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. IPR2017-01884**

Patent 8,679,487

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

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Petitioners' Exhibit List

Exhibit	Description
1001	U.S. Patent No. 8,679,487 ("the '487 Patent")
1002	Excerpts from the File History of U.S. Patent No. 8,679,487
1003	Excerpts from the File History of U.S. Patent Application No. 14/175,943, which is a continuation of U.S. Patent No. 8,679,487
1005	*Curriculum Vitae* of Dr. Gerard Zurawski, Ph.D.
1006	U.S. Patent No. 7,605,237 ("Stevens")
1007	European Patent Application No. EP 0604693 ("Schering-Plough")
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, 270:13869–13878 ("Zurawski")
1011	Agosti, et al., *Novel Therapeutic Approaches for Allergic Rhinitis*, 20 Immunology and Allergy Clinics of North America 1400, 20:401–423 ("Agosti")
1014	Thorsten, Hage et al., *Crystal Structure of the Interleukin-4/Receptor a Chain Complex Reveals a Mosaic Binding Interface*, Cell 1999, 97:271–281 ("Hage")
1015	Whitty, et al., *Interaction Affinity Between Cytokine Receptor Components on the Cell surface*, Proc. Natl. Acad. Sci. USA, 1998, 95:13165–13170 ("Whitty")
1018	Keegan, Interleukin 4 Receptor (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*, Eur. J. Biochem. 1994, 225:659-665 ("Tony")
1020	United States Patent Application No 60/382,152 ("the '152 Application")
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 ("Perez")
1049	*Curriculum Vitae* of Mike McKool
1051	*Curriculum Vitae* of John F. Garvish, II
1201	Immunex's November 23, 2016 Response to the Oppositions requested regarding European Patent No. 2 292 665 ("Immunex's EU Opposition Response")
1204	Hart, et al., *Diminished responses to IL-13 by human monocytes differentiated in vitro, 29 Eur. J. Immunol*. 1999, 2087–2097 ("Hart")
1205	PCT International Publication No. WO 98/08957 ("Penn State")
1206	MAb 230 technical information from R & D System's webpage circa 1996 and 1997 with Affidavit ("R&D Systems Catalog")
1207	Hefta, et al., Measuring antibody affinity using biosensors, Antibody Engineering. A Practical Approach, 99–117 (McCafferty et al., eds. 1996)
1208	Parks, D., Herzenberg, L., and Herzenberg L. Flow cytometry and fluorescence-activated cell sorting, in *Fundamental Immunology* 781–802 (Paul, W., ed. 1989)

1209	Zurawski et al., *Receptors for interleukin-13 and interleukin-4 are complex and share a novel component that functions in signal transduction*, 12 EMBO J., 1993, 2663–2670
1400	Third Declaration of Dr. Gerard Zurawski, Ph.D
1401	Certified Copy of Ex. 1204 (Hart), obtained from the collection of the Library of Congress, stamped July 22, 1999
1402	U.S. Patent No. 5,565,322 ("Hoogenboom")
1403	Hoogenboom, et al., *Converting Rodent into Human Antibodies by Guided Selection*, *in Antibody Engineering* 169–185 (McCafferty, Hoogenboom, and Chiswell Eds. 1996)
1404	Figini, et al., *Panning Phage Antibody Libraries on Cells: Isolation of Human Fab Fragments against Ovarian Carcinoma Using Guided Selectio*n, Cancer Research 1998, 58:991–996
1405	Queen, et al., *A humanized antibody that binds to the interleukin 2 receptor*, 86 Proc. Natl. Acad. Sci, USA 10029–10033 (1989) ("Queen 1989 Paper")
1406	U.S. Patent No. 5,530,101
1407	Excerpts from the File History of U.S. Patent Application No. 10/324,493
1408	Harlow & Lane, *Antibodies, A Laboratory Manual* 567–592 (1988)
1409	David King, *Applications and Engineering of Monoclonal Antibodies* (1998) ("King")
1410	Winter et al., *Humanized Antibodies*, TiPS 1993, 14(5):139–43

1411	Studnicka, et al., *Human-engineered monoclonal antibodies retain full specific binding activity by preserving non-CDR complementarity modulating residues*, Protein Engineering, 1994, 7(6):805-814
1412	United States Patent No. 6,030,792
1413	Roguska, et al., *Humanization of murine monoclonal antibodies through variable domain resurfacing*, Proc. Nati. Acad. Sci. USA, 1994, 91:969-973
1414	United States Patent No. 6,531,580
1415	Riechmann ,et al., *Reshaping human antibodies for therapy*, Nature 1988, 332:323–327
1417	Xing-Yue, He et al., *Humanization and Pharmacokinetics of a Monoclonal Antibody with Specificity for Both E- and P-Selectin* J. Immunol., 1998, 160:1029–1035
1418	Tsurushita, et al.,, *Design of humanized antibodies: From anti-Tac to Zenapax*, Methods, 2005, 36:69–83
1419	Rodríguez-Romero, et al., *Primary and Tertiary Structures of the Fab Fragment of a Monoclonal Anti-E-selectin 7A9 Antibody That Inhibits Neutrophil Attachment to Endothelial Cells*, J. Bio. Chem., 1998, 273(19):11770–11775
1420	Dr. Lara Marks, *The life story of a biotechnology drug: Alemtuzumab*, *available at* http://www.whatisbiotechnology.org/exhibitions/campath/introduction
1421	Corren, et al., *A Randomized, Controlled, Phase 2 Study of AMG 317, an IL-4Ra Antagonist, in Patients with Asthma*, Am. J. Respir. Crit. Care Med., 2010, 181:788–796.

1422	Junghans, et al., *Anti-Tac-H, a Humanized Antibody to the Interleukin 2 Receptor with New Features for Immunotherapy in Malignant and Immune Disorders*, Cancer Research, 1990, 50:1495–1502
1423	S. Lazareno, *Estimation of competitive antagonist affinity from functional inhibition curves using the Gaddum, Schild and Cheng-Prusoff equations*, Br. J. Pharmacol., 1993, 109:1110-1119
1424	G. McKenzie et al., *Simultaneously Disruption of Interleukin (IL)-4 and IL-13 Defines Individual Roles in T Helper Cell Type 2-mediated Responses*, J. Exp. Med., 1999, 189(10):1565-1572
1425	Bullens, et al., *Effects of anti-IL-4 receptor monoclonal antibody in in vitro T cell cytokine levels: IL-4 production by T cells from non-atopic donors*, Clin. Exp. Immunol., 1998, 113:320–326
1426	Wang, et al., *IL-4 Function Can Be Transferred to the IL-2 Receptor by Tyrosine Containing Sequences Found in the IL-4 Receptor α Chain*, Immunity, 1996, 4:113–121
1427	Immunex's First Set of RFPs in Case No. 2:17-cv-2613
1428	U.S. Patent No. 7,638,606
1429	International Publication No. WO 01/92340
1430	Affidavit of Mike McKool in Support of Motion for *Pro Hac Vice* Admission
1431	Affidavit of John F. Garvish, II in Support of Motion for *Pro Hac Vice* Admission

Pursuant to 35 U.S.C. § 312 and 37 C.F.R. § 42.100, Sanofi-Aventis U.S. LLC, Genzyme Corp., and Regeneron Pharmaceuticals, Inc. ("Petitioners") request *inter partes* review of U.S. Patent No. 8,679,487 (Ex. 1001), which issued March 25, 2014. Petitioners have shown herein that there is a reasonable likelihood that they will prevail in establishing that the '487 Patent is unpatentable as obvious.

I. INTRODUCTION

The '487 Patent is directed to human antibodies that block activity of interleukin-4 ("IL-4") and interleukin-13 ("IL-13") by binding to human IL-4 receptor ("hIL-4R")—*i.e.*, human anti-hIL-4R blocking antibodies. Rather than claim human anti-hIL-4R blocking antibodies by their amino acid sequence, the '487 Patent broadly claims a genus of "human" antibodies that "compete[]" for binding to hIL-4R with a so-called "reference antibody."

During prosecution, Patent Owner repeatedly maintained that the limitation requiring the claimed antibody to "compete[]" with a reference antibody was the sole ground distinguishing its claimed invention from the prior art. In a series of rejections, the Examiner asserted that the '487 Patent claims were invalid over prior art anti-hIL-4R blocking antibodies, which the Examiner argued necessarily compete with the '487 Patent's reference antibody—another anti-hIL-4R blocking antibody—because all such antibodies bind to hIL-4R. In response to each rejection, Patent Owner disputed the Examiner's argument and insisted that the

Examiner had to *prove* that the prior art antibodies compete with the '487 Patent's reference antibody. Unable to produce such evidence, the Examiner ultimately relented and allowed the '487 Patent.

Here, Petitioners pick up where the Examiner left off and provide the very evidence demanded by Patent Owner by showing that prior art anti-hIL-4R blocking antibodies compete with the '487 Patent's reference antibody for binding to hIL-4R, and thus render the '487 Patent invalid as obvious. One of Petitioners' primary references, Hart (Ex. 1204), teaches MAb230—a prior art murine (mouse) antibody that potently blocks IL-4 and IL-13 activity. Petitioners' expert, Dr. Gerard Zurawski, proved that MAb230 competes with a '487 Patent reference antibody for binding to IL-4R. Hart thus teaches an isolated antibody that is *murine*, rather than human, but otherwise embodies the '487 Patent's claimed invention. However, by the '487 Patent's claimed priority date of May 1, 2001, it would have been obvious for a person of ordinary skill in the art ("POSITA") to transform Hart's MAb230 into a *human* antibody by combining Hart with the teachings of Schering-Plough (Ex. 1007). Like Hart, Schering-Plough teaches murine anti-hIL-4R blocking antibodies. Schering-Plough further teaches methods for humanizing such murine antibodies—thus deriving human anti-hIL-4R blocking antibodies—so that they can be used as therapeutics for IL-4 related diseases. From the combination of Hart and Schering-Plough, it would have been

obvious for a POSITA to isolate a humanized version of MAb230 that meets every limitation of the '487 Patent's claimed invention.

Properly construed, the '487 Patent's claimed "human" antibodies include both partially human (*e.g.*, humanized) and fully human antibodies. Any attempt by Patent Owner to distinguish the '487 Patent claims from the combination of Hart and Schering-Plough by narrowly construing the claims to include only fully human antibodies fails.

First, the '487 Patent defines the antibodies of the invention to include partially human antibodies—like the humanized version of MAb230 taught by the combination of Hart and Schering-Plough. Excluding these partially human antibodies from the claims would conflict with the '487 Patent's intrinsic record and Patent Owner's very definition of its invention.

Second, even if the claims are construed to include only fully human antibodies, they are still rendered obvious by the prior art. One of Petitioners' secondary references, Hoogenboom (Ex. 1402), teaches epitope imprinted selection ("EIS"), which is a method for transforming a murine antibody into a *fully human* antibody. By combining Hart's MAb230 with Hoogenboom's EIS, it would have been obvious for a POSITA to isolate a fully human antibody that meets every limitation of the '487 Patent's claims.

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 for Petitioners. Additionally, Patent Owner asserted infringement of the challenged patent against Sanofi, Sanofi-Aventis U.S. LLC, Genzyme Corp., Aventisub LLC, and Regeneron Pharmaceuticals, Inc. in a lawsuit styled *Immunex Corp. v. Sanofi, et al.* (Case No. 17-cv-02613), pending in the United States District Court for the Central District of California. As a result, Petitioners further identify Sanofi and Aventisub LLC as real parties-in-interest, although neither Sanofi nor Aventisub LLC controls or funds this IPR.

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

On March 20, 2017, Petitioners filed a Complaint for Declaratory Judgment of Non-Infringement of U.S. Patent No. 8,679,487 against Amgen Inc. and Immunex Corporation in a lawsuit styled *Sanofi-Aventis U.S., LLC, et al. v. Amgen Inc., et al.* (Case No. 17-cv-10465), that was later voluntarily dismissed without prejudice by Petitioners on May 1, 2017, in the United States District Court of Massachusetts.

On March 23, 2017, Petitioners filed IPR2017-01129, which challenges the '487 Patent on grounds that are different than those in this Petition.

On April 5, 2017, Patent Owner asserted U.S. Patent No. 8,679,487 against Sanofi, Sanofi-Aventis U.S. LLC, Genzyme Corp., Aventisub LLC, and Regeneron Pharmaceuticals, Inc. in a lawsuit styled *Immunex Corp. v. Sanofi, et al.* (Case No. 17-cv-02613), pending in the United States District Court for the Central District of California.

On July 28, 2017, Petitioners filed IPR2017-01879, which challenges the '487 Patent on grounds that are different than those in this Petition.

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))

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Petitioners consent to electronic service.

III. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

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.

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 reasons:

Ground 1: Claims 1–17 are invalid under 35 U.S.C. § 103(a) based on Hart (Ex. 1204) combined with Schering-Plough (Ex. 1007).

Ground 2: Claims 1–17 are invalid under 35 U.S.C. § 103(a) based on Hart combined with Schering-Plough and Hoogenboom (Ex. 1402).

The '487 Patent's earliest claimed priority date is May 1, 2001. Published on June 7, 1994, Schering-Plough is prior art under 35 U.S.C. § 102(b). Issued on October 15, 1996, Hoogenboom is prior art under 35 U.S.C. § 102(b). Published on July 6, 1999, Hart is prior art under 35 U.S.C. § 102(b). Evidence of Hart's public availability before May 1, 2001 is found in Ex. 1401, which is a declaration from the Library of Congress that Hart was received by July 22, 1999. Ex. 1401.

Further evidence of public availability is found on the face of Hart, which indicates that it was copyrighted in 1999 and sold for $17.50. Ex. 1204 at 2087.

Grounds 1 and 2 assert that the Challenged Claims are invalid under prior art methods for transforming murine antibodies into partially human or fully human antibodies, respectively. Ground 2 is not cumulative because it adds the Hoogenboom reference to Ground 1, and addresses distinctions Patent Owner may advance using improperly narrow claim constructions.

In addition, Grounds 1–2 of this Petition are not cumulative with IPR2017-01129 or IPR2017-01879. In IPR2017-01129, Petitioners assert that the Challenged Claims are anticipated by Stevens—a U.S. Patent Publication from 2008—because the Challenged Claims are not entitled to the ’487 Patent’s purported May 1, 2001 priority date. IPR2017-01129 thus concerns priority and anticipation arguments that are substantially different from the obviousness arguments presented here. In IPR2017-01879, Petitioners assert that the challenged claims are anticipated by Immunex’s own ’132 Publication, which is prior art based on the ’487 Patent’s purported May 1, 2001 priority date and discloses a method of making fully human anti-hIL-4R antibodies from transgenic mice, including an antibody known as mAb 6-2. IPR2017-01879 thus concerns anticipation arguments that are substantially different from the obviousness arguments presented here. Petitioners could not have filed this Petition sooner,

because the testing of the prior art 230 antibody disclosed in Hart was only recently completed on July 19, 2017. Ex. 1400 ¶99.

Further, Grounds 1–2 present arguments not previously considered by the Patent Office during prosecution of the ’487 Patent. Each of Grounds 1–2 relies on cross-competition data between MAb230, a prior art anti-hIL-4R antibody that is disclosed in Hart, and MAb 12B5, one of the ’487 Patent’s reference antibodies. The Examiner did not have access to competition data between MAb 12B5 and any other antibody—much less MAb230—during prosecution. In addition, Hart (Grounds 1–2) and Hoogenboom (Ground 2) were not considered by the Patent Office during prosecution of the ’487 Patent.

V. FIELD OF TECHNOLOGY

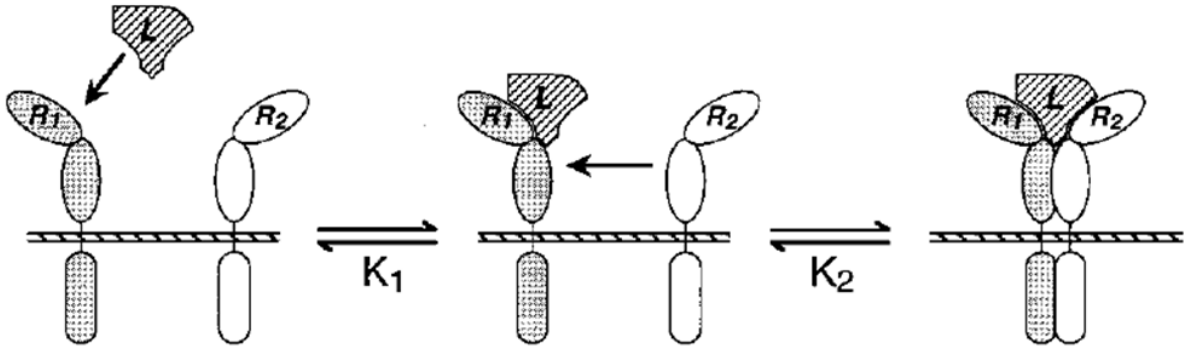
The ’487 Patent is directed to antibodies that block IL-4R and accordingly inhibit IL-4 and IL-13 induced signaling. Ex. 1001 at Title, 18:32–19:5, Claim 1; Ex. 1400 ¶71. The below sections provide an overview of IL-4 and IL-13 biology, monoclonal antibodies, and the distinction between human and non-human (*e.g.*, murine) antibodies.

A. IL-4 and IL-13

IL-4 and IL-13 are small signaling proteins (called cytokines) that regulate the adaptive immune system. Ex. 1400 ¶33. 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). Ex. 1400 ¶32. In particular, it was known that IL-4 induced signaling mediates a wide variety of immunogenic responses, including causing conversion of Th_o helper cells into Th_2 cells, isotype switching of antibodies secreted by B-cells, and B-cell proliferation. Ex. 1400 ¶33; Ex. 1011 at 406. These immunogenic responses ultimately culminate in the body releasing cytotoxic chemicals that cause many of the symptoms associated with allergies (*e.g.*, inflammation, flushing). Ex. 1400 ¶33; Ex. 1011 at 405–409; Ex. 1007 at 2:1–15. It was also known that IL-13 mediates many of the same immunogenic responses as IL-4. Ex. 1400 ¶33; Ex. 1010 at 13869.

Before 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. 1400 ¶34; Ex. 1010 at 13869. As illustrated below, IL-4 signals through IL-4 receptor ("IL-4R") in a two-step process. First, IL-4 (labeled "L") binds to IL-4Rα (labeled "R_1"). Second, the IL-4/IL-4Rα complex associates with one of two other subunits (labeled "R_2") to form a ternary (three-member) signaling complex.

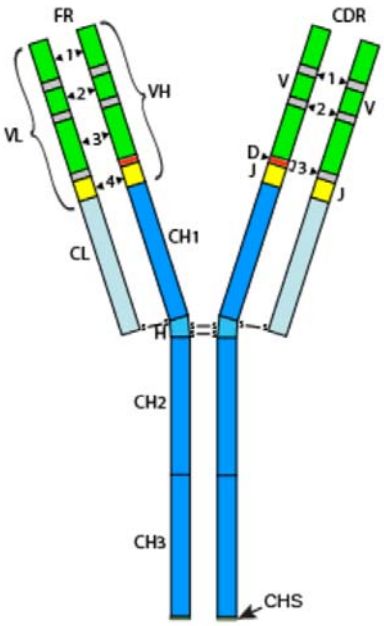


Ex. 1015 at 13166. The two potential subunits with which the IL-4/IL-4Rα complex may associate are called common gamma chain ("γc") and IL-13 receptor alpha 1 ("IL-13Rα1"). Ex. 1400 ¶¶35–37. When the IL-4/IL-4Rα complex associates with the γc subunit, it is termed a "Type 1" receptor complex. Ex. 1400 ¶36. When the IL-4/IL-4Rα complex associates with the IL-13Rα1 subunit, it is termed a "Type 2" receptor complex. Ex. 1400 ¶37.

IL-13 induced signaling utilizes the same receptor subunits that comprise the Type 2 receptor but the interaction begins with IL-13Rα1. Ex. 1400 ¶37; 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. 1400 ¶37; Ex. 1014 at 279. 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"). *See* Ex. 1400 ¶39; 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 the active site of IL-4Rα would simultaneously inhibit IL-4 and IL-13 induced signaling. Ex. 1400 ¶39; 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. 1400 ¶39; Ex. 1011 at 410–412; Ex. 1007 at 2:19–25. In particular, monoclonal antibodies that block IL-4Rα's active site ("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 410, 412; *see also* Ex. 1007 at 2:19–20 ("[S]uch blocking antibodies could be therapeutic entities for allergy.").

B. Monoclonal Antibodies



As shown in the below figure,[1] antibodies are generally understood as "Y-shaped proteins." They are composed of two identical heavy chains (VH, CH1, CH2, and CH3) and two identical light chains (VL and CL), which are bound together by disulfide bonds. Ex. 1400 ¶40. These chains are further subdivided into variable regions (VH, VL) and constant regions (CH1–3, CL). Ex. 1400 ¶40. 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. 1400 ¶¶41–42. The variable region for each heavy and light chain is subdivided into four framework regions (FRs) and three complementarity determining regions (CDRs). Ex. 1400 ¶41. The CDRs fold together to form the antibody's antigen binding site, *i.e.*, the paratope. Ex. 1400 ¶41. The specific part of an antigen to which the antibody binds is called the epitope. Ex. 1400 ¶41.

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

C. Distinction Between Human and Murine Antibodies

Although "human" and "murine" 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. 1400 ¶50. 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. 1400 ¶50. Accordingly, humans who have been systemically injected with murine antibodies often develop an undesirable human anti-mouse antibody ("HAMA") reaction. Ex. 1400 ¶50.

To mitigate the risk of a HAMA reaction, by May 1, 2001, skilled artisans had devoted considerable research toward developing techniques for transforming murine antibodies into human counterparts. Ex. 1400 ¶50; *see generally* Ex. 1007; Ex. 1402. Two of these techniques—CDR grafting and EIS—are discussed in Section VII.A.3 below.

D. Antibody Functional Assays

Most of the challenged claims recite various functions that can be performed by an antibody. Claims 1–3 pertain to antibody competition and cross-blocking. Antibody competition and cross-blocking assays generally assess the capability of two (or more) antibodies to bind to the same or overlapping epitopes on an antigen.

At a conceptual level, antibodies that bind to similar[2] epitopes can be said to "compete" with one another for binding to the same antigen because one antibody will interfere with the binding of the other antibody and *vice versa*. Ex. 1400 ¶66. Prior to May 1, 2001, several competition assays were known in the art. Ex. 1400 ¶67. Although the '487 Patent specification does not describe any antibody-antibody competition assay, Patent Owner has endorsed the flow cytometry assay described in Ex. 1026 ("Perez")—which was known before May 1, 2001—as being suitable for determining competition. Ex. 1201 at 12–13 ("[Perez] D24 provides methods for determining competition between antibodies and competition was identified successfully using those methods."). Accordingly, Dr. Zurawski used the assay described in Perez to assess competition between prior art antibodies and MAb 12B5. Ex. 1400 ¶111.

Claims 4–7 pertain to blocking and signaling inhibition. Blocking and signaling inhibition assays measure an antibody's ability to inhibit a biological activity. For example, one can measure an anti-hIL-4R antibody's ability to inhibit

[2] In some cases, even when the epitopes of two antibodies are non-overlapping, the antibodies may still inhibit one another's binding by steric hindrance because antibodies are large molecules.

IL-4 and/or IL-13 signaling by assessing the antibody's ability to suppress CD23[3] expression in cells that have been exposed to IL-4 and/or IL-13. The '487 Patent discloses such a CD23 assay in example 5, and Dr. Zurawski used this assay to assess the IL-4 and IL-13 inhibitory activity of prior art antibodies.

Claims 8–10 concern the binding affinity of anti-hIL-4R antibodies. An antibody with a relatively higher binding affinity constant ("K_a") binds more strongly to its antigen than an antibody with a relatively lower binding affinity constant. Ex. 1400 ¶64. Although no binding affinity assay is described in the '487 Patent, one assay that was known in the art for assessing antibody binding affinity prior to May 1, 2001 is called a surface plasmon resonance ("SPR") assay. Ex. 1400 ¶¶64–65. Accordingly, Dr. Zurawski measured the binding affinity of prior art antibodies with a SPR assay. Ex. 1400 ¶127.

VI. THE '487 PATENT

A. Admitted Prior Art and Alleged Improvement

[3] "CD23" is a cell surface receptor that binds to antibodies of the IgE isotype. Ex. 1400 ¶81. IL-4 and IL-13 induced signaling increases CD23 expression. Accordingly, an antibody that inhibits IL-4 and IL-13 signaling will reduce IL-4 and/or IL-13 induced CD23 expression. Ex. 1400 ¶81.

Patent Owner admits that anti-hIL-4R blocking antibodies were readily isolatable by skilled artisans before May 1, 2001. *See* Ex. 1001 ('487 Patent) at 19:6–7 ("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 antibodies could be isolated from transgenic mice by "conventional procedures." *See* Ex. 1001 ('487 Patent) at 19:59–20:13 (citing several transgenic animal references and stating "[m]onoclonal antibodies may be produced by conventional procedures, e.g., by immortalizing spleen cells harvested from the transgenic animal after completion of the immunization schedule").

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. Ex. 1001 at 20:9–13; 21:6–15.[4] However, the '487 Patent does not claim the sequence of any of these disclosed MAbs or their derivatives—earlier patents in the family claimed them. *Compare* Ex. 1001 *with* Ex. 1029 *and* 1031. The '487 Patent takes a radical step beyond the Patent Owner's contribution to the field. Claim 1, the

[4] The encoding nucleotides and amino acid sequences for these mAbs are disclosed in SEQ. ID. NOS. 5–26. Ex. 1001 at 41:11–24, 43:37–44:67.

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 at Claim 1. It further recites that the *reference* antibody—not the *claimed* antibody genus—"comprises" SEQ ID NOS: 10 and 12, which are the light and heavy chain variable region sequences for mAb 12B5.

As explained in detail below, the dependent claims do not meaningfully limit Claim 1. Claims 2–10 recite further functional limitations linked with the "compet[ing]" function recited in Claim 1 (cross-blocking the reference antibody, inhibiting IL-4 and IL-13 activity, and tightly binding to IL-4R). Claims 11–15 are directed to types of antibodies or antibody derivatives (full-length antibodies, isotypes, antibody fragments, fusion proteins, and single chain antibodies) that were "conventional" in the prior art. *See* Ex. 1001 at 15:39–62, 19:13–20, 22:29–31, 26:12–28. Claims 16–17 are directed to combining the competing antibody of Claim 1 with a pharmaceutically acceptable solvent or a "kit."

B. Prosecution History of the '487 Patent

Although the functionally claimed genus of antibodies "that compete[]" is not described in the '487 Patent specification, the Examiner's lack of evidence that prior art antibodies "compete" with a reference antibody was the central distinguishing factor that Patent Owner relied upon to overcome prior art asserted by the Examiner during prosecution. The Examiner first rejected Patent Owner's

claims as anticipated by U.S. Patent No. 5,717,072 ("Mosley"), which teaches "an isolated human antibody that 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-murine or 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.*, the extracellular potion of IL-4Rα] must *necessarily* compete for binding to the polypeptide, 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 assert that prior art antibodies compete with the reference antibody without testing them). Ultimately, unable to produce

evidence that prior art antibodies compete with the '487 Patent's reference antibody—evidence that is supplied by Petitioners in this Petition—the Examiner relented and issued a notice of allowance and the '487 Patent issued March 25, 2014. Ex. 1002 at 0001, 0021–29.

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 submit that for the purpose of this Petition, the broadest reasonable interpretation of most of the terms recited in Claims 1–17 of the '487 Patent would be clear on their face to one of ordinary skill in the art. *See supra* Section V, VII.A; Office Patent Trial Practice Guide, 77 Fed. 48756, 48764 (Aug. 14, 2012) ("Regarding the need for a claim construction, where appropriate, it may be sufficient for a party to provide a simple statement that the claim terms are to be given their broadest reasonable interpretation . . . ."). Petitioners therefore request that the claim terms be given their broadest reasonable interpretation (BRI), as understood by a POSITA and consistent with the specification.[5] With

[5] District courts apply other 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.

respect to terms that may need to be defined or further clarified, Petitioners request the following claim constructions to be adopted.

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 20:57–60 (emphasis added). And the specification consistently describes "human antibodies" as including partially human antibodies. *See* Ex. 1001 at 19:41–44 ("Procedures have been developed for generating ***human antibodies*** in non human animals. The antibodies may be ***partially human***, or preferably completely human.") (emphasis added), 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 19:21–22 (emphasis added). "Chimeric antibodies" are partially human antibodies. Ex. 1400 ¶96. 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.

2. "antibody" (Claim 1)

The term "antibody" should be given its BRI meaning herein.[6] Despite not providing its own express construction, Patent Owner states in the related

[6] In IPR2017-01129, Patent Owner incorrectly argues that institution should be denied because in litigation Petitioners assert that "antibody" should be limited to the sequences of the Six MAbs or their equivalents. IPR2017-01129, Paper No. 14 at 17. But the broadest reasonable interpretation applies here, and "may be the same as or broader than the construction of a term under the *Phillips* standard."

IPR2017-001129 that the term "antibody" requires construction, and attempts to take Petitioners to task for allegedly creating "unresolved ambiguity surrounding" the term. IPR2017-001129, Paper No. 14 at 15-16. To the contrary, Petitioners applied the '487 Patent's purported definition of the term "antibody" as broadly "encompass[ing] whole antibodies and antigen binding fragments thereof." Ex. 1001 at 16:29–31. Dependent claims 11–15 further demonstrate that "antibody" includes full-length antibodies of any isotype, antibody fragments, fusion proteins, and/or single chain antibodies. Accordingly, Petitioners continue to use the term "antibody" consistent in breadth with the definition offered in the '487 Patent's specification and dictated by the dependent claims. *See also supra* Section V(B) (providing a general overview of antibodies).

Facebook, Inc. v. Pragmatus AV, LLC, 582 F. App'x 864, 869 (Fed. Cir. 2014); *see also Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2145-2146 (2016). Patent Owner "does not concede" that the term "antibody" should be limited to the Six MAbs (IPR2017-01129, Paper No. 14 at 17)—indeed, Patent Owner contends that it should *not* be limited by asserting in litigation that Petitioners' antibody infringes. Petitioners therefore demonstrate herein that under Patent Owner's own interpretation, the claims are obvious in light of the prior art.

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

A. The Scope and Content of the Prior Art

1. The Prior Art Teaches a Need for Therapeutic Antibodies that Block IL-4 and IL-13 Signaling

As discussed above, IL-4 and IL-13 induced signaling was known to play a pivotal role in the development of allergic disorders. Indeed, in a parent application to the '487 Patent, Patent Owner acknowledges that hIL-4R was known in the prior art as "the perfect target" for therapeutic agents because it is an "important regulator" of allergic disorders. Ex. 1407 at 0007; *see also* Ex. 1407 at 0014 ("Several researchers say that perhaps a more promising drug target than either cytokine is the portion of the receptor molecule on immune system cells that is shared by both IL-4 and IL-13 . . . That kind of bottleneck is the perfect target for designing new therapies.") (internal quotations omitted).

Knowing that hIL-4R was "the perfect target" for treatment of allergic disorders, skilled artisans had developed therapeutic antibodies against hIL-4R prior to May 1, 2001. For example, Schering-Plough teaches that "[a]ntibodies specific for the IL-4 receptor which block the binding of IL-4 would permit one to inhibit IL-4 biological effects . . . [and accordingly] could be therapeutic entities for allergies." Ex. 1007 at 2:18–20. As another example, Agosti recognizes that anti-hIL-4R monoclonal antibodies provide "especially interesting" therapeutics

for allergic disorders and were in development before May 1, 2001. Ex. 1011 at 410, 412.

2. The Prior Art Teaches Anti-IL-4R Antibodies that Inhibit IL-4 and IL-13 Signaling

By May 1, 2001, murine anti-hIL-4R blocking antibodies had been successfully isolated and described in the prior art. For example, Hart teaches "MAB230, a neutralizing antibody to the IL-4Rα chain." Ex. 1204 at 2092–93. In Hart, the authors were interested in whether IL-4Rα constitutes an essential subunit of the IL-13R signaling complex in monocyte-derived macrophages ("MDMac").[7] Accordingly, the authors assessed MAb230's ability to inhibit both IL-4 and IL-13 signaling in monocytes and MDMac. Ex. 1204 at 2091, 94. As shown in Figure 8 of Hart, one μg/mL of MAb230 was able to completely abolish the effects of IL-4 and IL-13 induced expression of TNF-α and IL-1β in monocytes and MDMac, which confirmed to the authors that IL-4Rα "remains an essential component of

[7] Monocytes and MDMac are types of white blood cells that play a role in the inflammatory immune response. Ex. 1400 ¶46.

the IL-13 receptor complex on MDMac."[8] Ex. 1204 at 2087, 91–92, Fig. 8; *see also* Ex. 1400 ¶¶44–49.

The prior art further teaches partially and fully human anti-hIL-4R blocking antibodies. For example, Schering-Plough teaches murine anti-hIL-4R blocking antibodies and that such antibodies could "advantageously be humanized and thus be used for long term treatment of allergic disorders." Ex. 1007 at 2:21–22, 10:5–29 (internal citation omitted). As another example, Penn State teaches an "invention [that] provides for ***fully human*** anti-IL-4R antibodies[]," that "antibodies that specifically bind to and block the IL-4 receptor are well known to those of skill in the art," and that "[o]ne of skill in the art will appreciate that the antibodies may be human or humanized." Ex. 1205 at 19:21–22, 40:21–26 (emphasis added). Penn State further teaches that such fully human anti-hIL-4R blocking antibodies are isolatable from "murines transformed to express human immunoglobulin genes" and with "phage display screening." Ex. 1205 at 20:5–7.

3. The Prior Art Teaches Techniques to Transform Anti-IL-4R Antibodies into Partially and Fully Human Antibodies

[8] IL-4 and IL-13 regulate inflammatory responses, in part, by suppressing TNF-α and IL-1β expression in monocytes and MDMac. Ex. 1204 at 2087; *see also* Ex. 1424 at 1565.

By May 1, 2001, there were at least two methods by which a POSITA could predictably isolate at least one species of the '487 Patent's claimed genus of "human" antibodies. One such prior art technique is called CDR grafting. As explained in Schering-Plough, "the CDRs [*i.e.*, the portions of an antibody that bind to an antigen] from a rodent monoclonal antibody can be grafted onto a human antibody, thereby 'humanizing' the rodent antibody." Ex. 1007 at 2:19–22, 5:1–35. In addition to the CDRs, it was well-known to further graft key amino acid residues from the murine framework into the human antibody if those residues were necessary to preserve binding. *See* Ex. 1007 at 5:20–23 ("[I]t may be desirable to include one or more amino acid residues which, while outside the CDRs, are likely to interact with the CDRs or the human 130 kDa IL-4 receptor.").[9] The resultant humanized antibody is unlikely to trigger a HAMA reaction because it is primarily composed of characteristically human amino acid sequences. Ex. 1400 ¶¶136–37; Ex. 1007 at 2:19–22. However, because the murine parent antibody's binding-determinant residues are preserved (*i.e.*, the CDRs and non-CDR residues that are integral to proper CDR conformation and/or directly interact with the antigen), the humanized antibody retains the binding characteristics of its murine parent. Ex. 1400 ¶¶52–56.

[9] The "130 kDa IL-4 receptor" is the alpha subunit of hIL-4R. Ex. 1400 ¶137 n.15.

By May 1, 2001, it was well within the ability of a skilled artisan to engineer a humanized antibody that retains a murine antibody's specificity and relative affinity for hIL-4R. Ex. 1400 ¶¶55–56. For example, Schering-Plough incorporates-by-reference a 1989 paper to Queen et al. (Ex. 1405; "Queen") that teaches the successful humanization of a murine antibody to the alpha subunit of human interleukin-2 receptor ("hIL-2R") using computer-based molecular modeling to identify the murine antibody's binding determinant residues. Ex. 1007 at 3:28, 5:5–8, 5:17–23. The Queen reference introduced two techniques to assist in the derivation of humanized antibodies that retain the binding characteristics of their murine parents. Ex. 1405 at 10032–33 ("[W]e have introduced two ideas that may have wider applicability"). As explained in Queen:

> First, the human framework was chosen to be as homologous as possible to the original mouse antibody to reduce any deformation of the mouse CDRs. Second, computer modeling was used to identify several framework amino acids in the mouse antibody that might interact with the CDRs or directly with antigen, and these amino acids were transferred to the human framework along with the CDRs.

Ex. 1405 at 10033.

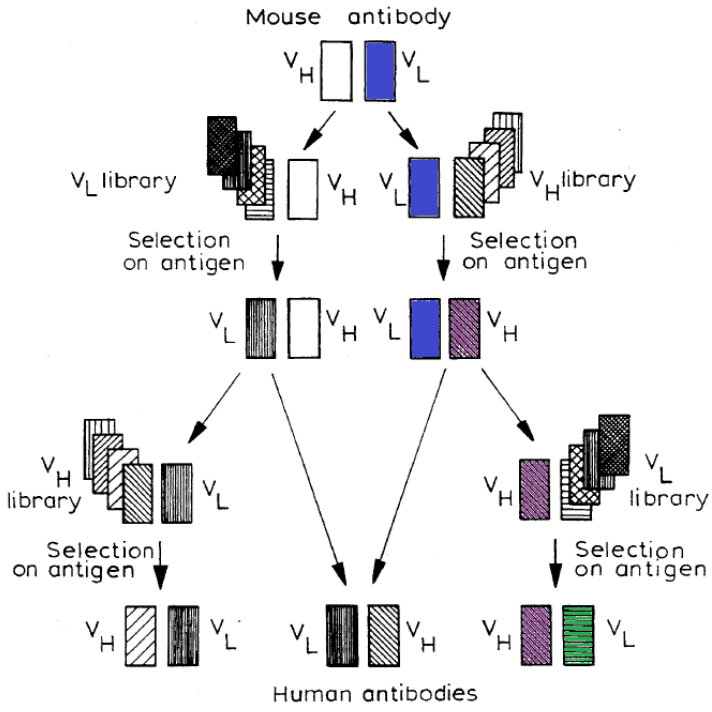
By grafting the murine antibody's binding-determinant residues into a homologous human framework, Queen was able to isolate a humanized anti-hIL-2R antibody that retained the specificity and relative affinity of its murine

parent.[10] Ex. 1405 at 10032–33, Fig. 4; Ex. 1400 ¶143. By May 1, 2001, it was routine to utilize the molecular modeling and homology searching techniques that were pioneered in Queen to preserve a murine antibody's specificity and relative affinity in a humanized counterpart. Ex. 1400 ¶¶56, 138; *see also* Ex. 1409 at 33 (observing, *in 1998*, that "[a]lthough difficulty in achieving full antigen binding activity was encountered early in the development of this technology, *humanisation of murine antibodies is now relatively routine* and many antibodies have been successfully humanised.") (emphasis added); Ex. 1418 at 70 (recounting that the teachings of Queen and coworkers made it possible to "routinely generate engineered antibodies, generally referred to as humanized antibodies, which retain the binding affinity and specificity of the parental mouse antibodies"). Accordingly, by May 1, 2001, a POSITA knew to isolate a humanized anti-hIL-4R antibody from a murine anti-hIL-4R antibody, as taught in Schering-Plough. Ex. 1400 ¶51–56.

[10] In 1997, the anti-hIL-2R antibody described in Queen became the first humanized antibody approved for therapeutic use by the FDA. Ex. 1418 at 70.

As an alternative to CDR grafting, a second prior art technique for isolating a human antibody to hIL-4R is taught in Hoogenboom. Ex. 1402 at 10:4–5. Like CDR grafting, Hoogenboom's epitope imprinted selection ("EIS") enables one to transform a murine antibody into a human antibody. Ex. 1402 at 13:5–9. Unlike CDR grafting, however, the product of EIS is fully human. Ex. 1402 at 9:67–10:5, 10:35–42.

FIG. 1



EIS uses a known murine antibody with desirable binding characteristics to guide the selection of a human antibody with analogous binding characteristics from a phage display library. *See* Ex. 1402 at 29:51–54 ("We have shown that a mouse antibody can be rebuilt into a human antibody with the same specificity by the process of epitope imprinted selection (EIS)"); Ex. 1403 at 174 (explaining that the "aim of guided selection [*i.e.*, EIS] is to confer all of the properties of binding specificity and affinity from the rodent antibody on to a human equivalent"); Ex. 1400 ¶¶59–60. As shown in the annotated figure above, in a first step of one embodiment, DNA encoding the light chain variable region of a

murine antibody (blue in the figure) is inserted into phages (virus particles) and "shuffled" with millions of random human heavy chain sequences, which forms a "library" of half-human, half-murine antibody fragments, each displayed on the surface of a phage. Ex. 1402 at 13:9–16. The resultant library is then culled for antibody fragments that retain the binding characteristics of the original, murine antibody, which results in the selection of one or more human variable heavy chains (purple in the figure)—*i.e.*, one half of a fully human variable region. Ex. 1402 at 13:16–20.

In a second step, the newly selected human variable heavy chain is used to guide the selection of a corresponding human variable light chain. Accordingly, DNA encoding the human heavy variable chain is inserted into phages and shuffled with a repertoire of millions of random human variable light chain sequences. Ex. 1402 at 13:21–23. As in the first step, the library of antibody fragments—now fully human—is culled for a fragment that retains the binding characteristics of the original, murine antibody. Ex. 1402 at 13:23–29. The resultant antibody (purple and green in the figure) is "entirely human," but is directed to the same epitope, and binds to that epitope with similar affinity, as the

murine antibody that was used to guide its selection.[11] Ex. 1402 at 9:67–10:5, 12:53–57, 27:1–5. Accordingly, by May 1, 2001, a POSITA knew to isolate a fully human anti-hIL-4R antibody from a murine anti-hIL-4R antibody by Hoogenboom's EIS. Ex. 1400 ¶61.

4. The Prior Art Teaches Anti-IL-4R Antibodies that "Compete" with a '487 Patent Reference Antibody

Patent Owner purports to have invented a novel genus of antibodies that bind to hIL-4R by "compet[ing]" with the '487 Patent's "reference antibody." But the '487 Patent's coined "reference antibody" is just another "blocking antibody that functions as an IL-4 antagonist and as an IL-13 antagonist" (Ex. 1001 at 42:63–65), like Hart's MAb230 (Ex. 2001 at 2091–92), Penn State's "[a]ntibodies that specifically bind to and block the IL-4 receptor" (Ex. 2004 at 40:21–22), and Schering-Plough's "monoclonal antibodies . . . having blocking or antagonistic effects [that] can be used to suppress IL-4 activity by binding to the IL-4 receptor instead of IL-4 binding to the receptor" (Ex. 1007 at 6:31–33). In an attempt to

[11] As shown in Figure 1 of Hoogenboom, one could also initiate EIS with a murine heavy chain instead of a light chain. Although there are multiple paths that one could take to transform a murine antibody into a human antibody by EIS, the result of each is the same—one or more fully human antibodies with binding characteristics analogous to a pre-existing murine antibody. Ex. 1402 at 21:1–9.

circumvent this art, Patent Owner defines its invention in functional terms—*i.e.*, by claiming a genus of antibodies by how they function in relation to a so-called reference antibody, namely that they "compete[]."[12]

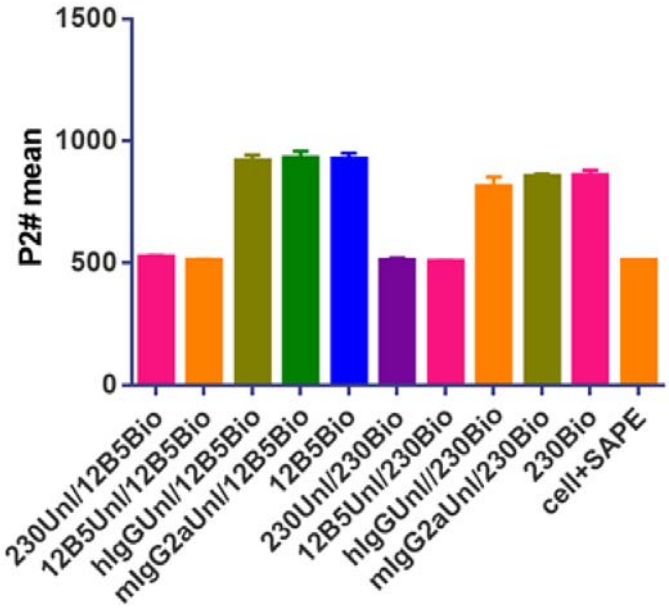
As shown in Dr. Zurawski's declaration, however, Patent Owner was not the first to isolate an antibody "that competes" with the '487 Patent's reference antibody. Dr. Zurawski confirmed that the anti-hIL-4R antibody disclosed in Hart (Ex. 1204) and known as MAb230 inherently possesses this functional characteristic. As explained in his declaration, Dr. Zurawski purchased MAb230 from its commercial supplier (R&D Systems), Ex. 1204 at 2094, and generated mAb 12B5 (an IgG1 isotype of the reference antibody) using the '487 Patent's disclosed SEQ ID NOS 10 and 12, which correspond to the light and heavy chain variable regions of MAb 12B5, respectively. Ex. 1400 ¶¶98–110. Subsequently, using the flow cytometry-based cross-competition assay taught in Perez (Ex. 1026

[12] The logical result of this draftsmanship is a claim limitation that can never be found explicitly in the prior art. Indeed, assuming that a patentee discloses a novel antibody in a patent, a claim drawn to all antibodies that "compete" with that antibody will never be found explicitly in the prior art, even if many prior art antibodies were inherently able to so do.

at 664–66), Dr. Zurawski assessed whether mAbs 230 and 12B5 compete for binding to hIL-4R. *See* Ex. 1400 ¶111.

This is reflected, for example, in Figure 2 of Dr. Zurawski's declaration, which depicts MAb230's ability to block mAb 12B5 from binding to hIL-4R and *vice versa*.

Figure 1: MAb230 vs. MAb12B5



Dr. Zurawski's assays demonstrate that MAb230 blocks the binding of the reference antibody (*i.e.*, mAb 12B5) to hIL-4R and that the reference antibody likewise blocks the binding of MAb230 to hIL-4R. Ex. 1400 ¶116. As shown in column 1, MAb230 blocks binding to mAb 12B5(Bio) as well as MAb230 blocks itself in column 6. Furthermore, mAb 12B5 blocks binding to MAb230(Bio) in column 7 as well as mAb 12B5 blocks itself in column 2. In contrast, neither of the

isotype-matched controls blocks MAb230 (columns 8 and 9) or mAb 12B5 (columns 3 and 4) to a significant degree. From this data, Dr. Zurawski calculated the percent binding inhibition caused by each of MAb230, mAb 12B5, IgG1 negative control, and mIgG2a negative control. Ex. 1400 ¶¶117–18. The results are reproduced below.

Antibody	**Biotin-12B5**	**Biotin-MAB 230**
12B5	**100%**	**100%**
hIgG1[13]	**2%**	**13%**
MAB230	**97%**	**100%**
mIgG2a	**0%**	**2%**

As specified in Perez, if the first antibody inhibits binding of the second antibody by at least 50%, then the antibodies compete. Ex. 1026 at 667 (using 50% as a "cut-off . . . to place the mAbs into four groups of mutually competitive antibodies"). Because MAb230 and the 12B5 reference antibody were found to inhibit the binding of one another by 97% or higher—well above Perez's 50% threshold—they compete for binding to hIL-4R. Ex. 1400 ¶119. Thus, Dr.

[13] hIgG1 and mIgG2a are negative controls. Neither of these antibodies binds to hIL-4R. Ex. 1400 ¶116.

Zurawski's Declaration demonstrates that the '487 Patent's "competes" limitation is inherent to Hart's MAb230.

B. Level of Ordinary Skill in the Art

A POSITA relevant to the '487 Patent as of May 1, 2001—the earliest priority date claimed by the '487 Patent—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. Ex. 1400 ¶27. 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 or partially human antibodies. Ex. 1400 ¶27.

C. Ground 1 – The Asserted Claims Are Unpatentable as Obvious Over Hart Combined with Schering-Plough

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."*

The combination of Hart and Schering-Plough renders obvious Claim 1 of the '487 Patent. Hart teaches MAb230, a murine anti-hIL-4R blocking antibody that was known to block hIL-4Rα and accordingly neutralize IL-4 and IL-13

signaling. Ex. 1204 at 2091–92, 94 (describing MAb230 as both a "blocking antibody to IL-4Rα" and "a neutralizing antibody to the IL-4Rα chain"). Hart provides experimental results in Figure 8 that demonstrate that MAb230 inhibits both IL-4 and IL-13 signaling by blocking hIL-4Rα. Ex. 1204 at 2092–93; Ex. 1400 ¶¶45–48. Although not expressly taught in Hart, Dr. Zurawski demonstrated that MAb230 inherently "competes" with mAb 12B5 (a "reference antibody") for binding to hIL-4R. *See supra* Section VII(A)(4). Hart thus teaches an anti-hIL-4R antibody that meets every limitation of '487 Patent Claim 1, except that it is a murine instead of human antibody.

Schering-Plough, in turn, teaches techniques for humanizing murine anti-hIL-4R blocking antibodies so that they can be employed "for long term treatment of allergic disorders." Ex. 1007 at 2:18–22, 5:1–23, 6:30–34. By May 1, 2001, it would have been obvious for a POSITA to modify Hart's MAb230 with Schering-Plough's humanization techniques to derive a potential therapeutic for allergic diseases. Ex. 1007 at 2:18–22, 5:1–23; Ex. 1400 ¶132.

To humanize MAb230, a POSITA would have first known to determine the amino acid sequences of MAb230's light and heavy chain variable regions using conventional protein sequencing techniques (*e.g.*, Edman degradation). Ex. 1400 ¶62; *see also* Ex. 1414 at 21:1–22:63 ("The Edman degradation method is the chemical procedure routinely used over the past 40 years for determining the

amino acid sequence of proteins."). After obtaining MAb230's variable region sequences, it would have been obvious for a POSITA to identify MAb230's CDRs and framework residues that, "while outside the CDRs, are likely to interact with the CDRs or the human 130 kDa IL-4 receptor." Ex. 1007 at 5:20–27. Schering-Plough teaches computer-based molecular modeling to predict such binding-determinant residues. Ex. 1007 at 5:17–23; Ex. 1405 at 10029 ("For the humanized antibody, sequence homology and molecular modeling were used to select a combination of mouse and human sequence elements that would reduce immunogenicity while retaining high binding affinity."). Subsequently, it would have been obvious for a POSITA to graft MAb230's binding-determinant residues into a homologous human framework to isolate a humanized antibody that retains MAb230's specificity and relative affinity for hIL-4R. Ex. 1007 at 5:27–35 (teaching recombinant DNA technology to express humanized antibodies); Ex. 1405 at 10030–32 (teaching computer-based searching to identify a homologous human framework); Ex. 1400 ¶¶52–54, 137–38.

As was well-known in the prior art, the ultimate goal of humanization is to decrease the immunogenicity of a parental, non-human mAb while still maintaining its antigen binding specificity and affinity, by transferring its CDRs and a minimal number of key framework residues to an acceptor, human framework. Ex. 1400 ¶138, 142; *see also* Ex. 1413 at 969 ("'Humanization' or

'reshaping' of murine antibodies is an attempt to transfer the full antigen specificity and binding avidity of murine monoclonal antibodies to a human antibody by grafting the murine complementarity determining regions (CDRs) onto a human variable region framework."). This is why Schering-Plough teaches a POSITA to preserve a murine anti-hIL-4R antibody's CDRs and framework residues that "are likely to interact with the CDRs or the human 130 kDa IL-4 receptor"—preserving these binding-determinant residues is necessary to replicate the murine anti-hIL-4R antibody's specificity and relative affinity for hIL-4R in a humanized counterpart. Ex. 1007 at 5:20–27; Ex. 1400 ¶138. Accordingly, it would have been obvious—indeed imperative—to a POSITA to ensure that MAb230's specificity and relative affinity for hIL-4R were retained by CDR grafting. Ex. 1400 ¶138; Ex. 1411 at 805 ("[H]umanization is practical only if it does not diminish or destroy the ability of the antibody to bind its target ligand."). Thus, the combination of Hart and Schering-Plough renders obvious a partially human antibody (*i.e.*, an "isolated human antibody") that retains MAb230's specificity and relative affinity for hIL-4R.

Although neither Hart nor Schering-Plough explicitly teaches an antibody that performs the '487 Patent's functional limitation—"that competes with a "reference antibody"—Dr. Zurawski found that the '487 Patent's "competes" limitation an inherent functional characteristic of Hart's MAb230. *See supra*

Section VII(A)(4). And it is well settled that "[i]t is not invention to perceive that the product which others had discovered had qualities they failed to detect." *Gen. Elec. Co. v. Jewel Incandescent Lamp Co.*, 326 U.S. 242, 249 (1945); *see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) ("To hold otherwise would allow any formulation – no matter how obvious – to become patentable merely by testing and claiming an inherent property."). "[I]nherency may supply a missing claim limitation in an obviousness analysis" if the limitation-at-issue is "necessarily . . . present, or the natural result of the combination of elements explicitly disclosed by the prior art." *PAR Pharm., Inc. v. TWI Pharms., Inc*., 773 F.3d 1186, 1194–96 (Fed. Cir. 2014).

Here, at least one species of the '487 Patent's claimed genus of human antibodies that "compete[]" with a reference antibody is the natural result of humanizing Hart's MAb230 according to Schering-Plough's CDR grafting techniques. Ex. 1400 ¶140. As explained above, MAb230 possesses the inherent ability[14] to compete with MAb 12B5. *See In re Papesch*, 315 F.2d 381, 391 (CCPA

[14] In other words, MAb230 bound to hIL-4R with the requisite specificity to compete with mAb 12B5 long before mAb 12B5 was first isolated. Ex. 1204 at 2091–92 (relying on MAb230's specificity for hIL-4R to assess IL-4 and IL-13

1963) ("From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing."). Also as explained above, it would have been obvious for a POSITA to engineer MAb230's binding-determinant residues into a human framework to derive a humanized antibody that retains MAb230's specificity and relative affinity for hIL-4R. Because the humanized antibody would have been engineered to bind to hIL-4R with MAb230's specificity and relative affinity, it would have necessarily exhibited the same binding functions as MAb230. Ex. 1400 ¶141–42. This includes MAb230's known functions, such as inhibiting IL-4 and IL-13 activity, as well as its inherent functions, such as competing with mAb 12B5, because each of these functions directly flows from MAb230's specificity for hIL-4R. Ex. 1400 ¶141–42.[15] Accordingly, the necessary consequence of replicating MAb230's binding

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signaling in MDMac in 1998); Ex. 1206 at 0015 (advertising MAb230's specificity for hIL-4R in 1996).

[15] Skilled artisans generally perform competition assays to assess antibody specificity. Ex. 1007 at 8:31–40, 10:21–26, Table II (using "cross-competition" assays to characterize the relative specificities of anti-hIL-4R antibodies); Ex. 1026 at 665 (teaching, under the heading "[c]ompetition assays," that "[f]low cytometric analyses were performed in order to determine the epitope specificity . . .").

characteristics in a humanized equivalent is an antibody that—like MAb230—competes with mAb 12B5. *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999) ("Where . . . the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results.").

As explained in Dr. Zurawski's declaration and illustrated by the following examples,[16] it was well-known that a murine antibody's competitive functionality is preserved during the humanization process. Ex. 1400 ¶¶143–47; Ex. 1405 10032–33, Fig. 4 (showing that a successfully humanized anti-hIL-2R antibody retained its murine parent's competitive characteristics); Ex. 1406 at (explaining that "the humanized antibodies compete approximately as well as the corresponding mouse antibodies . . ."); Ex. 1413 at 971–72, Fig. 4 ("In competitive binding assays, the resurfaced[17] N901 and anti-B4 antibodies were equal to murine

[16] Petitioners may demonstrate inherency with examples and expert testimony explaining the relationship between humanizing MAb230 and retaining its ability to compete with mAb 12B5. *Par Pharm., Inc. v. TWi Pharms., Inc.*, 120 F. Supp. 3d 468, 473–75 (D. Md. 2015), *aff'd*, 624 F. App'x 756 (Fed. Cir. 2015).

[17] The phrase "resurfaced N901 and anti-B4" refers to humanized versions of murine antibodies named N901 and anti-B4. Ex. 1413 at 969.

N901 or murine anti-B4 . . ."); Ex. 1414 at 25:50–63, 33:57–34:30, Fig. 4B (determining by competition assay that "Vitaxin," a humanized antibody to $\alpha_v\beta_3$, "maintains essentially all of the binding characteristics and specificity exhibited by the parental murine monoclonal antibody").

Thus, the natural result of converting MAb230 into a humanized equivalent—as explicitly rendered obvious by Hart and Schering-Plough—is a human antibody that retains MAb230's competitive functionalities, including its inherent ability to compete with the '487 Patent's reference antibody for binding to hIL-4R. *PAR Pharm.*, 773 F.3d at 1194–95. Regardless of whether it was known in the prior art that MAb230 "competes" with mAb 12B5, Hart teaches that MAb230 binds to a therapeutically relevant epitope on hIL-4R (*i.e.*, one that interferes with IL-4 and IL-13 signaling), and, as discussed *infra*, a POSITA would have been motivated to derive a humanized antibody that likewise binds to MAb230's therapeutically relevant epitope. Ex. 1204 at 2091–92; Ex. 1400 ¶141. In doing so, a POSITA would have derived a humanized antibody that competes with mAb 12B5, even if the POSITA did not appreciate this inherent functionality at the time. Ex. 1400 ¶141; *In re Kubin*, 561 F.3d 1351, 1357–58 (Fed. Cir. 2009) (quoting *In re Wiseman*, 596 F.2d 1019, 1023 (CCPA 1979) as "rejecting the notion that 'a

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structure suggested by the prior art, and, hence, potentially in the possession of the public, is patentable . . . because it also possesses an inherent, but hitherto unknown, function which [patentees] claim to have discovered."). Accordingly, the combination of Hart and Schering-Plough renders obvious at least one species of "isolated human antibody that competes with a reference antibody" of Claim 1.

A POSITA would have been motivated to combine Hart with Schering-Plough to derive at least one species of the '487 Patent's claimed genus of antibodies. As explained above, skilled artisans knew that hIL-4R was a "perfect target" for therapeutics because of its key role in mediating allergic disorders. *See supra* Section VIII(A)(1). Schering-Plough expressly motivates a POSITA to humanize murine anti-hIL-4R blocking antibodies to derive potential therapeutics "for long term treatment of allergic disorders." Ex. 1007 at 2:18–22, 6:30–35. Hart, in turn, teaches MAb230—a murine anti-hIL-4R blocking antibody. Ex. 1204 at 2091–92. Thus, from the explicit teachings of Schering-Plough, a POSITA would have been motivated to combine Schering-Plough with Hart to isolate a potential therapeutic for allergic disorders. Ex. 1400 ¶132.

In fact, a POSITA would have known that Hart's MAb230 was an excellent candidate with which to conduct Schering-Plough's humanization because Hart teaches that MAb230 was able to block both IL-4 and IL-13 signaling activity. Ex. 1204 at 2091–92, Fig. 8. While Schering-Plough does not expressly teach IL-13

inhibition, Hart does, and by May 1, 2001, a POSITA would have known that it is particularly desirable to humanize anti-hIL-4R blocking antibodies that block both IL-4 and IL-13 activity because these cytokines mediate many overlapping immunogenic functions, at least in part due to the shared IL-4Rα receptor subunit. *See supra* Sections V(A), VII(A)(1); Ex. 1400 ¶39.

Furthermore, it was generally known in the art that it is desirable to use a highly potent antibody as a precursor for a humanized antibody therapeutic. Ex. 1400 ¶148. A POSITA would have known that MAb230 is an exceptionally potent blocking antibody because R&D System's 1996 anti-cytokine antibody catalog discloses that MAb230 has a 50% neutralization constant ("ND_{50}") of 0.003–0.006 ug/mL. Ex. 1206 at 0015; Ex. 1400 ¶49. As would have been known to a POSITA, MAb230's advertised ND_{50} converts to a 50% inhibition constant ("IC_{50}") in the range of 20–40 pM. Ex. 1400 ¶49. For comparative purposes, the anti-hIL-4R blocking antibodies disclosed in Schering-Plough exhibit IC_{50}s between 0.7 and 3.6 **n**M (*i.e.*, 700 and 3,600 **p**M). Ex. 1007 at Table I. In other words, MAb230 is approximately 50-fold more potent than the anti-hIL-4R blocking antibodies specifically taught as therapeutic candidates in Schering-Plough. Accordingly, a POSITA would have appreciated that MAb230 is an especially potent blocking antibody and thus a promising candidate from which to derive a therapeutic. Ex. 1400 ¶148.

In addition to being motivated to combine Hart and Schering-Plough, a POSITA would have had a reasonable expectation of success in isolating at least one species of the '487 Patent's claimed genus of antibodies from this combination. As explained above, humanization techniques were well-developed by May 1, 2001, and skilled artisans would have reasonably expected to apply these techniques to transform MAb230 into a promising therapeutic with the same specificity and relative affinity for hIL-4R. Ex. 1400 ¶¶56, 149; Ex. 1007 at 5:5–8; Ex. 1405 at 10033. For example, in connection with the humanized anti-hIL-2R antibody derived in Queen ("anti-Tac"), the authors confirmed that humanized "anti-Tac" antibody retained the binding specificity and relative affinity of its murine parent by performing a competitive binding assay for cells that express hIL-2R.[18] Ex. 1405 at 10030–32. Specifically, as shown in Figure 4 of Queen, the humanized anti-Tac antibody was able to compete with its murine parent

[18] IL-2R is closely related to IL-4R. *See, e.g.*, Ex. 1426 at 113 ("The receptors for IL-4 and IL-2 have several features in common; both use the γc as a receptor component, and both activate the Janus kinases JAK-1 and JAK-3."); Ex. 1014 at 271 (observing that the IL-4/IL-4Rα complex "is likely the paradigm for the receptors of IL-2, IL-7, IL-9, and IL-15").

(represented by triangles) nearly as well as its murine parent was able to compete with itself (represented by circles) for binding to cells that express hIL-2R.

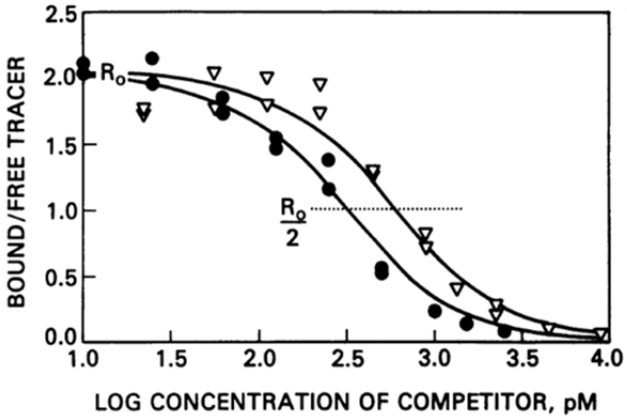

FIG. 4. Competitive binding of labeled anti-Tac tracer to Hut-102 cells. Duplicate samples are shown. ●, Mouse anti-Tac competitor; ▽, humanized anti-Tac competitor.

Ex. 1405 at 10033, Fig. 4; Ex. 1400 ¶143. Accordingly, the authors were able to confirm that the humanized anti-Tac retained the binding characteristics of its murine parent. Ex. 1405 at 10029, 32–33.

In view of Schering-Plough's explicit teachings to humanize murine anti-hIL-4R antibodies, Queen's successful humanization of an antibody to hIL-2R (a closely related receptor to hIL-4R) and the "over 100 then known examples in which humanisation of the variable domains had been successfully achieved," Ex. 1409 at 33, a POSITA would have had a reasonable expectation of success in isolating a humanized antibody that retains MAb230's specificity and relative affinity for hIL-4R. Ex. 1400 ¶149. A POSITA thus would have been motived to isolate a humanized antibody—*i.e.*, "an isolated human antibody"—that retains the

binding characteristics of MAb230—*i.e.*, "competes" with a '487 Patent reference antibody for binding to hIL-4R—and would have had a reasonable expectation of success in doing so.

Patent Owner may argue that a POSITA would not have been motivated to humanize MAb230 because it was merely a laboratory reagent. This argument is unavailing because it is based on a distinction without difference. Every murine antibody is both a laboratory reagent and potential parent to a humanized antibody with therapeutic potential. Ex. 1420 (recounting the background of Alemtuzumab, a humanized antibody that was FDA approved in 2001, which "started life, in 1979, not as a drug but as a laboratory tool for understanding why the immune system can mount an attack against foreign invaders, such as bacteria and viruses"); Ex. 1406 at 20:54–21:10 (noting that Queen's anti-Tac antibody was originally used to elucidate the human IL-2 receptor's structure and function). The very point of humanization is that it "allows access to a large pool of well characterized rodent mAbs [*e.g.*, MAb230] for therapy." Ex. 1410 at 139. Thus, irrespective of whether MAb230 was commonly used as a laboratory reagent, its well-known ability to inhibit IL-4 and IL-13 activity would have motivated a POSITA to humanize it to derive a potential therapeutic for allergic diseases.

Patent Owner may also argue that a POSITA could not have been motivated to isolate an antibody that competes with the '487 Patent's reference antibody

before May 1, 2001 because the reference antibody was not publically known prior to May 1, 2001. This argument is a red herring. As explained in *KSR*, "[i]n determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103." *KSR Intern. Co. v. Teleflex Inc*., 127 S. Ct. 1727, 1741–42 (2007). Here, Patent Owner's broad, functional claims extend to a humanized version of MAb230, which would have been obvious for a POSITA to isolate prior to May 1, 2001. It is irrelevant whether the '487 Patent's "reference antibody" (*e.g.*, mAb 12B5) was known to a POSITA before May 1, 2001, because a POSITA would have been motivated to generate a humanized version of MAb230 as a potential therapeutic for allergic diseases, *not* by knowledge of the '487 Patent's reference antibody.

Accordingly, the combination of Hart and Schering-Plough renders obvious a humanized antibody that embodies every limitation of Claim 1 of the '487 Patent.

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."*

Claim 2 of the '487 Patent is obvious for similar reasons. As shown in Section VII(A)(4), Dr. Zurawski found that the '487 Patent's reference antibody inhibits MAb230 from binding to hIL-4R. Because it would have been obvious for a POSITA to isolate a humanized antibody that retains MAb230's binding characteristics, Claim 2's isolated human antibody that is inhibited by the '487 Patent's reference antibody from binding to IL-4R is obvious. Ex. 1400 ¶¶153–54.

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."*

The same analysis applies to Claim 3. As shown in Section VII(A)(4), Dr. Zurawski confirmed that MAb230 inhibits the reference antibody from binding to hIL-4R. Because it would have been obvious for a POSITA to isolate a humanized antibody that retains MAb230's binding characteristics, Claim 3's isolated human antibody that inhibits the '487 Patent's reference antibody from binding to hIL-4R is obvious. Ex. 1400 ¶157.

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."*

Hart teaches that MAb230 is a "blocking antibody to IL-4Rα," which means that it inhibits the binding of IL-4 to IL-4R. Ex. 1204 at 2091; Ex. 1400 ¶160. This is further shown in Figure 8 of Hart, which depicts that MAb230 neutralizes the

effects of IL-4 induced IL-1β and TNF-α suppression in monocytes and MDMac. Ex. 1204 at 2092; Ex. 1400 ¶47. Because it would have been obvious for a POSITA to isolate a humanized antibody that retains MAb230's binding characteristics, Claim 4's "isolated human antibody . . . that inhibits the binding of human IL-4 to human IL-4 receptor" is obvious. Ex. 1400 ¶160.

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."*

Again, Hart teaches that MAb230 is a "blocking antibody to IL-4Rα." Ex. 1204 at 2091. As would have been known to a POSITA, because MAb230 blocks IL-4Rα, it blocks the IL-13/IL-13Rα1 complex from associating with IL-4Rα to form a ternary signaling complex. *See supra* Section V(A). This is shown in Figure 8 of Hart, which depicts that MAb230 neutralizes the effects of IL-13 induced IL-1β and TNF-α suppression in monocytes and MDMac. Ex. 1204 at 2092; Ex. 1400 ¶47. Accordingly, MAb 230 "inhibits the binding of human IL-13 interleukin-13 (IL-13) to human IL-4 receptor" to the extent that any antibody can do so. Ex. 1400 ¶¶163–165; *see also* Ex. 1225 at 2665 ("IL-13 does not bind to the IL-4R ligand binding protein"). Because it would have been obvious for a POSITA to isolate a humanized antibody that retains MAb230's binding characteristics, Claim 5's "isolated human antibody . . . that inhibits the binding of human IL-13 to human IL-4 receptor" is obvious. Ex. 1400 ¶¶163–165.

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."*

Because MAb230 blocks IL-4 from binding to IL-4R, it also inhibits IL-4 induced signaling through IL-4R. *See* Ex. 1204 at 2092–93 (teaching that MAb230 is "neutralizing antibody to IL-4Rα" and providing supporting experimental data in Figure 8); Ex. 1400 ¶168. This was confirmed by Dr. Zurawski using a CD23 assay like that described in Example 5 of the '487 Patent. Ex. 1400 ¶169, Fig. 4. Because it would have been obvious for a POSITA to isolate a humanized antibody that retains MAb230's binding characteristics, Claim 6's "isolated human antibody . . . that inhibits human IL-4 signaling through human IL-4 receptor" is obvious. Ex. 1400 ¶¶168–170.

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."*

Because MAb230 blocks the IL-13/IL-13Rα1 complex from associating with IL-4Rα, it also inhibits IL-13 induced signaling through IL-4R. *See* Ex. 1204 at 2092–93 (teaching that MAb230 is "neutralizing antibody to IL-4Rα" and proving supporting experimental data in Figure 8); Ex. 1400 ¶173. This was confirmed by Dr. Zurawski using a CD23 assay like that described in Example 5 of the '487 Patent. Ex. 1400 ¶174, Fig. 5. Because it would have been obvious for a POSITA to isolate a humanized antibody that retains MAb230's binding

characteristics, Claim 7's "isolated human antibody . . . that inhibits human IL-13 signaling through human IL-4 receptor" is obvious. Ex. 1400 ¶¶173–175.

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 [$1\times10^{8}/1\times10^{9}/1\times10^{10}$]."*

MAb230's reported ND_{50} value of 0.003–0.006 μg/mL (IC_{50} of 20–40 pM) corresponds to a binding affinity constant ("K_a") of at least 1×10^{10}. Ex. 1400 ¶181. As explained in Dr. Zurawski's declaration, a POSITA would have approximated MAb230's K_a at 9.1×10^{10} 1/M from its known IC_{50} value using prior art mathematical equations. Ex. 1400 ¶¶180–82. MAb230's affinity for hIL-4R was also measured in real time using a SPR-based assay. *See* Ex. 1400 ¶127 (providing detailed experimental protocol). The results show that MAb230 binds to hIL-4R with a binding affinity of 1.61×10^{12} 1/M under the specified parameters. Ex. 1400 ¶183, Table 3.[19]

As explained in Section VII(C)(1) above, the purpose of CDR grafting is to isolate a humanized antibody that retains the desirable binding characteristics of a

[19] As explained above, the way that one assesses affinity can materially impact the result. Neither the claims nor the specification of the '487 Patent provide guidance for how one should determine if the claimed "isolated human antibody" has "a binding affinity (Ka) of at least [$1\times10^{8}/1\times10^{9}/1\times10^{10}$]," as recited in claims 8–10.

known murine antibody. MAb230's high binding affinity is one of its desirable attributes, and a POSITA would have been motivated to replicate MAb230's affinity for hIL-4R in a humanized counterpart. Ex. 1400 ¶185; *see also* Ex. 1410 at 141 ("High binding affinities may be critical for neutralization of a cytokine . . ."). Although humanized antibodies sometimes exhibit slightly lower affinity than their murine parents, prior to May 1, 2001, skilled artisans had developed protocols to assist in the derivation of humanized antibodies with high affinity (such as those taught in Queen), and a POSITA would have reasonably expected that a humanized version of MAb230 would "retain substantially the same affinity as the donor immunoglobulin to the antigen (such as a protein or other compound containing an epitope)." Ex. 1406 at 3:34–43, 10:55–61; Ex. 1400 ¶185; *see also* Ex. 1405 at 10031–33; Ex. 1409 at 33. Given that MAb230 binds to IL-4R with an affinity of 1.61×10^{12} 1/M under the SPR assay described in Dr. Zurawski's declaration—which is more than one-hundred fold higher than the claim 10's threshold of 1×10^{10} 1/M—it would have been obvious for a POSITA to isolate a humanized equivalent that binds to hIL-4R with a binding affinity of at least 1×10^{10} 1/M. Ex. 1400 ¶186.

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

It would have been obvious for a POSITA to isolate a humanized version of Hart's MAb230 that is a full-length antibody. Schering-Plough teaches that, in humanizing an antibody, "the CDRs can be grafted into a human antibody variable region ***with*** or without ***human constant regions***." Ex. 1007 at 5:5–6 (emphasis added). A humanized antibody "with . . . human constant regions" is a full-length antibody. Ex. 1400 ¶189.

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."*

It would have been obvious for a POSITA to isolate a humanized version of Hart's MAb230 that is any one of the isotypes listed in Claim 12. Techniques for combining a selected constant region (*e.g.*, IgG1, IgM, etc.) with a humanized variable region, thus deriving an antibody of a chosen isotype, were well-known in the prior art. Ex. 1007 at 5:5–8; Ex. 1400 ¶192.

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

Schering-Plough teaches that humanized anti-hIL-4R blocking antibodies can be made into fragments. Ex. 1007 4:22–32, 5:27–33 (listing references and noting that "[t]he use and generation of fragments of antibodies are also well known"). It thus would have been obvious for a POSITA to derive an "isolated

human antibody . . . [that] is a fragment of an antibody" from a humanized version of Hart's MAb230. Ex. 1400 ¶195.

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

Schering-Plough teaches that humanized anti-hIL-4R blocking antibodies can be made into single chain antibodies or bi-specific antibodies, which are types of fusion proteins. Ex. 1007 at 4:25–32, 5:9–13; Ex. 1400 ¶¶198–99. Thus, it would have been obvious for a POSITA to derive an "isolated human antibody . . . [that] is a fusion protein" from a humanized version of Hart's MAb230.

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

Schering-Plough teaches that humanized anti-hIL-4R blocking antibodies "can be used to produce engineered antibodies and single-chain binding proteins [*i.e.*, scFv's] by standard methods." Ex. 1007 4:28–32, 5:9–13. Thus, it would have been obvious for a POSITA to derive an "isolated human antibody . . . [that] is a single chain antibody (scFv)" from a humanized version of Hart's MAb230. Ex. 1400 ¶201.

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

Schering-Plough teaches humanized anti-hIL-4R blocking antibodies where "at least one of the monoclonal antibodies . . . or binding fragments or single-chain Fvs thereof, [is] in a pharmaceutically effective carrier" and that "[p]harmaceutically acceptable adjuvants (buffering agents, dispersing agents) may also be incorporated into the pharmaceutical composition." Ex. 1007 at 6:30–42; *see also* 1007 at 2:51–3:6. Thus, it would have been obvious for a POSITA to derive an "isolated human antibody . . . [that is combined with] a pharmaceutically acceptable diluent, buffer, or excipient" from a humanized version of Hart's MAb230. Ex. 1400 ¶205.

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

Schering-Plough teaches humanized anti-hIL-4R blocking antibodies that are part of a "kit." Ex. 1007 at 6:6–30. Thus, it would have been obvious for a POSITA to derive Claim 17's "kit" with a humanized version of Hart's MAb230. Ex. 1400 ¶209.

D. Ground 2 – The Asserted Claims Are Unpatentable as Obvious Over Hart Combined with Schering-Plough and Hoogenboom

As an alternative to CDR grafting, which results in a humanized or partially human antibody, it also would have been obvious to convert Hart's MAb230 into a *fully human* antibody by Hoogenboom's EIS (Ex. 1402). Like CDR grafting, EIS would have resulted in a human anti-hIL-4R antibody based on MAb230. *See*

supra Section VII(A)3); Ex. 1402 at 13:7–9. Also like CDR grafting, MAb230's binding properties—including its inherent functional ability to compete with MAb 12B5—would have been retained by EIS. *See* Ex. 1402 at 27:1–5, 29:51–54 (observing "the retention of affinity, as well as specificity, through epitope imprinted selection"); 1402 at 26:20–29, Fig. 4 (observing that fine specificity is replicated by EIS because "[e]ach of the [EIS-derived] fragments competes with the [original antibody fragment] for binding to TNF . . ."); Ex. 1400 ¶217. Indeed, just as in CDR grafting, the "aim of guided selection [*i.e.*, EIS] is to confer all of the properties of binding specificity and affinity from the rodent antibody on to a human equivalent." Ex. 1403 at 174. The difference between CDR grafting and EIS is that the resultant antibody is partially human when derived by CDR grafting, yet "entirely human" when derived by EIS. Ex. 1402 at 10:35–45.

A POSITA would have been motivated to combine Hoogenboom with Schering-Plough and Hart. As explained above, the purpose of humanizing a murine anti-hIL-4R blocking antibody (such as MAb230) by CDR grafting is to replicate the murine antibody's binding characteristics in an antibody that is less immunogenic in humans. Ex. 1400 ¶217. Although humanized antibodies are often safe for use as human therapeutics, in some instances they may still trigger a HAMA response because they are partially composed of characteristically murine amino acid sequences (*e.g.*, at least in the CDRs). Ex. 1400 ¶214. Accordingly, EIS

is advantageous over CDR grafting in some cases because it results in fully human antibodies that "are likely to be better than conventional CDR-grafted humanized[20] antibodies, in the sense that they will be less likely to invoke an anti-idiotypic [*e.g.*, HAMA] response." Ex. 1402 at 13:40–45. Thus, a POSITA would have been motivated to combine the teachings of Hoogenboom with the teachings of Hart and Schering-Plough to derive a fully human antibody based on MAb230 as a potential therapeutic for allergic diseases. Ex. 1400 ¶214; Ex. 1007 at 2:1–23; *see also* Ex. 1205 at 20:6–7 (teaching that "this invention provides for fully human anti-IL-4R antibodies" and suggesting isolating such antibodies by "phage display screening"[21]).

Furthermore, a POSITA would have had a reasonable expectation of success in deriving at least one species of fully human antibody that falls within the '487 Patent's claimed antibody genus from the combined teachings of Hart,

[20] Hoogenboom sometimes refers to EIS as form of humanization. *See, e.g.*, Ex. 1402 at Abstract, 21:31–35. For clarity, as used in this Petition, the phrase "humanized" refers to partially human antibodies derived by CDR-grafting, such as taught in Schering-Plough and Queen.

[21] As noted in Section VII(A)(3) above, EIS is a type of phage display screening. *See also* Ex. 1400 ¶¶57–59; Ex. 1402 at Abstract, 24:40–60, 41:60–67.

Hoogenboom, and Schering-Plough. Ex. 1400 ¶219. Hoogenboom provides detailed disclosure of the successful isolation of a fully human anti-TNF antibody[22] that exhibited the same binding characteristics as the murine antibody upon which it was based—including competing with its murine parent for binding to TNF. Ex. 1402 at 26:20–29, Fig. 4; Ex. 1403 at 173–185 (providing step-by-step instructions for guided selection). Just as a murine anti-TNF antibody was successfully transformed into a fully human anti-TNF antibody with Hoogenboom's EIS, a POSITA would have expected to likewise achieve success in transforming Hart's MAb230 into a fully human anti-hIL-4R antibody by EIS. Ex. 1400 ¶219; *see also* Ex. 1404 at 991 (observing that guided selection provides "a simple means to deriving human Ab against cell surface Ag [*e.g.*, hIL-4R] for which a rodent Ab [*e.g.*, MAb230] is available").

The analysis with respect to Ground 2 of this Petition largely tracks the analysis with respect to Ground 1—the combination with Hoogenboom simply results in a fully human antibody rather than a partially human antibody. Ex. 1400 ¶221. Just as it would have been obvious for a POSITA to derive a humanized antibody that competes with the '487 Patent's reference antibody (Claim 1),

[22] Hoogenboom's exemplary antibody was ultimately branded HUMIRA, which has become a blockbuster drug.

cross-blocks the ’487 Patent’s reference antibody (Claims 2 and 3), inhibits IL-4 and IL-13 binding/signaling (Claims 4–7), and binds tightly to IL-4R (Claims 8–10) from Hart’s MAb230, so too would it have been obvious for a POSITA to derive a fully human version of Hart’s MAb230 by Hoogenboom’s EIS that retains these functional limitations. Ex. 1400 ¶221. As explained in Sections VII(C)(1)–(8) above, MAb230 binds to hIL-4R with the requisite specificity and affinity to possess each of the ’487 Patent’s claimed functions, either inherently or as explicitly taught in Hart. It would have been obvious for a POSITA to isolate a fully human version of MAb230 that also exhibits each of the ’487 Patent’s claimed functions using EIS because EIS would have replicated MAb230’s binding characteristics into a fully human antibody. Ex. 1400 ¶217–18, 21; Ex. 1402 at Abstract, 27:1–5, 29:51–54; Ex. 1403 at 174.

Analogously, a POSITA would have known that the teachings of Schering-Plough regarding the ’487 Patent’s claimed types of antibodies and derivatives (Claims 11–15) and antibody compositions (Claims 16–17) are also applicable to a fully human version of MAb230 derived by Hoogenboom’s EIS. Ex. 1400 ¶¶222–23. Regardless of whether an antibody is partially human or fully human, it was well-known in the prior art that it could be made into a full-length antibody of any isotype, fragmented, made into a single chain antibody and/or fusion protein, combined with a pharmaceutically acceptable buffer, or used as part

of a kit. Ex. 1400 ¶¶222–23; Ex. 1402 (Hoogenboom, 1996) at 7:55–67, 11:36–41 (explaining that EIS-derived antibodies are originally isolated as Fab or scFv fragments expressed on the surface of a phage); Ex. 1402 (Hoogenboom, 1996) at 6:1–12, 11:41–45 (explaining that EIS-derived antibodies may be transformed into full-length antibodies of any isotype or other derivatives); Ex. 1402 (Hoogenboom, 1996) at 9:17–30 (explaining that EIS-derived antibodies may be incorporated into kits and/or pharmaceutical compositions).

E. Any Secondary Considerations Patent Owner May Raise Do Not Overcome the Prima Facie Case of Obviousness

Patent Owner may attempt to identify purported secondary considerations of non-obviousness. Such an attempt would be in vain. Objective evidence of non-obviousness, even when available, cannot defeat a strong case of obviousness based on the prior art references themselves, as is the case here with the Hart, Schering Plough, and Hoogenboom references. *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364–65 (Fed. Cir. 2012). To rely on secondary considerations, the Patent Owner must further establish that the evidence is due to the claimed invention, and not from something already known in the art. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (holding that the evidence must be due to the claimed invention rather than something previously known in

the prior art). There is no relevant objective evidence of non-obviousness with respect to the ’487 Patent.

Patent Owner may assert that Stevens (Ex. 1006) evinces that Petitioners copied the ’487 Patent’s claimed invention because Stevens discloses that “U.S. Pat. No. 7,186,809; SEQ ID NOs: 10 and 12” was used as a control antibody. Any such argument by Patent Owner would be misguided.

First, Petitioners’ antibodies are neither copies nor derivatives of any of Patent Owner’s antibodies. Petitioners’ antibodies were isolated *de novo* by immunizing Petitioners’ proprietary VelocImmune mice with hIL-4R, generating hybridomas from the immunized mice, and screening the resultant antibodies for those that exhibited “desirable antigen binding affinity, potency, and/or ability to block hIL-4 binding to hIL-4R.” Ex. 1006 at 13:44–45. In Stevens, for example, Petitioners’ efforts resulted in twenty-three human anti-hIL-4R blocking antibodies that are unrelated to any antibody disclosed in the ’487 Patent.

Second, Patent Owner cannot demonstrate a nexus between its claimed invention and Petitioners’ antibodies. Patent Owner was not the first to isolate an antibody “that competes” with the ’487 Patent’s reference antibody. Dr. Zurawski determined that Hart’s MAb230 competes with the reference antibody for binding to IL-4R using an assay endorsed by Immunex. Ex. 1400 ¶¶111–20. Furthermore, Patent Owner’s “reference antibody”—*e.g.*, MAb 12B5—does not bind to IL-4R in

some new or unusual way. It antagonizes IL-4 and IL-13 activity by blocking IL-4Rα, as many prior art antibodies did before it. *See, e.g.*, 1204 at 2091 (disclosing MAb230); Ex. 1205 at 40–41 ("Antibodies that specifically bind to and block the IL-4 receptor ***are well known to those of skill in the art*** . . . [o]ne of skill in the art will appreciate that the antibodies may be human or humanized as described above.") (emphasis added). Moreover, no unexpected results are tied to the claims of the '487 Patent. While Patent Owner did not identify any unexpected results during prosecution of the '487 Patent, Patent Owner has asserted in a European Opposition proceeding on a related European patent that "[t]he technical problem to be solved is considered to be the provision of an inhibitory human anti-human IL-4R antibody to take forward into development as a therapeutic." Ex. 1201 ¶5.2. The '487 Patent does not disclose a solution to this problem. Patent Owner has not taken any anti-hIL-4R antibody to market, including the 12B5 antibody, so the '487 Patent does not facilitate the identification of an "antibody to take forward into development as a therapeutic." In fact, Patent Owner's parent entity, Amgen, tested a human anti-hIL-4R blocking antibody that was allegedly derived from the '487 Patent's reference antibody in clinical trials—called AMG-317, but it failed. *See* Ex. 1421 at 788. ("AMG 317 did not demonstrate clinical efficacy across the overall group of patients."); Ex. 1427 (indicating that AMG-317 refers to an antibody "with the light and heavy chain variable regions set forth in SEQ ID

NO:6 and SEQ ID NO:42, respectively, in U.S. Patent No. 7,638,606"). As explained in Example 5 of U.S. Patent No. 7,638,606 (Ex. 1428), SEQ ID NO:6 and SEQ ID NO:42 (*i.e.*, AMG-317) are the result of affinity maturing the '487 Patent's reference antibody. Ex. 1428 at 63:31–64:12 (explaining that SEQ ID NOs 6 and 42 are derivatives of the antibody that "was isolated as described in Example 8 of WO 01/92340," which is identical to the '487 Patent's example 8).

VIII. CONCLUSION

For the foregoing reasons, Petitioners respectfully request institution.

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Respectfully submitted,

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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 13,643 words, excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

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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 July 31, 2017, a complete copy of this Petition for *Inter Partes* Review and all exhibits were served on Patent Owner at the correspondence address of record listed below by FedEx®:

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