1006 ¶¶0006, 0037; Ex. 1004 ¶¶97-98. Stevens anticipates Claim 13.

12. Claim 14: "The isolated human antibody of claim 1, wherein said isolated human antibody is a fusion protein."

Stevens teaches isolated human antibodies that compete with MAb 12B5 and are fusion proteins. For example, Stevens teaches that a full-length isolated human antibody could be made into a single chain antibody. Ex. 1006 ¶0006. A POSITA would understand that a single chain antibody is a type of fusion protein. Ex. 1004 ¶¶99-100; Ex. 1006 ¶0037 ("Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single contiguous chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv)."). Thus, Stevens anticipates Claim 14.

13. Claim 15: "The isolated human antibody of claim 1, wherein said isolated human antibody is a single chain antibody (scFv)."

As discussed under Claim 14 above, Stevens teaches isolated human antibodies that are single chain antibodies. Ex. 1004 ¶¶101-102. Thus, Stevens anticipates Claim 15.

14. Claim 16: "A composition comprising said isolated human antibody of claim 1 and a pharmaceutically acceptable diluent, buffer, or excipient."

Stevens teaches isolated human antibodies that compete with MAb 12B5 and are incorporated into a pharmaceutically acceptable solution. *See* Ex. 1006 ¶0056 ("Administration of therapeutic entities in accordance with the invention can be achieved with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like."); Ex. 1004 ¶¶103-104. Thus, Stevens anticipates Claim 16.

15. Claim 17: "A kit comprising said isolated human antibody of claim 1."

Stevens teaches several "kits" that incorporate one or more isolated human antibodies that compete with MAb 12B5. For example, Stevens teaches that the isolated human antibodies may be administered as a sterile preparation with a syringe, implant or inhaler. Ex. 1006 ¶0057 ("The therapeutic molecules of the invention may be administered to a patient in a manner appropriate to the indication, for example, parenterally, topically, or by inhalation. . . . Other

alternatives include eyedrops; oral preparations including pills, syrups, lozenges or chewing gum; and topical preparations such as lotions, gels, sprays, and ointments."). Any of the disclosed combinations (*e.g.*, isolated human antibodies plus a syringe, isolated human antibodies plus an inhaler) are kits. Ex. 1004 ¶¶105-107. Thus, Stevens anticipates Claim 17.

IX. CONCLUSION

For the foregoing reasons, Petitioners respectfully request institution.

Dated: March 23, 2017

Respectfully submitted,

/John B. Campbell/

John B. Campbell (Reg. No. 54,665)
MCKOOL SMITH P.C.
300 W. 6th Street, Suite 1700
Austin, Texas 78701
Telephone: (512) 692-8700
Facsimile: (512) 692-8744
Email: RS-IPR@McKoolSmith.com

Mike McKool (*pro hac vice* pending)
MCKOOL SMITH P.C.
300 Crescent Court, Suite 1500
Dallas, Texas 75201
Telephone: (214) 978-4000
Facsimile: (214) 978-4044
Email: RS-IPR@McKoolSmith.com

John F. Garvish (*pro hac vice* pending)
MCKOOL SMITH P.C.
300 W. 6th Street, Suite 1700
Austin, Texas 78701
Telephone: (512) 692-8700
Facsimile: (512) 692-8744
Email: RS-IPR@McKoolSmith.com

Counsel for Petitioners

CERTIFICATE OF COMPLIANCE WITH WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition for *Inter Partes* Review complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). According to the word count feature of the word-processing system used to prepare this Petition, the Petition contains 13,963 words, excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

Dated: March 23, 2017

/John B. Campbell/
(Reg. No. 54,665)

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e) and 37 C.F.R. § 42.105(a), the undersigned certifies that on March 23, 2017, a complete copy of this Petition for *Inter Partes* Review and all exhibits were served on Patent Owner at the correspondence addresses of record listed below by FedEx®:

Immunex Corporation
Law Department
1201 Amgen Court West
Seattle, WA 98119
Attn: Jae Cho

Amgen Inc.
Law – Patent Operations, M/S 28-2-C
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

/John B. Campbell/
(Reg. No. 54,665)