UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.
Petitioner

v.

GENENTECH, INC.
Patent Owner

U.S. Patent No. 9,249,218
Issue Date: February 2, 2016
Title: PROTEIN PURIFICATION

Inter Partes Review No. Unassigned

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,249,218 UNDER 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42

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(Filed Pursuant to 37 C.F.R. § 42.6)

Pfizer Exhibit Number	Description
1001	U.S. Patent No. 9,249,218 to Basey, C. D. and Blank, G. S., *Protein Purification* ("'218 patent")
1002	Declaration of Drew N. Kelner, Ph.D. ("Kelner Decl.")
1003	File History excerpts for U.S. Appl. Ser. No. 13/313,931, which issued as the '218 patent ("'931 file history")
1004	International PCT Publication No. WO 1997/04801 to Andya, J., et al., *Stable Isotonic Lyophilized Protein Formulation* ("Andya")
1005	Harris, R. J., *Chromatographic Techniques for the Characterization of Human Mabs*, Waterside Monoclonal Conference, Omni Waterside Hotel, Norfolk, Virginia, April 22, 1996 ("Waterside")
1006	International PCT Publication No. WO 1992/22653 to Carter, P. J., et al., *Method of Making Humanized Antibodies* ("Carter PCT")
1007	Harris, R. J., *Processing of C-Terminal lysine and arginine residues of proteins isolated from mammalian cell culture*, Journal of Chromatography A, 1995, 705, 129-134 ("Harris")
1008	Carter, P., et al, *Humanization of an Anti-p185^{HER2} Antibody for Human Cancer Therapy*, Proceedings of the National Academy of Sciences USA, 1992, 89, 4285-4289 ("Carter 1992")
1009	Chothia, C., et al., *Conformations of immunoglobulin hypervariable regions*, Nature, 1989, 342,877-883 ("Chothia")

1010	Cacia, J., et al., *Isomerization of an Aspartic Acid Residue in the Complementarity-Determining Regions of a Recombinant Antibody to Human IgE: Identification and Effect on Binding Affinity*, Biochemistry, 1996, 35, 1897-1903 ("Cacia")
1011	Geiger, T. and Clarke, S., *Deamidation, isomerization, and racemization at asparaginyl and aspartyl residues in peptides. Succinimide-linked reactions that contribute to protein degradation*," J. Biol. Chem., 1987, 262, 785-94 ("Geiger")
1012	Aswad, D. W., *Deamidation and Isoaspartate Formation in Peptides and Proteins*, Chs. 1, 2, 5, 6, 10 and 13, pp. 1-29, 65-113, 167-191, and 229-251, CRC Press, Inc., 1995 ("Aswad")
1013	International PCT Publication No. WO 1992/57134 to Basey, C. D. and Blank, G. S., *Protein Purification By Ion Exchange Chromatography* ("Basey PCT")
1014	European Patent No. EP 1 308 455 B9 to Basey, C. D. and Blank, G. S., *A composition comprising anti-HER2 antibodies* ("EP '455")
1015	Declaration of Richard Buick, Ph.D. ("Buick Decl.")
1016	Padlan, E. A., et al., *Structure of an antibody-antigen complex; Crystal structure of the NyHEL-10 Fab-lysozyme complex*, 1989, 86, 5938-5942 ("Padlan")
1017	Harris, R. L. et al., *Identification of multiple sources of charge heterogeneity in a recombinant antibody*, Journal of Chromatography. B. Biomedical Sciences & Applications, 2001, 752, 233-245 ("Harris 2001")
1018	File History excerpts for U.S. Appl. Ser. No. 12/418,905, which was abandoned ("'905 file history")
1019	Jordan, M., et al., *Transfecting mammalian cells: optimization of critical parameters affecting calcium-phosphate precipitate formation*, Nucleic Acids Research, 1996, Vol. 24, No. 4, pp. 596-601 ("Jordan 1996")

1020	Declaration of Keith L. Carson ("Carson Decl.")
1021	Eigenbrott, C., et. al., *X-ray Structures of the Antigen-binding Domains from Three Variants of Humanized anti-p185Her2 Antibody 4D5 and Comparison with Molecular Modeling*, J. Mol. Biol., 1993, vol. 229, pp. 969-995 ("Eigenbrott")
1022	Gagnon, P., *Ion/Exchange Chromatography*, Purification Tools for Monoclonal Antibodies Validated Biosystems, Inc., Tucson, 1996, Ch. 4, pp. 57-86 ("Gagnon")
1023	Jefferis R. and Lefranc M.-P., *Human immunoglobulin allotypes*, mAbs, 2009, 1, 332-338 ("Jefferis")
1024	Kroon, D. J., et al., *Identification of Sites of Degradation in a Therapeutic Monoclonal Antibody by Peptide Mapping*, Pharm. Res., 1992, 9, 1386-1393 ("Kroon")
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I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42 et seq., Petitioner Pfizer, Inc. petitions for *Inter Partes* Review ("IPR") of claims 1 and 5-7 ("Challenged Claims") of U.S. Patent No. 9,249,218 ("'218 patent," Ex. 1001). With this Petition is a Power of Attorney pursuant to 37 C.F.R. §42.10(b); and pursuant to 37 C.F.R. §42.103, the fee set forth in §42.15(a).

This Petition establishes that the Challenged Claims are invalid over the prior art and should be cancelled. Anticipating prior art disclosed the same anti-HER2 antibody, with the same "acidic variant," and with levels of the acidic variant falling within the scope of the Challenged Claims. General knowledge of the person of ordinary skill in the art ("POSA") as of the filing date of the '218 patent further render the claims obvious in view of the cited art.

II. MANDATORY NOTICES – 37 C.F.R. § 42.8(A)(1) AND (B)

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

Pfizer, Inc. ("Pfizer" or "Petitioner") is the real party-in-interest.

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

A petition requesting IPR of the '218 patent was filed on August 29, 2017. (IPR2017-02020.) The '218 patent has been asserted in *Genentech, Inc. et al v. Pfizer, Inc.*, (17-cv-01672) (D. Del.). The complaint in that litigation was served on November 20. 2017.

The ’218 patent is also related to U.S. Patent Nos. 6,339,142, 6,417,335, 6,489,447, 7,074,404, and 7,531,645. In addition, U.S. Appl. Ser. Nos. 14/988,657 and 15/494,362 claim priority, directly or indirectly, to the ’218 patent.

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

Petitioner designates the following counsel:

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

Please address all correspondence to lead counsel at the contact information above. Pfizer consents to service by electronic mail at tmeloro@willkie.com and mjohnson1@willkie.com. A Power of Attorney is being filed concurrently herewith under 37 C.F.R. § 41.10(b).

III. PAYMENT OF FEES – 37 C.F.R. § 42.103

The undersigned authorizes the Patent Office to charge the fee set forth in 37 C.F.R. § 42.15(a) for this Petition and any additional fees that may be due to deposit account 232405.

IV. GROUNDS FOR STANDING – 37 C.F.R. § 42.104(A)

Petitioner certifies that the '218 patent is available for IPR, and that Petitioner is not barred or estopped from requesting IPR of any claim of the '218 patent on the grounds set forth herein. 35 U.S.C. § 315.

V. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

IPR of claims 1 and 5-7 of the '218 patent under pre-AIA 35 U.S.C. §§ 102 and 103 is requested. Pursuant to 37 C.F.R. § 42.6(c), copies of the Exhibits are filed herewith. This Petition is supported by the declarations of Drew N. Kelner, Ph.D. (Ex. 1002), Richard Buick, Ph.D. (Ex. 1015), and Keith L. Carson (Ex. 1020).

Pursuant to 37 C.F.R. §§ 42.104(b)(1) and (2), the following grounds are offered as reasons for cancelling the Challenged Claims of the '218 patent:

Ground	Reference(s)	Statutory Basis	Claims
1	Andya (Ex. 1004)	§ 102(b)	1 and 5-7
2	Andya (Ex. 1004)	§ 103(a)	1 and 5-7
3	Waterside (Ex. 1005)	§ 103(a)	1 and 5-7
4	Harris (Ex. 1007)	§ 103(a)	1 and 5-7

VI. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW

A petition for IPR must demonstrate "a reasonable likelihood that the petitioner would prevail with respect to at least one of the claims challenged in the petition." 35 U.S.C. §314(a). This Petition meets and exceeds this threshold

because there is more than a reasonable likelihood that Petitioner will prevail with respect to at least one of the Challenged Claims.

VII. STATEMENT OF THE PRECISE RELIEF REQUESTED

A. Summary of the Argument

The Challenged Claims are directed to compositions of humMAb4D5-8, an anti-HER2 antibody, comprising certain levels of acidic variants, predominantly deamidated at asparagine, and further where the deamidation occurs at asparagine position 30 ("Asn30") to form an aspartate residue. (Ex. 1002, ¶¶38-40.) The Challenged Claims are not novel, as humMAb4D5-8 compositions having less than the claimed amounts of acidic variant were disclosed in the prior art. (§VIII.A-D; Ex. 1002, ¶¶141-282.) Moreover, the prior art taught that deamidation of asparagine is a major degradation pathway for all antibodies, not just humMAb4D5-8. (Exs. 1002, ¶¶105-114; 1012.)

Claims 1 and 5-7 were anticipated by Andya (Ground 1). (§VIII.A; Ex. 1002, ¶¶142-187.) Andya disclosed aqueous pharmaceutical formulations of humMAb4D5-8 that have been reconstituted from lyophilized material. (§VIII.A.1; Ex. 1002, ¶¶142-144.) Andya also taught that deamidation at Asn30 is the "predominant" acidic variant for humMAb4D5-8 in solution. (§VIII.A.1.b; Ex. 1002, ¶¶145-155.) Analysis of the reconstituted humMAb4D5-8 solutions shows that the compositions contain less than the claimed amounts of all acidic variants,

and therefore less than the claimed amount of the deamidated Asn30 acidic variant. (§VIII.A.1.c; Ex. 1002, ¶¶156-160.) The humMAb4D5-8 acidic variants having deamidated asparagine are thus necessarily the "predominant" acidic variant, as required by the Challenged Claims, because they are the *only* acidic variant observed in humMAb4D5-8, and thus Andya disclosed a composition where the total acidic variant concentration is within the claimed concentration. (§VIII.A.1.c; Ex. 1002, ¶¶151-153.) Andya further disclosed the humMAb4D5-8 amino acid sequence, and humMAb4D5-8 compositions for the treatment of HER2-related disorders and pharmaceutically acceptable carriers. (§§VIII.A.1.a, d; Ex. 1002, ¶¶142-144, 161-163, 183-187.) Accordingly, Andya *explicitly* anticipates the Challenged Claims of the '218 patent. (Ex. 1002, ¶¶144, 155, 160, 163, 184, 186.)

To the extent the prior art is found not to explicitly disclose humMAb4D5-8 compositions having the deamidated Asn30 acidic variant in CDR1 of the light chain variable region (V_L) of humMAb4D5-8 converted to aspartate, as required by claim 1, such a disclosure is *inherently* present in the prior art compositions. (Ex. 1002, ¶¶164-182.) In order to confirm that the deamidated Asn30 acidic variant is necessarily and inevitably formed when practicing the prior art, Dr. Richard Buick expressed, purified and analyzed the humMAb4D5-8 antibody as described in the prior art. (§VIII.A.2; Exs. 1002, ¶¶167-177; 1004; 1005; 1007;

1008; 1015, ¶¶5-69; 1017; 1019; 1023.) The humMAb4D5-8 antibody was expressed in both Chinese Hamster Ovary ("CHO") cells and human embryonic kidney ("HEK") cells, and compared with humMAb4D5-8 from commercial trastuzumab. (Exs. 1002, ¶¶168-170; 1015, ¶¶16-67; 1019.) In each case, CHO and HEK humMAb4D5-8 was found to be comparable to the commercial antibody, and at least one acidic variant was observed in each sample. (Exs. 1002, ¶171; 1004; 1005; 1007; 1015, ¶¶47-67.) Moreover, sequence data of a peptide digest of peak 1 of commercial trastuzumab confirmed the presence of the deamidated Asn30 acidic variant in the commercial composition. (Exs. 1002, ¶¶172-174; 1015, ¶¶59-61, Figures E, F.) Comparison to HEK- and CHO-derived humMAb4D5-8 using cation-exchange chromatography ("CEX") showed the same acidic variant. (Exs. 1002, ¶175; 1015, ¶62-65, Figure G.) Furthermore, deamidation of asparagine was the *only* acidic variant observed from the commercial source. (Exs. 1002, ¶¶174-176; 1015, ¶¶59-61, Figures E, F.) Thus, Dr. Buick's analysis is consistent with teachings in the art that deamidation of asparagine is the *only* acidic variant observed for humMAb4D5-8. (Ex. 1002, ¶¶174, 180, 236; 1004; 1005; 1007.) Accordingly, Andya explicitly and/or *inherently* anticipates the Challenged Claims of the '218 patent. (Ex. 1002, ¶¶187.)

The Challenged Claims, would also have been obvious over any one of Andya, Waterside, or Harris in combination with the general knowledge of a POSA (Grounds 2-4). (Ex. 1002, ¶¶220-282.) Andya, Waterside, and Harris all disclose that humMAb4D5-8 is deamidated to form an acidic variant. This deamidation occurs at asparagine 30 (Asn30). (§VIII.A.1.b, VIII.B.1.b, VIII.C.1.b, VIII.D.1.b; Ex. 1002, ¶¶145-155, 192-195, 226-234, 262-264.) A POSA would have been aware of the humMAb4D5-8 amino acid sequence, and would also have known that humMAb4D5-8 compositions, in pharmaceutically acceptable carriers, were useful for the treatment of HER2-related disorders. (§VIII.A-D; Ex. 1002, ¶¶183-187, 210-216, 248-253, 275-279.) A POSA would have been motivated to obtain a humMAb4D5-8 composition having a level of acidic variants at least as low as that described in the prior art because the deamidation in humMAb4D5-8 acidic variants was known to occur in the antibody recognition region, and were known to exhibit reduced activity. (§VIII.B.1.c; Ex. 1002, ¶156-160, 196-206, 235-243, 265-271.)

Further, a POSA would have had a reasonable expectation of success in obtaining a humMAb4D5-8 composition having an amount of acidic variants falling within the scope of the Challenged Claims based on Andya, Waterside and Harris. (Ex. 1002, ¶¶199-204, 242, 270.) Andya, Waterside, and Harris all teach compositions having levels of acidic variant that fall within the scope of the

Challenged Claims. (§VIII.A.1.c, VIII.B.1.c, VIII.C.1.c, VIII.D.1.c; Ex. 1002, ¶¶157-159, 236-240, 266-267.) A POSA would have known that CEX was the method of choice for separating proteins based on charge difference and therefore could be readily used to reduce the amount of acidic variants in protein compositions. (§VIII.B.1.c; Ex. 1002, ¶¶115-125.) A POSA would also have had a reasonable expectation of success in obtaining a therapeutic humMAb4D5-8 composition in a pharmaceutically acceptable carrier based on their general knowledge and the state of the art. (Ex. 1002, ¶¶207-209, 244-247, 272-274.) Thus, a POSA would have been motivated and able to obtain a humMAb4D5-8 composition having a level of acidic variants at least as low as that disclosed in the prior art. (Ex. 1002, ¶¶197-209, 240-247, 268-274.) Accordingly, the Challenged Claims would have been obvious over any one of these prior art references in combination with the general knowledge of the POSA. (Ex. 1002, ¶¶217-219, 254-256, 280-282.)

B. The ’218 Patent and Background

1. The ’218 Patent

The ’218 patent issued on February 2, 2016 from U.S. Appl. Ser. No. 13/313,931 (“’931 application”), which was filed on December 7, 2011. The ’931 application is a continuation of U.S. Appl. Ser. No. 12/418,905 filed April 6, 2009, which was abandoned. The ’218 patent claims priority to U.S. Provisional Appl.

Ser. No. 60/084,459 ("'459 provisional") filed May 6, 1998, the earliest priority date. International PCT Application No. PCT/US99/09637 ("Basey PCT," Ex. 1013.) and European Patent No. EP 1 308 455 ("EP '455," Ex. 1014), among other U.S. and foreign counterparts (Ex. 1002 ¶¶58-89), also claim priority to the '459 provisional.

The '218 patent has 7 claims, claim 1 being the sole independent claim. The '218 claims are directed to compositions comprising the humMAb4D5-8 anti-HER2 antibody comprising certain levels of "acidic variants" of humMAb4D5-8, where deamidation is the "predominant" acidic variant, and where amino acid Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 is converted to aspartate."

The '218 patent acknowledges that the full length amino acid sequence of humMAb4D5-8 was known, and that "humMAb4D5-8" was previously disclosed as "rhuMAb HER2." (Exs. 1001 at 20:39-43; Ex. 1002 at ¶¶ 53, 97.) The '218 patent also acknowledges that ion exchange chromatography is "commonly used for the purification of proteins," and that separation is based on the attraction between the charged protein (referred to as solute) and the chromatography matrix. (Exs. 1001, 2:9-10; Ex. 1002, ¶¶49.) Thus, the fact that ion-exchange chromatography resolves proteins based on charge was well known in the art and acknowledged by the '218 patent. (Ex. 1002, ¶¶50-52.)

The ’218 patent specification purports to disclose a novel ion exchange chromatographic method. (Ex. 1001, 17:60-66 (emphasis added).) This “reverse” wash step, however, is not claimed in the ’218 patent, and no methods limitations appear in the Challenged Claims. Thus, the purported novelty disclosed by the ’218 patent is not present in the Challenged Claims. Moreover, as discussed herein, the POSA would have had no difficulty obtaining a humMAb4D5-8 composition having the requisite levels of acidic variants, and in particular the Asn30 acidic variant, as evidenced by the prior art that disclosed such compositions, and the fact that methods to obtain such compositions were known to the skilled artisan prior to the ’218 patent.

The specification also makes clear that a novel chromatographic technique is not required in order to obtain a humMAb4D5-8 composition falling within the claims. (Ex. 1002, ¶¶43-48.) Example 1, the sole example in the ’218 patent, disclosed obtaining a humMAb4D5-8 composition in which “deamidated and other acidic variants constituted about 25% (calculated as area under the integrated curve or profile obtained by CSx chromatography) of the composition *obtained from the initial Protein A chromatography step*.” (Exs. 1001, 22:60-63; Ex. 1002, 45-46.) Thus, the inventors obtained a humMAb4D5-8 composition having 25% acidic variants, without performing *any* CEX. (Ex. 1002, ¶¶47-48.)

2. Prosecution History and Related Proceedings

a. U.S. prosecution history

'905 Application Prosecution. The '218 patent is a continuation of the '905 application, filed on April 6, 2009. (Exs. 1002, ¶¶58-63; 1018, 1.) The pending claims of the '905 application are nearly identical to the issued claims of the '218 patent. (Exs. 1002, ¶58; 1018, 2-6.)

The Patent Office rejected the pending claims as anticipated by Andya, stating that figures 5-8 "show 81-82% native protein at the start of each stabilization experiment. This means there are 18-19% non-native variants; this range is clearly 'less than about 25%.'" (Exs. 1002, ¶¶59-61; 1018, 20-26, 35-42, 71-80.) The Patent Owner did not respond to the last Office Action and the application was abandoned. (Exs. 1002, ¶62-63; 1018, 84.)

'931 Application Prosecution. The '218 patent issued from the '931 application, which was filed on December 7, 2011. (Exs. 1002, ¶55-57; 1003, 1.) Pending claims 32-38 are identical to issued claims 1-7, respectively. (Exs. 1002, ¶55; 1003, 19.)

Despite the nearly identical nature of the abandoned '905 claims and the '218 claims (*id*.), the sole rejection issued by the Patent Office was a double patenting rejection over the '404 patent, a family member having claims directed to methods for obtaining antibody compositions comprising similar levels of acidic

variant. (Exs. 1002, ¶¶56-57; 1003, 22-27.) After the filing of a terminal disclaimer, all pending claims were allowed. (Exs. 1002, ¶57; 1003, 29-40.)

b. Related foreign proceedings

European Patent No. 1 308 455 ("EP '455"), entitled "A composition comprising anti-HER2 antibodies," EP '455 was granted on March 22, 2006. (Exs. 1002, ¶74; 1014.) Claim 1 of EP '455 is nearly identical to claim 1 of the '218 patent. (Ex. 1002, ¶75)

EP '455 was challenged in *Hospira UK Limited v. Genentech Inc.*, HC12C03487 ("U.K. litigation," Ex. 1025.) The U.K. Court found that a "case for anticipation by Andya is proved." (Ex. 1002, ¶¶76-78.) The U.K. Court further held that Andya is an enabling disclosure, comprising no more than 18% acidic variants." (Ex. 1002, ¶¶77.) The Court also found that all of the claims of EP '455 lacked inventive step over Waterside. (Ex. 1002, ¶78.)

EP '455 was also revoked in a European opposition proceeding for lack of novelty over Andya (EP Appl. No. 02029008.6) (Ex. 1026), but reinstated on appeal. (Exs. 1002, ¶¶79-82; 1027.) With regard to Andya, the EP Technical Board of Appeal ("TBA") concluded that it did not "directly and unambiguously" disclose "the feature that the acidic variants are predominantly deamidated variants, wherein the deamidated variants have Asn30 in CDR1 of either or both VL regions of humMAb4D5-8 converted to aspartate." (Exs. 1002, ¶¶80; 1027,

¶13.) However, the facts and evidence before the TBA were different than those presented in this Petition. (*Id*.) First, it was apparently "undisputed" that Andya failed to explicitly disclose the features of claim 1 (Ex. 1027, ¶5), which is not the case here for the reasons presented in this Petition. (Ex. 1002 ¶80-81.) Second, the evidence presented in this Petition is not dependent on "starting materials [that] were clearly defined" in Andya. (Exs. 1002, ¶82; 1027, ¶13.) As discussed herein below, Andya both explicitly and inherently disclosed humMAb4D5-8 compositions meeting the Challenged Claims.

CN '836, entitled "Protein Purification by Ion Exchange Chromatography," issued on June 21, 2006. (Ex. 1002, ¶¶83.) Claims 1-3 of CN '836, collectively, are similar and recite the same limitations as claim 1 of the '218 patent. (Ex. 1002, ¶84.) The Intermediate Court in Beijing found that claims 1-3 of CN '836 were not novel or inventive over Andya. (Exs. 1002, ¶85; 1028, 9.) The High Court in Beijing affirmed, holding that Andya is "sufficient enough to prove that Claims 1-3 of the present patent do not possess inventiveness." (Exs. 1002, ¶86; 1029, 12.)

3. State of the Art as of the '218 Patent

Proteins were known to undergo deamidation of asparagine to form acidic variants, which can lead to "dramatic changes" in biological activity of the protein. (Exs. 1002, ¶¶105-114; 1011, 1024; 1012, 3-4.) Antibodies for therapeutic use were also known to be deamidated at asparagine to form acidic variants. (Exs.

1002, ¶¶ 109-114; 1011, Abstract, 785; 1024, 1386, 1389.) Deamidation of asparagine to aspartate was also known to be a major degradation pathway for proteins and antibodies, well before the filing of the '218 patent. (Exs. 1002, ¶¶113; 1012, 3-4.)

A POSA would also have known that CEX was capable of reducing the amount of acidic variants in a protein composition, and was the method of choice for doing so. (Ex. 1002, ¶¶115-125.) Acidic variants are charge variants, meaning they have a different charge than the native protein. (Exs. 1002, ¶¶124; 1012, 66-67.) As such, they can be separated using CEX because CEX was known to be able to separate mixtures of proteins, such as antibodies, based on charge differences. (Exs. 1002, ¶¶123-125; 1005; 1007; 1010; 1011; 1022; 1024.)

C. Level of Ordinary Skill in the Art

A person of ordinary skill in the art ("POSA") is presumed to be aware of the pertinent art, think along the line of conventional wisdom, and possess ordinary creativity in the relevant field. A POSA also has "common sense" and is "not an automaton." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420-21 (2007). The subject matter of the '218 patent relates to the purification of a monoclonal antibody. (Ex. 1002, ¶30.) The POSA for the '218 patent would have an advanced degree, such as a Ph.D., and several years of experience in a relevant discipline such as biochemistry, protein chemistry, analytical chemistry, and chemical and/or

biochemical engineering. (Ex. 1002, ¶31.) Such a person would also understand that protein purification is a multidisciplinary field. (*Id.*) As such they would work as part of an interdisciplinary team, and would benefit from the skills of others on that team using a collaborative approach. (*Id.*)

D. Claim Construction (37 C.F.R. § 42.104(b)(3))

In accordance with 37 C.F.R. § 42.100(b), the Challenged Claims must be given their broadest reasonable construction in light of the specification of the '218 patent. Except to the extent they are addressed below, the terms of the Challenged Claims should be accorded their ordinary and customary meaning based on the broadest reasonable construction of the claim language in view of the specification.

1. The term "therapeutic composition"

The term "therapeutic composition" in claim 1 of the '218 patent should be construed in accordance with its broadest reasonable construction to mean a composition appropriate for administration in a therapeutic treatment regimen, and should ***not*** be construed to require a specific amount of the composition, nor should it require a specific process or scale of manufacture. (Ex. 1002, ¶90.) Support for this construction comes from the claim itself, which contains no requirement for therapeutic effectiveness, nor does the claim contain limitations directed to a specific process or scale. (Ex. 1002, ¶91.) As such, a POSA would

not understand the term to be limited to any particular dose amount, process, or scale of manufacture. (*Id.*)

The intrinsic evidence also supports Petitioner's proposed construction. (*Id.*, ¶¶92-95.) The '218 patent specification disclosed, "'[t]reatment' refers to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include those already with the disorder as well as those in which the disorder is to be prevented." (Exs. 1001, 14:27-30; 1002, ¶92.) The '218 patent further disclosed, "[a] therapeutic formulation comprising the polypeptide, optionally conjugated with a heterologous molecule, may be prepared by mixing the polypeptide having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions." (Exs. 1001, 19:27-33; 1002, ¶93.) Neither of these definitions disclose a specific dose amount or treatment regimen. (Ex. 1002, ¶¶94.) Moreover, neither definition explicitly or implicitly requires the composition to be made by any specific process, or manufactured at any scale. (Ex. 1002, ¶¶95.) Thus, a POSA would understand that the term "treatment," as defined in the '218 patent, is not limited to any specific dose amount, process, or scale of manufacture. (Ex. 1002, ¶96.)

2. The term "humMAb4D5-8"

The term "humMAb4D5-8" should be construed to be synonymous with the terms "rhuMAb HER2" and "huMAb4D5-8."[1] (Ex. 1002, ¶97-100.) The '218 patent disclosed "[f]ull length human IgG ***rhuMAb HER2*** (***humAb4D5-8*** in Carter et al. *Proc. Natl. Acad. Sci.* 89: 4285-4289 (1992) [Carter 1992, Ex. 1008] comprising the light chain amino acid sequence of SEQ ID NO: 1 and heavy chain amino acid sequence of SEQ ID NO: 2) was produced recombinantly in CHO cells." (Exs. 1001, 20:39-43 (emphasis added); 1002, ¶97.) Therefore, the '218 patent disclosure explicitly characterizes the prior art terms "rhuMAb HER2" and "humAb4D5-8" to have the same amino acid sequence as "humMAb4D5-8," as disclosed in SEQ ID NOs l and 2 of the '218 patent. (*Id*.)

"Admissions in the specification regarding the prior art are binding on the patentee for purposes of a later inquiry into obviousness." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007) (citation omitted); *see also Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1569–70 (Fed. Cir. 1988) ("A statement in a patent that something is in the prior art is binding on the applicant and patentee for determinations of anticipation and

[1] The term "humMAb4D5-8" is also sometimes referred to as "humAb4D5-8" and "huMAb4D5-8." A POSA would have known that these terms all refer to a "humanized" (hum) monoclonal antibody (MAb) denoted "4D5-8," and thus these variations would be understood to be synonymous. (Ex. 1002, ¶98.)

obviousness." (citation omitted). Thus, the disclosure of the terms "rhuMAb HER2" and "humAb4D5-8" as comprising the amino acid SEQ ID NOs l and 2 of the '218 patent is binding on the Patent Owner.

In addition, named inventor Dr. Gregory Blank submitted a declaration to the Patent Office during prosecution of U.S. Appl. Ser. No. 12/418,905 ("'905 application), which is the immediate parent application from which the '218 patent claims priority as a continuation. (Exs. 1002, ¶99; 1018, 53-58.) In his declaration, Dr. Blank informed the Patent Office, "It is true that the rhuMAbHER2 antibody of Andya et al. [Ex. 1004] is the same as humMAb4D5-8 of the present application." (Exs. 1002, ¶99; 1018, 54.) "Prosecution history estoppel requires that the claims of a patent be interpreted in light of the proceedings in the PTO during the application process." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 122 S. Ct. 1831, 1838 (2002). As the Patent Owner has admitted that rhuMAbHER2 "is the same" as humMAb4D5-8 in the '218 patent, they are estopped from arguing otherwise.

The Patent Owner's consistent use of the term "rhuMAb HER2" repeatedly throughout Example 1, which is the sole embodiment disclosed in the patent, further supports Petitioner's proposed construction. (Exs. 1001, 20:67-21:1, 21:21-25, 55-56, 22:1-4, 57-59, 23:23-24:33, Table 3; 1002, ¶100.) A POSA would

therefore understand the term "rhuMAb HER2" to be synonymous with "humMAb4D5-8." (Ex. 1002, ¶¶100.)

3. The term "acidic variant"

The term "acidic variant" should be construed to mean a variant of a polypeptide of interest which is more acidic than the polypeptide of interest. (Ex. 1002, ¶¶101-104.) The '218 patent specification specifically defines the term, "[a]n 'acidic variant' is a variant of a polypeptide of interest which is more acidic (e.g. as determined by cation exchange chromatography) than the polypeptide of interest. An example of an acidic variant is a deamidated variant." (Exs. 1001, 5:60-63; 1002, ¶102.) The '218 patent specification further states that "a 'deamidated' variant of a polypeptide molecule is a polypeptide wherein one or more asparagine residue(s) of the original polypeptide have been converted to aspartate, *i.e.*, the neutral amide side chain has been converted to a residue with an overall acidic character." (Exs. 1001, 5:64-6:1; 1002, ¶103.) Moreover, according to the '218 patent specification, the deamidated humMAb4D5-8 antibody from Example 1 has "Asn30 in CDR1 of either or both of the VL regions thereof converted to aspartate." (Exs. 1001, 6:2-5; 1002, ¶104.) A POSA would understand that an aspartate has a more acidic side chain than asparagine. (Ex. 1002, ¶104.) Thus, the example uses the term "acidic variant" in a manner consistent with the definition provided by the specification. (*Id*.)

E. Prior Art Relied On In Grounds

Although Andya, Waterside, and Harris were before the Patent Office during prosecution of the '218 patent, they were not relied upon in a rejection under §102 or §103. (Ex. 1002, ¶¶127, 131, 134.) And while Andya was relied on for an anticipation rejection during prosecution of the parent '905 application, the Patent Owner abandoned that application without overcoming the rejection. (§VII.B.2.a; Ex. 1002, ¶¶58-63.)

1. Andya (Ex. 1004)

Andya is an International PCT Publication entitled *Stable Isotonic Lyophilized Protein Formulation*. (Ex. 1004.) Andya was published on February 13, 1997, which is more than one year before May 6, 1998, the earliest possible priority date of the '218 patent, and is therefore prior art under 35 U.S.C. § 102(b). (Ex. 1002, ¶¶126.)

Andya disclosed reconstituted compositions "comprising full length humanized antibody humMAb4D5-8." (§VIII.A.1.a; Ex. 1002, ¶¶127.) Andya further taught that deamidation occurs at Asn30 of humMAb4D5-8. (§VIII.A.1.b; Ex. 1002, ¶127.) Moreover, Andya taught "the major degradation route for rhuMAb HER2 in aqueous solutions is deamidation or succinimide formation." (*Id*.) Andya further taught a composition having 82% native humMAb4D5-8,

which could comprise no more than 18% acidic variant. (§VIII.A.1.c; Ex. 1002, ¶127.)

2. Waterside (Ex. 1005)

Waterside is printed copy of a slide presentation entitled *Chromatographic Techniques for the Characterization of Human Mabs* from the Waterside Monoclonal Conference on April 22, 1996. (Ex. 1005.) Waterside was available to the public as of April 22, 1996 (Ex. 1020, Carson Decl.), which is more than one year before May 6, 1998, the earliest possible priority date of the '218 patent, and is therefore prior art under 35 U.S.C. § 102(b). (Ex. 1002, ¶¶129.)

Waterside is a printed slide presentation that was made available at "The Waterside Monoclonal Conference," which was held on April 22 to 25, 1996. (Ex. 1020, ¶¶1-3.) The Conference was publicized to skilled persons in the field of monoclonal antibodies and recombinant protein processing and purification. (*Id.*, ¶¶4-5.) The attendees received a binder with printed slide presentations from the Conference. (*Id.*, ¶¶6-7.) Mr. Keith Carson was personally involved in the organization and proceedings of the Conference, and declares that Waterside (Ex. 1005) is a true and correct copy of an excerpt from the exhibit binder that was distributed at the Conference in 1996. (Ex. 1020, ¶¶8-12.) Thus, Waterside is a printed publication under 35 U.S.C. § 102(b). *See Captioncall, L.L.C., v. Ultratec Inc.*, Case No. IPR2013-00541, Paper 76, at 36-45 (PTAB March 3, 2015.)

Waterside disclosed cation-exchange chromatograms of the rhuMAb HER2 (humMAb4D5-8) antibody having an "acidic variant." (§VIII.C.1.c; Ex. 1002, ¶¶130.) Waterside disclosed Peak IEX-1 ("peak 1") in the "acidic" region of the chromatogram to contain a mutation where the asparagine at amino acid position 30 has been deamidated to aspartate. (*Id*.) Waterside further disclosed that the deamidated Asn30 acidic variant of "peak 1" retains only 82% of the specific activity of the parent antibody. (*Id*.)

3. Harris (Ex. 1007)

Harris is a journal article entitled *Processing of C-Terminal lysine and arginine residues of proteins isolated from mammalian cell culture*. (Ex. 1007.) Harris was published on June 23,1995, which is more than one year before May 6, 1998, the earliest possible priority date of the '218 patent, and is therefore prior art under 35 U.S.C. § 102(b). (Ex. 1002, ¶¶132.)

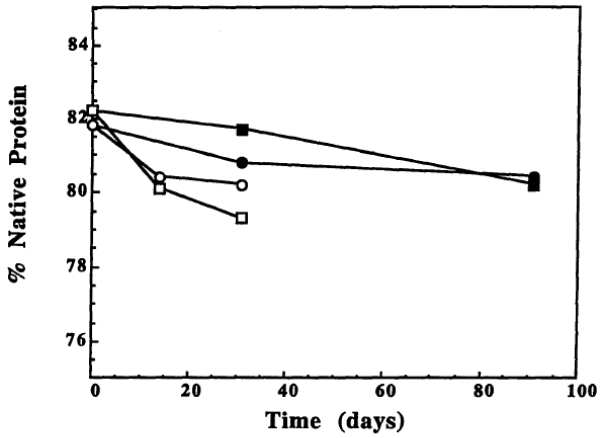
Harris disclosed cation-exchange chromatograms of three "lots" of rhuMAb HER2 (humMAb4D5-8) antibody having only two major "acidic variants." (§VIII.D.1.c; Ex. 1002, ¶¶133.) Harris further disclosed that "rhuMAb HER2 shows five charge species," where "[t]he more acidic peaks 1 and 2 are deamidated at Asn^{30} in one light chain." (*Id*.) Accordingly, Harris disclosed that the two major "acidic variants" are deamidated at Asn30 in one light chain.

VIII. THE PRIOR ART RENDERS THE CHALLENGED CLAIMS ANTICIPATED AND/OR OBVIOUS

A. Ground 1: Andya Anticipates Claims 1 and 5-7

Andya anticipates claims 1 and 5-7 as shown in the following chart and discussed below. (Ex. 1002, ¶¶141-187.)

Claim Limitations	Disclosed in Ex. 1004
1.[a] A therapeutic composition comprising a mixture of anti-HER2 antibody and	"This example describes the development of a lyophilized formulation comprising full length humanized antibody huMAb4D5-8 described in WO 92/22653." (Ex. 1004, 19:1-2.) "It is contemplated that a reconstituted formulation of the anti-HER2 antibody may be used to treat breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon and/or bladder cancer." (Ex. 1004, 18:7-9.)
[b] one or more acidic variants thereof,	"In the liquid state, rhuMAb HER2 was observed to degrade by deamidation (30Asn of light chain)." (Ex. 1004, 19:13-14.)
[c] wherein the amount of the acidic variant(s) is less than about 25%, and	"Figure 5 demonstrates stability of reconstituted rhuMAb HER2 lyophilized in 5 mM sodium succinate, pH 5.0, 60 mM trehalose, 0.01% Tween 20™." (Ex. 1004, 4:20-21.) "The % native protein was defined as the peak area of the native (not degraded) protein relative to the total peak area as measured by cation exchange chromatography." (Ex. 1004, 4:23-24.)

Claim Limitations	Disclosed in Ex. 1004
	 FIG. 5 (Ex. 1004, Fig. 5.)
[d]wherein the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated, and	See claim element [b]. "As mentioned previously, the major degradation route for rhuMAb HER2 in aqueous solutions is deamidation or succinimide formation. The loss of native protein due to deamidation or succinimide formation was assessed for the four reconstituted rhuMAb HER2 formulations." (Ex. 1004, 26:14-16.)
[e]wherein the anti-HER2 antibody is humMAb4D5-8, and	See claim element [a].
[f]wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate, and	See claim element [b].
[g]a pharmaceutically acceptable carrier.	"A stable lyophilized protein formulation is described which can be reconstituted with a suitable diluent to generate a high protein concentration reconstituted formulation which is suitable for subcutaneous

Claim Limitations	Disclosed in Ex. 1004
	administration." (Ex. 1004, Abstract.) "The 'diluent' of interest herein is one which is pharmaceutically acceptable (safe and non-toxic for administration to a human) and is useful for the preparation of a reconstituted formulation." (Ex. 1004, 9:19-20.)

Anticipation requires that a "single prior art reference discloses, either expressly or inherently, each limitation of the claim." *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002). Where the patent claims a range, it is anticipated by prior art disclosing a point within the range. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985). A reference may anticipate inherently if a claim limitation that is not expressly disclosed "is necessarily present, or inherent, in the single anticipating reference." *In re Montgomery*, 677 F.3d 1375, 1379–80 (Fed. Cir. 2012) (citing *Verizon Servs. Corp. v. Cox Fibernet Va., Inc.*, 602 F.3d 1325, 1337 (Fed.Cir.2010).) The inherent result must inevitably result from the disclosed steps and "[i]nherency . . . may not be established by probabilities or possibilities." *Id*. (citation omitted).

1. Claim 1 was anticipated by Andya

a. Elements [a] and [e]

Claim 1 requires, "A therapeutic composition comprising a mixture of anti-HER2 antibody" (element [a]) and "wherein the anti-HER2 antibody is

humMAb4D5-8" (element [e]). Andya disclosed "a lyophilized formulation comprising full length humanized antibody humMAb4D5-8 described in WO 92/22653." (Exs. 1002, ¶142; 1004, 19:1-2.) Andya further taught that "a reconstituted formulation of the anti-HER-2 antibody may be used to treat breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon and/or bladder cancer." (Exs. 1002, ¶142; 1004, 18:7-9.) Therefore, Andya disclosed a therapeutic composition comprising an anti-HER2 antibody, as called for by claim 1 element [a]. (Ex. 1002, ¶¶141-143.)

Andya further taught that humMAb4D5-8 is a "full length humanized antibody (Exs. 1002, ¶¶144; 1004, 19:1-2.) Example 1 of Andya disclosed an "ANTI-HER2 FORMULATION" comprising humMAb4D5-8, an anti-HER2 antibody. (Exs. 1002, ¶¶144; 1004, 18:34-19:2.) Therefore, Andya disclosed the anti-HER2 antibody humMAb4D5-8, as called for by claim 1 element [e]. (Ex. 1002, ¶¶141-144.) Thus, Andya disclosed elements [a] and [e] of claim 1. (*Id.*)

b. Elements [b], [d] and [f]

Claim 1 requires "one or more acidic variants thereof" (element [b]), "wherein the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated" (element [d]), and "wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate" (element [f]). Andya

taught "[i]n the liquid state, rhuMAb HER2 was observed to degrade by deamidation (30Asn of light chain)." (Exs. 1002, ¶145; 1004, 19:13-14.) Deamidation of asparagine (Asn) converts the amide-containing amino acid to aspartate (Asp), thus creating an "acidic variant." (Ex. 1002, ¶149.) Moreover, during prosecution of the '218 patent, the Patent Owner admitted that "rhuMAb HER2" is the same antibody as humMAb4D5-8. (§VII.D.2; Ex. 1002, ¶146.) The term "rhuMAb HER2" is furthermore used throughout the '218 patent interchangeably with humMAb4D5-8. (Ex. 1002, ¶146.) Therefore, Andya disclosed one or more acidic variants of humMAb4D5-8, an anti-HER2 antibody, as called for by claim 1 element [b]. (Ex. 1002, ¶¶145.)

Andya further taught that humMAb4D5-8 acidic variants are predominantly deamidated asparagine. (Ex. 1002, ¶¶149-153.) Andya disclosed only two degradative modifications of humMAb4D5-8, the deamidation of asparagine at position 30 ("Asn30") to aspartate, and the formation of an isoaspartate variant of aspartate at position 102 ("Asp102"). (Exs. 1002, ¶149; 1004, 19:13-15.) Deamidation creates an acidic variant. (Exs. 1002, ¶152; 1012, 9-11.) Isoaspartate formation from aspartate, however, does not create an acidic variant because the aspartate and isoaspartate side chains have the same charge. (*Id*.) Therefore, the Asp102 isoaspartate disclosed by Andya is not an acidic variant. (Ex. 1002, ¶152.)

Thus, the only "acidic variant" observed and disclosed by Andya was deamidation of aspartate. (*Id*.)

Andya also taught that "the major degradation route for rhuMAb HER2 in aqueous solutions is deamidation or succinimide formation." (Exs. 1002, ¶153; 1004, 26:14-16.) Succinimide is the intermediate through which asparagine is deamidated, and itself is not an acidic variant. (Ex. 1002, ¶153-154.) Thus, Andya taught that the "major degradation route" for the anti-HER2 humMAb4D5-8 antibody in solution is deamidation of asparagine. (Ex. 1002, ¶153.) As such, Andya taught that deamidation of asparagine is the "predominant" acidic variant of humMAb4D5-8 because it was the only acidic variant observed, and it was the "major degradation route" for humMAb4D5-8 in solution. (Ex. 1002, ¶¶150-153.) Therefore, Andya taught that humMAb4D5-8 acidic variants are predominantly deamidated variants where asparagine has been deamidated, as called for by claim 1 element [d]. (Ex. 1002, ¶¶153.)

Andya also taught that the deamidated asparagine in humMAb4D5-8 occurs at Asn30 (Exs. 1002, ¶147; 1006, 19:13-15), which is located in the CDR1 domain of the two V_L regions of humMAb4D5-8. (Ex. 1002, ¶147.) The location of an amino acid in a protein or antibody is an inherent property of that protein or antibody. (*Id.*) Moreover, the fact that Asn30 is located in the CDR1 domain of the V_L region of humMAb4D5-8 is consistent with the known location of CDR1

domains in IgG antibodies at the time.[2] (Exs. 1002, ¶148; 1006, 1:26-27; 1009, Table 1, 878-879, Table 2, 882; 1016, 5938.) Therefore, Andya taught that the deamidated variants of humMAv4D5-8 occur in the CDR1 domain of the V_L region of humMAb4D5-8, as called for by claim 1 element [f]. (Ex. 1002, ¶148.) Thus, Andya disclosed elements [b], [d] and [f] of claim 1. (Ex. 1002, ¶¶155.)

c. Element [c]

Claim 1 requires "wherein the amount of the acidic variant(s) is less than about 25%" (element [c]). Thus, element [c] of claim 1 requires that *all* acidic variants in the composition comprise less than 25% of the total antibody present in the mixture. (Ex. 1002, ¶156.) Example 1 of Andya disclosed stability testing of liquid humMAb4D5-8 formulations, reconstituted from lyophilized formulations. (Exs. 1002, ¶¶157; 1004, 24:11-27:17.) Figures 5 to 8 report humMAb4D5-8 stability as "% Native Protein." (Exs. 1002, ¶158; 1004, Figs. 5-8.) Andya defines "% Native Protein" as "the peak area of the native (not degraded) protein relative to the total peak area as measured by cation exchange chromatography." (Exs. 1002, ¶158; 1004, 4:23-24.) "% Native Protein" is the percentage of humMAb4D5-8 that has not degraded or aggregated and therefore, does *not* include acidic variants of humMAb4D5-8. (Ex. 1002, ¶158.)

[2] The phrases "at the time" and "prior to the '218 patent" refer to May 6, 1998, the earliest priority date claimed by the '218 patent.

The "% Native Protein" reported for the 4 mL humMAb4D5-8 composition in Figure 5 of Andya is 82% at time zero. (Exs. 1002, ¶159; 1004, Fig. 5, 4:20-24.) Therefore, the *maximum* amount of acidic variant that could be present in the 4 mL humMAb4D5-8 composition in Figure 5 is 18%. (Ex. 1002, ¶159.) Therefore, Andya taught a composition of humMAb4D5-8 having less than about 25% acidic variants, as called for by claim 1 element [c]. (*Id.*) Thus, Andya disclosed element [c] of claim 1. (*Id.,* ¶¶160.)

d. Element [g]

Claim 1 requires that the composition comprise "a pharmaceutically acceptable carrier" (element [g]). Andya disclosed "[a] stable lyophilized protein formulation is described which can be reconstituted with a suitable diluent to generate a high protein concentration reconstituted formulation which is suitable for subcutaneous administration." (Exs. 1002, ¶162; 1004, Abstract.) The "diluent" disclosed by Andya is a "pharmaceutically acceptable carrier" because Andya taught several diluents that when reconstituted are "safe and non-toxic for administration to a human." (Exs. 1002, ¶162; 1004, 9:19-22.) Thus, Andya disclosed element [g] of claim 1. (Ex. 1002, ¶162.) Accordingly, Andya explicitly disclosed each and every element [a]-[g] of claim 1 of the '218 patent. (*Id.*, ¶163.)

2. Deamidation at Asn30 is a predominant and inherent acidic variant of humMAb4D5-8

As discussed above, Andya explicitly disclosed each and every element [a]-[g] of claim 1 of the '218 patent. (§VIII.A.1; Ex. 1002, ¶¶141-163.) To the extent it is found that Andya does not explicitly disclose elements [b], [c], [d], or [f] of claim 1, Andya inherently disclosed them. (Ex. 1002, ¶¶164-182.) In order to evaluate the predominance and inherency of deamidation in humMAb4D5-8, Dr. Richard Buick expressed humMAb4D5-8 in both HEK cells and CHO cells, purified and characterized the antibodies, and performed a series of analyses comparing the antibodies to commercial trastuzumab, based on standard techniques disclosed in the prior art. (Exs. 1002, ¶¶167-171; 1015, ¶¶5-69.)

The facts disclosed in Dr. Buick's declaration establish that humMab4D5-8 compositions naturally and inevitably contain one or more acidic variants, as required by element [b], and that they are predominantly deamidated acidic variants, as required by element [d] of claim 1. (Exs. 1002, ¶165.) Therefore, elements [b] and [d] of claim 1 were inherently anticipated by Andya. (*Id.*) Moreover, the facts disclosed in Dr. Buick's declaration establish that humMab4D5-8 acidic variants naturally and inevitably comprise the deamidated Asn30 acidic variant inCDR1 of either or both VL regions of humMAb4D5-8, as required by element [f] of claim 1. (*Id.*, ¶166.) Andya further inherently disclosed less than about 25% acidic variants," as required by element [c] because the

composition of Figure 5 contained no less than 82% humMAb4D5-8, and therefore could not have contained more than 18% acidic variant. Therefore, elements [c] and [f] of claim 1 were inherently anticipated by Andya. (*Id.*)

In section IV of Dr. Buick's declaration, he sets out the materials and methods that he used to perform his experiments. (Exs. 1002, ¶167, 1015, ¶¶16-46; Appendix C.) All of the methods and materials used by Dr. Buick would have been available to the POSA prior to the filing of the '218 patent. (Ex. 1002, ¶167; 1015, ¶¶8-15.) Dr. Buick constructed an expression vector comprising a nucleic acid encoding the humMab4D5-8 antibody, using the amino acid sequence disclosed in Carter PCT (Exs. 1002, ¶168; 1015, ¶17-19), transfected the expression vector into HEK and CHO cells (Exs. 1002, ¶168; 1015, ¶20-22), and expressed the antibody. (Exs. 1002, ¶168; 1015, ¶23-36.) The HEK-derived and CHO-derived humMAb4D5-8 were purified from the HEK and CHO cell culture supernatants using Protein A affinity chromatography and analyzed using MonoS cation-exchange chromatography, as disclosed in Waterside and Harris. (Exs. 1002, ¶169-170; 1005; 1007; 1015, ¶¶37-44.)

The composition of the HEK- and CHO-derived humMAb4D5-8 antibodies were analyzed by comparing to commercial trastuzumab using cation-exchange chromatography. (Exs. 1002, ¶171; 1015, ¶¶47-56, 59-67.) The purified HEK- and CHO-derived humMAb4D5-8 exhibited cation exchange chromatograms

similar to that of commercial trastuzumab, and humMAb4D5-8 disclosed by Harris, confirming that the expressed antibodies matched that of commercial trastuzumab and that reported in the literature. (Exs. 1002, ¶171; 1015, ¶¶62-65, Figure G.)

Having established this, Dr. Buick next describes a peak analysis of commercial trastuzumab. This analysis was performed by collecting the antibody comprising peak 1, the largest acidic variant antibody peak, and "digesting" it with the trypsin protease. (Exs. 1002, ¶172; 1015, ¶¶59-61, Figures E and F.) A protease "digest" is a process where a protease enzyme "cuts" the antibody at specific locations to form peptide fragments, which can then be sequence analyzed using mass spectrometry. (Ex. 1002, ¶172.) The trypsin-digested peptide fragments were analyzed in this manner to confirm the presence of an Asp30 peptide, thus confirming that Asn30 in humMAb4D5-8 has been deamidated to Asp30. (Exs. 1002, ¶173; 1015, ¶¶59-61, Figures E and F.) As peak 1 represents the largest amount of acidic variant in the sample, and peak 1 is deamidated acidic variant, Dr. Buick's experiments confirm that deamidation is the predominant acidic variant of commercial trastuzumab. (Ex. 1002, ¶173.) In this experiment, and consistent with the prior art, deamidation of Asn30 was observed. (*Id*.) Moreover, deamidation of asparagine was the *only* acidic variant observed from the commercial source. (*Id*., ¶174.)

In order to evaluate the presence of the same acidic variant in HEK- (as in Andya) and CHO-derived (as in Waterside) humMAb4D5-8 compositions, Dr. Buick performed a cation exchange chromatography analysis and confirmed that the same acidic variant at peak 1 was present in both the commercial trastuzumab and HEK- and CHO-derived antibodies. (Exs. 1002, ¶175; 1015, ¶¶62-65; Figure G.) Thus, the Asn30 deamidation of the Asp30 acidic variant of humMAb4D5-8 is inherently produced when the humMAb4D5-8 antibody is produced in either HEK or CHO cells. (Ex. 1002, ¶176.)

Dr. Buick also quantified the amount of deamidated light chain Asn30 acidic variant in a sample of commercial trastuzumab. (Exs. 1002, ¶177; 1015, ¶¶66-67, Figure H.) A tryptic-digested sample of unseparated commercial trastuzumab (*i.e.*, not subjected to cation-exchange chromatography) was analyzed using quantitative mass spectroscopy. (Exs. 1002, ¶177; 1015, ¶66.) Area under the curve analysis showed that 93.5% of the native Asn30 peptide and 6.5% of the deamidated Asp30 peptide. (Exs. 1002, ¶177; 1015, ¶67, Figure H.) Thus, the deamidation is inherently the predominant acidic variant of the humMAb4D5-8 antibody, as evidenced by its predominance in commercial trastuzumab, and its disclosure as the only acidic variant in the prior art (Exs. 1004, 1005, 1007) and the contemporary literature (Ex. 1017). (Ex. 1002, ¶178-180.)

The experiments performed by Dr. Buick were standard for a person of ordinary skill in the art as of the time the '218 patent was filed. (*Id*., ¶181.) Any differences between the experiments performed by Dr. Buick and the prior art are not significant. (Exs. 1002, ¶170.) Subsequent disclosures in Harris 2001 further support Dr. Buick's findings. (Exs. 1002, ¶¶178-181; 1017, Figure 2, 238, Table 6, 243.) Thus, Dr. Buick's experiments, and subsequently published data, establish that Andya inherently disclosed elements [b], [c], [d], and [f] of claim 1, if not already disclosed explicitly. (Ex. 1002, ¶¶178-181.)

Therefore, Andya explicitly and/or inherently disclosed every element [a]-[g] of claim 1 of the '218 patent. (*Id.*, ¶182.)

3. Andya anticipates claim 5

Claim 5 depends from any one of claims 1 to 4 and further requires the antibody "comprises the light chain amino acid sequence of SEQ ID NO 1 and the heavy chain amino acid sequence of SEQ ID NO: 2." Andya disclosed, "[Example 1] describes the development of a lyophilized formulation comprising full length humanized antibody huMAb4D5-8 described in WO 92/22653." (Exs. 1002, ¶183; 1004, 19:1-2.) "WO 92/22653" is Carter PCT, which disclosed the amino acid sequence of humMAb4D5-8, therefore, by referencing Carter PCT, Andya explicitly disclosed the amino acid sequence of humMAb4D5-8, which is identical to SEQ ID NO 1 and 2. (Ex. 1002, ¶183.)

Moreover, an amino acid sequence is an inherent property of an antibody. Therefore, by disclosing humMAb4D5-8, Andya inherently disclosed the amino acid sequence of SEQ ID NO 1 and 2 because the amino acid sequences of SEQ ID NO 1 and 2 are humMAb4D5-8. (*Id.* at 184) Thus, Andya explicitly and inherently disclosed each and every element of claim 5 of the '218 patent. (*Id*.)

4. Andya anticipates claims 6 and 7

Claim 6 depends from any one of claims 1 to 4, and claim 7 depends from claim 5. Claims 6 and 7 further require the composition "is in the form of a lyophilized formulation or an aqueous solution."

Andya disclosed compositions of the humMAb4D5-8 antibody that had been reconstituted in aqueous solution from lyophilized material. (§VIII.A.1.d; Ex. 1002, ¶¶142-144.) Thus, Andya disclosed both lyophilized and aqueous compositions as called for by claims 6 and 7. (Ex. 1002, ¶¶185-186.) Thus, Andya disclosed each and every element of claims 6 and 7 of the '218 patent. (*Id.*)

Accordingly, Andya explicitly and/or inherently disclosed each and every element of claims 1 and 5 to 7 of the '218 patent. (*Id.*, ¶¶187.)

B. Ground 2: Andya and a POSA's General Knowledge Render Claims 1 and 5-7 Obvious

A patent claim is invalid under 35 U.S.C. § 103(a) if the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1,

17-18 (1966). Moreover, a claim cannot escape obviousness merely by claiming a specific value, where the general conditions of a claim are disclosed in the art. *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) ("it is not inventive to discover the optimum or workable ranges by routine experimentation.") (*citing In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955)). Furthermore, a court may take into account the creative steps that a person of ordinary skill in the art would employ. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007). An obviousness analysis must, however, avoid hindsight analysis. To preclude hindsight in an obviousness analysis, one must "seek[] evidence from before the time of the invention in the form of some teaching, suggestion, or even mere motivation (conceivably found within the knowledge of an ordinarily skilled artisan) to make the variation or combination." *Rolls-Royce, PLC v. United Techs. Corp*., 603 F.3d 1325, 1338 (Fed. Cir. 2010) (citations omitted.)

Claims 1 and 5-7 as a whole would have been obvious under 35 U.S.C. § 103 over Andya in combination with the general knowledge of a POSA. (Ex. 1002, ¶¶188-219.) As discussed above, Andya disclosed each and every element of claims 1 and 5-7 of the '218 patent. (§VIII.A; Ex. 1002, ¶¶141-187.)

1. Andya and a POSA's general knowledge render claim 1 obvious

a. Elements [a] and [e]

As explained above, Andya disclosed elements [a] and [e] of claim 1 (§VIII.A.1.a), which is incorporated by reference here. Elements [a] and [e] would also have been obvious under 35 U.S.C. § 103 in view of Andya and the general knowledge of a POSA, for the reasons set forth below. (Ex. 1002, ¶¶189-191.) Claim 1 requires, "A therapeutic composition comprising a mixture of anti-HER2 antibody" (element [a]) and "wherein the anti-HER2 antibody is humMAb4D5-8" (element [e]). As discussed above, Andya disclosed "a lyophilized formulation comprising full length humanized antibody humMAb4D5-8 described in WO 92/22653." (Exs. 1002, ¶189; 1004, 19:1-2.) Therefore, Andya disclosed the anti-HER2 antibody humMAb4D5-8, as called for by claim 1 elements [a] and [e]. (Ex. 1002, ¶¶189.)

A POSA would have known that humMAb4D5-8 was "the most potent" and "most preferred" humanized anti-HER2 antibody. (Exs. 1002, ¶190; 1006, 68:25-26, 82:11-13; 1008, 4288.) A POSA would therefore have been motivated to use humMAb4D5-8 in an anti-HER2 therapeutic composition as taught by Andya. (Ex. 1002, ¶191.) Further, based on the teachings of Andya and their general knowledge, a POSA would have had a reasonable expectation of success in obtaining a humMAb4D5-8 therapeutic composition. (*Id.*) Therefore, it would have been obvious to a POSA at the time to use humMAb4D5-8 in an anti-HER2 therapeutic composition, as required by elements [a] and [e] of claim 1. (*Id.*)

b. Elements [b], [d] and [f]

As explained above, Andya disclosed elements [b], [d] and [f] of claim 1 (§VIII.A.1.b), which is incorporated by reference here. Elements [b], [d] and [f] would also have been obvious under 35 U.S.C. § 103 in view of Andya and the general knowledge of a POSA, for the reasons set forth below. (Ex. 1002, ¶¶192-195.) Claim 1 requires "one or more acidic variants thereof" (element [b]), "wherein the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated" (element [d]), and "wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate" (element [f]). Deamidation of asparagine was known to be a major degradation pathway for proteins in general, including antibodies. (Exs. 1002, ¶192; 1012, 3-4.) Thus, a POSA would have known that deamidation creates an acidic variant, as required by element [b], and that CEX could purify such compositions. (Ex. 1002, ¶192.)

Andya taught "[i]n the liquid state, rhuMAb HER2 was observed to degrade by deamidation (30Asn of light chain)." (§VIII.A.1; Exs. 1002, ¶193; 1004, 19:13-14.) A POSA would have known that Asn30 is located in CDR1 of the humMAb4D5-8 V_L region, as required by element [f], and that V_L regions "are involved directly in binding the antibody to the antigen." (§VIII.B.1.c; Ex. 1002, ¶193.)

Andya taught that the Asn 30 acidic variant is the "predominant" acidic variant of the humMAb4D5-8 antibody, as required by element [d]. (§VIII.A.1.b; Exs. 1002, ¶194; 1004, 19:13-15, 26:14-16.) Therefore, it would have been obvious to a POSA that the humMAb4D5-8 acidic variants taught by Andya were predominantly deamidated acidic variants where Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 was converted to aspartate, as required by elements [b], [d], and [f] of claim 1. (Ex. 1002, ¶¶195.)

c. Element [c]

As explained above, Andya disclosed element [c] of claim 1 (§VIII.A.1.c), which is incorporated by reference here. Element [c] would also have been obvious under 35 U.S.C. § 103 in view of Andya and the general knowledge of a POSA, for the reasons set forth below. (Ex. 1002, ¶¶196-206.) Element [c] of claim 1 requires that *all* acidic variants in the composition comprise less than 25% of the total antibody present. As discussed in Ground 1, Andya disclosed each and every element of claim 1 element [c]. (§§VIII.A.1c and 3.) Andya specifically taught humMAb4D5-8 compositions having less than 25% acidic variants. (Ex. 1002, ¶196.) Andya further taught that deamidation of asparagine is the "predominant" acidic variant for humMAb4D5-8 in solution. (§VIII.A.1.b; Ex. 1002, ¶151-154.)

A POSA would have been motivated to obtain a humMAb4D5-8 composition having a level of acidic variants at least as low as that disclosed in Andya. (Ex. 1002, ¶¶197-198.) A POSA would have known that at least one of the sites of deamidation in the humMAb4D5-8 acidic variant, Asn30, was located in CDR1 of the humMAb4D5-8 V_L region, and thus "involved directly in binding the antibody to the antigen." (Exs. 1002, ¶198; 1006, 1:26-27; 25:23-28; 1008, Figure 1, 4286; 1009, Table 1, 878-879, Table 2, 882; 1016, 5938; 1008; 1021.) This understanding is confirmed by the disclosure in Waterside that the deamidated Asn30 acidic variant exhibited only 82% of the activity of humMAb4D5-8. (§VIII.B.1.c; Ex. 1002, ¶198.) (Ex. 1002, ¶198.)

A POSA would further have had a reasonable expectation of success in obtaining a humMAb4D5-8 composition having less than about 25% acidic variants, as called for by claim 1, based on Andya and a POSA's general knowledge at the time. (Ex. 1002, ¶¶199-204.) Andya disclosed humMAb4D5-8 compositions having 18% acidic variant. (§VIII.A.1.c; Ex. 1002, ¶199.) A POSA would have known that CEX was capable of further reducing the amount of acidic variants, and was the method of choice for doing so. (§VII.B.3; Ex. 1002, ¶¶200-204.)

A POSA would further have known that levels of acidic variants in an antibody composition could be reduced even lower than that disclosed by Andya,

by employing known techniques such as optimizing load, wash and elution buffers, flow rate, gradient elution, and peak-cutting. (Ex. 1002, ¶200.) Dr. Buick performed CEX purification of humMAb4D5-8 composition on Bakerbond and MonoS CEX columns using methods known in the art at the time. (Exs. 1002, ¶¶203; 1015, ¶¶8-15, 43-46.) Dr. Buick's chromatography procedure did not include the "reverse" wash step purported to be required by the '218 patent (Exs. 1002, ¶204; 1015, ¶¶43-46), yet pure humMAb4D5-8 antibody was obtained and verified by subsequent CEX. (Exs. 1002, ¶204; 1015, ¶¶47-69.) Dr. Buick's experiments establish that CEX could have been used, on either a Bakerbond or MonoS cation exchange column and using methods standard at the time, to efficiently reduce the amount of acidic variant in a humMAb4D5-8 composition. (Exs. 1002, ¶204; 1015, ¶¶47-56, 62-65, 68-69, Figures I and J.) Thus, a POSA would have had a reasonable expectation of success in obtaining a humMAb4D5-8 composition having less than the level of acidic variants called for by element [c] of claim 1 of the '218 patent. (Ex. 1002, ¶¶204.)

Therefore, it would have been obvious to a POSA at the time to reduce the amount of acidic variant(s) to an amount less than 25%, as required by claim 1 element [c]. (Ex. 1002, ¶¶205.)

d. Element [g]

As explained above, Andya disclosed element [g] of claim 1 (§VIII.A.1.d), which is incorporated by reference here. Element [g] would also have been obvious under 35 U.S.C. § 103 in view of Andya and the general knowledge of a POSA, for the reasons set forth below. (Ex. 1002, ¶¶207-209.) Claim 1 requires that the composition comprise "a pharmaceutically acceptable carrier" (element [g]).

As discussed above, Andya disclosed a humMAb4D5-8 composition in a pharmaceutically acceptable carrier. (§VIII.A.1.d; Ex. 1002, ¶207.) Moreover, a POSA would have known that antibodies, such as humMAb4D5-8, were formulated for administration in pharmaceutically acceptable carriers. (Exs. 1002, ¶208; 1006, 61:3-7.) Therefore, a POSA would have been motivated to obtain a humMAb4D5-8 composition in a pharmaceutically acceptable carrier and would have had a reasonable expectation of success. (Ex. 1002, ¶208.) Therefore, it would have been obvious to a POSA at the time to use humMAb4D5-8, as taught by Andya, in a pharmaceutically acceptable carrier, as required by element [g] of claim 1. (Ex. 1002, ¶¶209.)

For all of the reasons described above, it would have been obvious to a POSA to reduce the amount of acidic variant(s) to an amount less than about 25%, where the acidic variant(s) are predominantly deamidated variants where one or

more acidic variants of the anti-HER2 antibody have been deamidated, and where the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate. (*Id.*, ¶¶217-219.) Therefore, claim 1 as a whole would have been obvious over Andya in combination with the general knowledge of a POSA. (*Id.*)

2. Andya and a POSA's general knowledge render claim 5 obvious

Claim 5 depends from any one of claims 1 to 4 and further requires the anti-HER2 antibody comprise "the light chain amino acid sequence of SEQ ID NO 1 and the heavy chain amino acid sequence of SEQ ID NO: 2." As explained above, Andya disclosed the amino acid sequence required by claim 5 (§VIII.A.3), which is incorporated by reference here. Claim 5 would have been obvious for all the reasons outlined above for claim 1 (§VIII.B.1), and further over Andya and the general knowledge of a POSA, for the reasons set forth below. (Ex. 1002, ¶¶210-212.)

Andya taught that Carter PCT disclosed the humMAb4D5-8 amino acid sequence. (Exs. 1002, ¶173, 211; 1004, 19:1-2.) The humAb4D5-8 amino acid sequence was also disclosed in Carter 1992. (Exs. 1002, ¶210; 1008, Figure 1, Table 1, 4286-4287.) A POSA would also have known that humAb4D5-8 was "the most potent" and "most preferred" humanized anti-HER2 antibody. (§VIII.B.1.a; Ex. 1002, ¶211.) Therefore, it would have been obvious to a POSA

at the time to use humAb4D5-8, which is encoded by SEQ ID NOS 1 and 2, in an anti-HER2 composition, as required by claim 5. (Ex. 1002, ¶¶211-212.)

3. Andya and a POSA's general knowledge render claims 6 and 7 obvious

Claim 6 depends from any one of claims 1 to 4, and claim 7 depends from claim 5. Claims 6 and 7 further require the composition "is in the form of a lyophilized formulation or an aqueous solution." As explained above, Andya disclosed the compositions required by claims 6 and 7 (§VIII.A.4), which is incorporated by reference here. Claims 6 and 7 would have been obvious for all the reasons outlined above for claims 1 and 5 (§VIII.B.1), and further over Andya and the general knowledge of a POSA, for the reasons set forth below. (Ex. 1002, ¶¶213-216.)

Andya disclosed therapeutic antibody compositions as called for by claim 1. (§VIII.A.1, VIII.A.2; Ex. 1002, ¶¶214.) A POSA would have known that water is a pharmaceutically acceptable carrier, which forms an "aqueous solution." (§VIII.B.1.d; Ex. 1002, ¶215.) Therefore, it would have been obvious to a POSA at the time to use the therapeutic antibody composition disclosed by Andya in a pharmaceutically acceptable carrier such as water, as required by claims 6 and 7. (Ex. 1002, ¶¶214-216.)

For all the reasons described above, claims 1 and 5-7 would have been obvious over Andya in combination with the general knowledge of a POSA. (*Id.*, ¶217-219.)

C. Ground 3: Waterside and a POSA's General Knowledge Render Claims 1 and 5-7 Obvious

Claims 1 and 5-7 as a whole would have been obvious under 35 U.S.C. § 103 over Waterside in combination with the general knowledge of a POSA. (Ex. 1002, ¶¶220-256.)

1. Waterside and a POSA's general knowledge render claim 1 obvious

a. Elements [a] and [e]

Claim 1 requires, "A therapeutic composition comprising a mixture of anti-HER2 antibody" (element [a]) and "wherein the anti-HER2 antibody is humMAb4D5-8" (element [e]). Waterside disclosed an antibody directed against the extracellular domain of the HER2 protein. (Exs. 1002, ¶222; 1005, 3.) The antibody, identified as rhuMAb HER2, "renders HER2-overexpressing cell lines cytostatic," "halts growth of implanted $HER2^+$ tumors," and "increases chemotherapeutic susceptibility." (Exs. 1002, ¶222; 1005, 3.) Waterside also disclosed that the antibody is "in phase III clinical trials (breast cancer)." (Exs. 1002, ¶222; 1005, 3.) Waterside thus disclosed a therapeutic composition comprising an anti-HER2 antibody. (Ex. 1002, ¶222.) As discussed above, rhuMAb HER2 is the humMAb4D5-8 antibody. (§§VII.D.2, VIII.A.1.b; Ex. 1002,

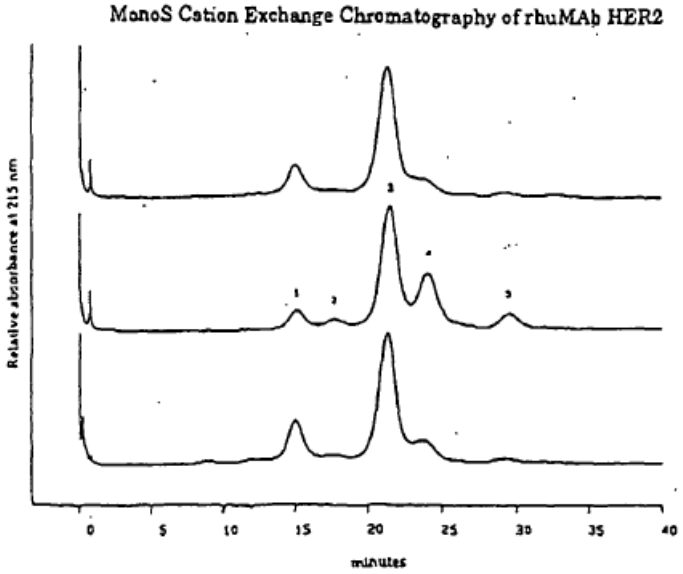
¶223.) A POSA would therefore have understood that the "rhuMAb HER2" antibody disclosed by Waterside was the same antibody as "humMAb4D5-8." (Ex. 1002, ¶223.) Thus, Waterside disclosed elements [a] and [e] of claim 1. (Ex. 1002, ¶223.)

A POSA would also have known that humAb4D5-8 was "the most potent" and "most preferred" humanized anti-HER2 antibody. (§VIII.B.1.a; Ex. 1002, ¶224.) A POSA would therefore have been motivated to use humMAb4D5-8 in an anti-HER2 therapeutic composition as taught by Waterside. Further, based on the teachings of Waterside and their knowledge of the art, a POSA would also have had a reasonable expectation of success in obtaining a humMAb4D5-8 therapeutic composition. (Ex. 1002, ¶224.) Therefore, it would have been obvious to a POSA at the time to use humMAb4D5-8 in an anti-HER2 therapeutic composition, as required by elements [a] and [e] of claim 1. (Ex. 1002, ¶225.)

b. Elements [b], [d] and [f]

Claim 1 requires "one or more acidic variants thereof" (element [b]), "wherein the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated" (element [d]), and "wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate" (element [f]).

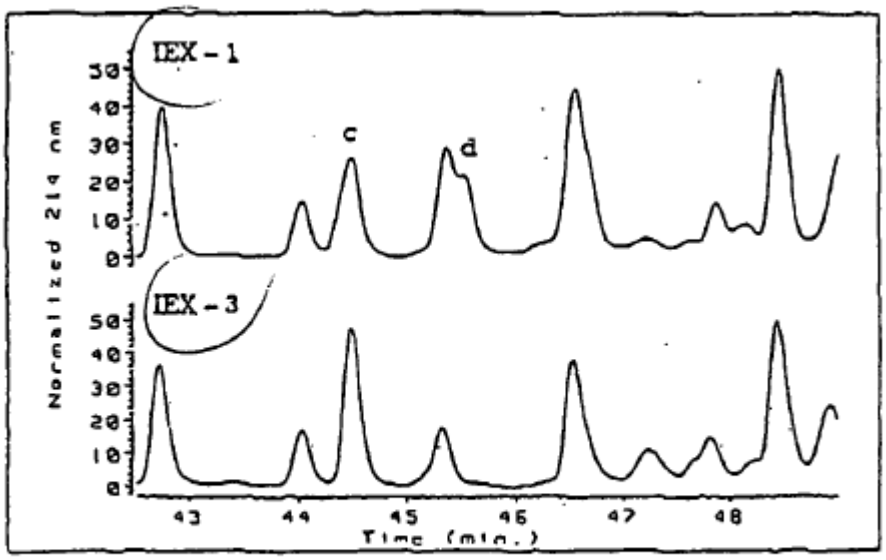
Waterside disclosed three cation exchange chromatograms entitled "MonoS Cation Exchange Chromatography of rhuMAb HER2," as shown below:



(Exs. 1002, ¶227; 1005, 4.) "MonoS" is a type of cation exchange column, which was available at the time. (Ex. 1002, ¶227.) The middle chromatogram contains five peaks labeled 1 to 5 from left to right. (Exs. 1002, ¶227; 1005, 4.) Each "peak" represents a different charged species. (Ex. 1002, ¶227.) The parent antibody is usually the largest (main) peak, with the additional peaks representing "charged variants" of the parent antibody. (*Id.*) These charged variants may appear to the left, *i.e.*, "more acidic," or to the right, *i.e.*, "more basic," of the parent antibody. (*Id.*) Peak 3 of the MonoS chromatogram is the parent antibody peak, comprising humMAb4D5-8. (Exs. 1002, ¶228; 1005, 4.) Peaks 1 and 2 are "more acidic" than the main peak, and thus comprise the "acidic variants" in the chromatogram, having either no lysine residues (peak 1), or one lysine residue

(peak 2), at the C-terminus of the antibody heavy chain. (Ex. 1002, ¶¶228.) Peaks 4 and 5 are "more basic," and would be recognized by a POSA as comprising either one (peak 4) or two (peak 5) lysine residues at the C-terminus of the antibody heavy chain. (*Id.*) Thus, Waterside disclosed a composition having an anti-HER2 antibody having "one or more acidic variants," as called for by claim 1 element [b]. (*Id.*)

Waterside also disclosed that the acidic variants in the three Waterside MonoS chromatograms are "predominantly deamidated variants," and that "one or more asparagine residues have been deamidated," as required by element [d]. (*Id.,* 229.) Waterside disclosed the following cation exchange chromatogram:



Peak c: LC:25-42 ASQDVNTAVAWYQQKPGK (Asn^{30})
Peak d: LC:25-42 ASQDVDTAVAWYQQKPGK (Asp^{30})

(Exs. 1002, ¶229; 1005, 6.) IEX-1 corresponds to peak 1 (Ion Exchange peak 1 – one of the acidic variants), and IEX-3 corresponds to peak 3 (Ion Exchange peak 3

– parent antibody) of the three MonoS chromatograms on page 4 of Waterside. (Exs. 1002, ¶229; 1005, 4.)

A POSA would have known that the chromatogram on page 6 of Waterside is a cation exchange chromatogram of a tryptic digest of peak 1 (IEX-1, top) and peak 3 (IEX-3, bottom). (Ex. 1002, ¶229.) Trypsin is an enzyme that cleaves proteins, such as antibodies, at specific positions of their amino acid sequence. (*Id.*) A "tryptic digest" is the resulting amino acids obtained after "digesting" a protein with trypsin. (*Id.*) By digesting the antibody, peptide fragments that can be further chromatographed and analyzed are obtained.

Waterside identifies two peaks in the tryptic peptide chromatogram, peak c and peak d (appearing as a shoulder at approx. 45.6 min.). (Exs. 1002, ¶230; 1005, 6.) Peak c appears in both the top (acidic variant) and bottom (humMAb4D5-8) chromatogram, indicating that this peptide is present in both, while peak d ("shoulder") only appears in the top chromatogram, indicating that it only appears in the acidic variant. (Exs. 1002, ¶230; 1005, 6.) A legend below the chromatogram disclosed the identity of the peptides comprising peaks c and d, as shown below:

Peak c: LC:25-42 ASQDVNTAVAWYQQKPGK (Asn^{30})
Peak d: LC:25-42 ASQDVDTAVAWYQQKPGK (Asp^{30})

Peak c is a peptide corresponding to amino acid residues 25-42 (denoted "LC : 25-42") of the light chain of the rhuMAb HER2 antibody. (*Id*.) Peak c is labeled Asn^{30} because it contains an asparagine (denoted "N") at position 30. (*Id*.) Peak d is a peptide corresponding to amino acid residues 25-42 (denoted "LC : 25-42"), also of the light chain of the rhuMAb HER2 antibody, however, peak d is labeled Asp^{30} because it contains an aspartate (denoted "D") at position 30. (*Id*.)

Because peak d originated from a tryptic digest of the humMAb4D5-8 acidic variant (peak 1 of the MonoS chromatograms on page 4 of Waterside), a POSA would have known that peak 1 corresponds to humMAb4D5-8 where asparagine has been deamidated to aspartate. (Ex. 1002, ¶230.) Thus, Waterside disclosed an acidic variant of humMAb4D5-8 where "one or more asparagine residues have been deamidated," as called for by element [d]. (*Id.*)

Waterside also disclosed that the acidic variants in the three Waterside MonoS chromatograms are "predominantly deamidated variants." (Ex. 1002, ¶231.) As discussed above, peak 1 of the Waterside chromatograms is a deamidated humMAb4D5-8 acidic variant. In the top and bottom MonoS chromatograms of Waterside, peak 1 is the *only* "acidic variant." (Exs. 1002, ¶231; 1005, 4.) Therefore, the acidic variant in the top and bottom MonoS chromatograms of Waterside are "predominantly deamidated." (Ex. 1002, ¶231.) The middle chromatogram of Waterside contains two acidic variants, peak 1 and

peak 2. (Exs. 1002, ¶231; 1005, 4.) As peak 1 is larger than peak 2, and peak 1 represents a deamidated humMAb4D5-8 acidic variant, deamidation is therefore also the "predominant" acidic variant in the middle Waterside chromatogram. (Ex. 1002, ¶231.) Therefore, Waterside disclosed an acidic variant that is "predominantly deamidated," and that "one or more asparagine residues have been deamidated," as required by element [d] of claim 1. (*Id.*)

Waterside further disclosed that the "deamidated variants" in the MonoS chromatograms "have Asn30 in CDR1 of either or both VL regions of humMAb4D5-8 converted to aspartate," as required by element [f]. (*Id.*, 232.) The legend underneath the tryptic digest chromatogram shows that Asn^{30}, an asparagine at amino acid position 30, is converted to Asp^{30}, an aspartate at position 30. (§VIII.C.1.b; Ex. 1002, ¶232.) As Asn30 is located in CDR1 of either or both V_L regions of humMAb4D5-8 (§VIII.B.1.c), Waterside disclosed that the "deamidated variants" in the Waterside MonoS chromatograms "have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate," as required by element [f] of claim 1. (Ex. 1002, ¶232.)

Therefore, it would have been obvious to a POSA that the humMAb4D5-8 acidic variants taught by Waterside were predominantly deamidated acidic variants where Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 was

converted to aspartate, as required by elements [b], [d], and [f] of claim 1. (*Id.*, ¶¶233-234.)

c. Element [c]

Claim 1 element [c] would have been obvious over Waterside in combination with the general knowledge of a POSA. (*Id.*, ¶¶235-243.) Element [c] of claim 1 requires that *all* acidic variants in the composition comprise less than 25% of the total antibody present. (Ex. 1002, ¶235.) A POSA would have known, based on their understanding of CEX and the definition of "acidic variant" in the '218 patent, that peaks 1 and 2 in the MonoS chromatograms are the *only* acidic variants in the chromatograms. (Exs. 1002, ¶236; 1005, 6.) The '218 patent defines acidic variant as "more acidic . . . than the polypeptide of interest." (§VII.D.3; Exs. 1001, 5:60-63; 1002, ¶236.) A POSA would have known that peak 3 represents native humMAb4D5-8, and therefore is "the polypeptide[s] of interest." (Ex. 1002, ¶236.) Peaks 1 and 2 would therefore have been understood by a POSA to be acidic variants because they are the only peaks in the chromatogram that are "more acidic" than peak 3. (Exs. 1001, 5:46-48; 1002, ¶236.)

In a chromatogram, the amount of material in one peak can be compared with the amount of material in another peak by comparing the "area under the curve" for each peak. (Ex. 1002, ¶237.) As such, it is possible to determine the

percent acidic variants by dividing the area of peaks 1 and 2 (acidic variants) by the area of peaks 1 to 5 (total antibody present) and multiplying by 100. (*Id*.) Based on this analysis, the amount of acidic variants in the three Waterside chromatograms are 14.2% for the top chromatogram, 9.5% for the middle chromatogram, and 16.4% for the bottom chromatogram. (*Id.*, ¶¶237-239.) Therefore, all three chromatograms disclosed in Waterside contain "less than about 25%" acidic variants, as called for by claim 1. (*Id.*, ¶239.)

A POSA would have been motivated to obtain a humMAb4D5-8 composition having a level of acidic variants at least as low as that described in Waterside. (§VIII.B.1.c; Ex. 1002, ¶240-241.) A POSA would have known that the site of deamidation in at least one humMAb4D5-8 acidic variant, Asn30, was located in CDR1 of the humMAb4D5-8 V_L region, and thus "involved directly in binding the antibody to the antigen." (§VIII.B.1.c; Ex. 1002, ¶241.) A POSA would a have been motivated to reduce the amount of acidic variants in a humMAb4D5-8 composition based on the disclosure in Waterside that the deamidated Asn30 acidic variant exhibits less activity than the parent antibody. (Ex. 1002, ¶240-241.) Waterside taught that the deamidated Asn30 acidic variant exhibits only 82% specific activity compared to humMAb4D5-8. (Exs. 1002, ¶140; 1006, 7.)

A POSA would further have had a reasonable expectation of success in obtaining a humMAb4D5-8 composition having less than about 25% acidic variants, as called for by claim 1, based on the disclosures in Waterside and a POSA's general knowledge at the time. (Ex. 1002, ¶242.) Waterside taught humMAb4D5-8 compositions having less than 25% acidic variants. (§VIII.A.1, element [c]; Ex. 1002, ¶242.) Further, a POSA would have known that CEX was the method of choice for reducing the amount of acidic variants in protein compositions, because CEX was known to be able to separate proteins based on charge difference. (§VIII.B.1.c; Ex. 1002, ¶242.) Thus, a POSA would have had a reasonable expectation of success in obtaining a humMAb4D5-8 composition within the scope of claim 1. (*Id.*, ¶¶242.)

Therefore, it would have been obvious to a POSA at the time to reduce the amount of acidic variant(s) to an amount less than 25%, as required by claim 1 element [c]. (*Id.*, ¶¶243.)

d. Element [g]

Claim 1 element [g] would have been obvious over Waterside in combination with the general knowledge of a POSA. (*Id.*, ¶¶244-247.) Claim 1 requires that the composition comprise "a pharmaceutically acceptable carrier" (element [g]).

Waterside disclosed that the rhuMAb HER2 antibody was "in phase III clinical trials (breast cancer)." (§VIII.C.1.a; Ex. 1002, ¶245.) A POSA would have known that because rhuMAb HER2 antibody was being administered to humans, it would have been formulated in a pharmaceutically acceptable carrier. (Ex. 1002, ¶245.) Moreover, a POSA would have known that antibodies, such as humMAb4D5-8, were formulated for administration in pharmaceutically acceptable carriers. (Exs. 1002, ¶¶246; 1004, Abstract, 9:19-22; 1006, 61:3-7.) Thus, a POSA would have been motivated to obtain a humMAb4D5-8 composition in a pharmaceutically acceptable carrier and would have had a reasonable expectation of success. (Ex. 1002, ¶¶246.) Therefore, it would have been obvious to a POSA at the time to use humMAb4D5-8, as taught by Waterside, in a pharmaceutically acceptable carrier, as required by element [g] of claim 1. (Ex. 1002, ¶247.)

For all of the reasons described above, it would have been obvious to a POSA to reduce the amount of acidic variant(s) to an amount less than about 25%, where the acidic variant(s) are predominantly deamidated variants where one or more acidic variants of the anti-HER2 antibody have been deamidated, and where the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate. (*Id.*, ¶¶254-256.) Therefore, claim 1 as a

whole would have been obvious over Waterside in combination with the general knowledge of a POSA. (*Id.*)

2. Waterside and a POSA's general knowledge render claim 5 obvious

Claim 5 depends from any one of claims 1 to 4 and further requires the anti-HER2 antibody comprise "the light chain amino acid sequence of SEQ ID NO 1 and the heavy chain amino acid sequence of SEQ ID NO: 2." Claim 5 would have been obvious for all the reasons outlined above for claim 1 (§VIII.C.1), and further over Waterside in combination with the general knowledge of a POSA, for the reasons set forth below. (*Id.*, ¶¶148-150.)

A POSA would have known the humAb4D5-8 amino acid sequence. (Exs. 1002, ¶249; 1006, Table 3, 72.) A POSA would have known that humAb4D5-8 was "the most potent" and "most preferred" humanized anti-HER2 antibody. (§VIII.B.1.a; Ex. 1002, ¶249) Therefore, it would have been obvious to a POSA at the time to use humAb4D5-8, which is encoded by SEQ ID NOS 1 and 2, in an anti-HER2 composition, as required by claim 5. (Ex. 1002, ¶¶249-250.)

3. Waterside and a POSA's general knowledge render claims 6 and 7 obvious

Claim 6 depends from any one of claims 1 to 4, and claim 7 depends from claim 5. Claims 6 and 7 require the composition "is in the form of a lyophilized formulation or an aqueous solution." Claims 6 and 7 would have been obvious for

all the reasons outlined above for claims 1 and 5 (§VIII.C.1), and further over Waterside in combination with the general knowledge of a POSA, for the reasons set forth below. (*Id.*, ¶¶251-253.)

Waterside disclosed therapeutic antibody compositions as called for by claim 1. (§VIII.C.1; Ex. 1002, ¶252.) A POSA would have known that water is a pharmaceutically acceptable carrier, which forms an "aqueous solution." (§VIII.B.1.d; Ex. 1002, ¶252.) Therefore, it would have been obvious to a POSA at the time to use the therapeutic antibody composition disclosed by Waterside in a pharmaceutically acceptable carrier such as water, as required by claims 6 and 7. (Ex. 1002, ¶¶252-253.)

For all the reasons described above, claims 1 and 5-7 would have been obvious over Waterside in combination with the general knowledge of a POSA. (*Id.*, ¶254-256.)

D. Ground 4: Harris and a POSA's General Knowledge Render Claims 1 and 5-7 Obvious

Claims 1 and 5-7 as a whole would have been obvious under 35 U.S.C. § 103 over Harris in combination with the general knowledge of a POSA. (Ex. 1002, ¶¶257-282.)

1. Harris and a POSA's general knowledge render claim 1 obvious

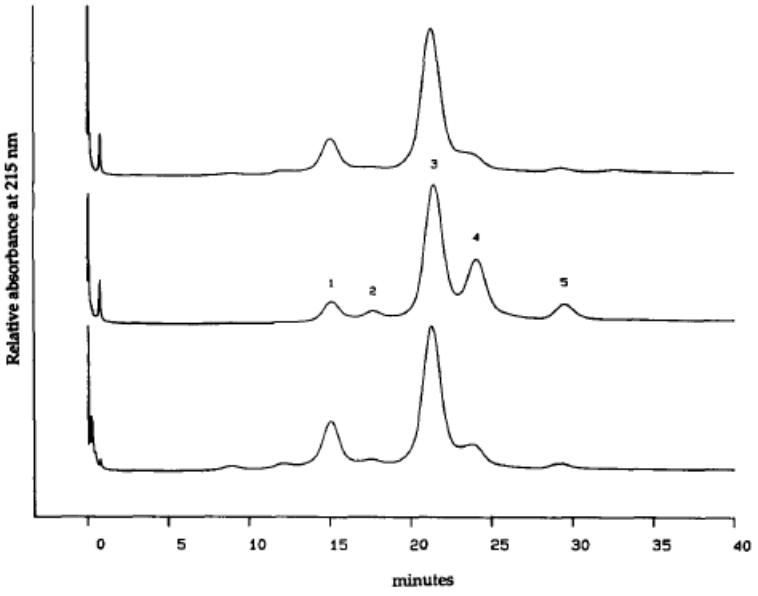
a. Elements [a] and [e]

Claim 1 requires, "A therapeutic composition comprising a mixture of anti-HER2 antibody" (element [a]) and "wherein the anti-HER2 antibody is humMAb4D5-8" (element [e]). Harris disclosed rhuMAb HER2 as "a recombinant humanized antibody produced in transfected CHO cells." (Exs. 1002, ¶259; 1007, 130.) As discussed above, rhuMAb HER2 is the humMAb4D5-8 antibody. (§§VII.D.2, VIII.A.1.b; Ex. 1002, ¶259.) Therefore, the "rhuMAb HER2" antibody disclosed by Harris is the same antibody as "humMAb4D5-8," as called for by claim 1. (Ex. 1002, ¶259.) Thus, Harris disclosed elements [a] and [e] of claim 1. (*Id.*)

A POSA would also have known that humAb4D5-8 was "the most potent" and "most preferred" humanized anti-HER2 antibody. (§VIII.B.1.a; Ex. 1002, ¶260.) A POSA would therefore have been motivated to use humMAb4D5-8 in an anti-HER2 therapeutic composition as taught by Harris. (Ex. 1002, ¶260.) Further, based on the teachings of Harris and their knowledge of the art, a POSA would also have had a reasonable expectation of success in obtaining a humMAb4D5-8 therapeutic composition. (*Id*.) Therefore, it would have been obvious to a POSA at the time to use humMAb4D5-8 in an anti-HER2 therapeutic composition, as required by elements [a] and [e] of claim 1. (*Id.*, ¶261.)

b. Elements [b], [d] and [f]

Claim 1 requires "one or more acidic variants thereof" (element [b]), "wherein the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated" (element [d]), and "wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate" (element [f]). Harris disclosed three cation exchange chromatograms of rhuMAb HER2 in Figure 2, as follows:



(Exs. 1002, ¶263; 1007, Fig. 2, 132.) Harris described the chromatogram in Figure 2 to have a main antibody peak (peak 3), two "basic" peaks having one lysine residue (peak 4) and two lysine residues (peak 5) at the C-terminus of the antibody heavy chain, and two "acidic" peaks, both deamidated at Asn30, with one having no lysine residues (peak 1) and the other having one lysine residue (peak 2) at the C-Terminus of the heavy chain. Thus, Harris taught that *both* peaks 1 and 2 are

"acidic variants" where Asn30 has been deamidated to aspartate. (Ex. 1002, ¶263.) Thus, Harris disclosed "one or more acidic variants" of humMAb4D5-8, as required by element [b], that the acidic variants are "predominantly" deamidated variants of asparagine, as required by element [d], and that the deamidation occurs at Asn30 to form aspartate, as required by element [f]. (*Id*.) Thus Harris disclosed elements [b], [d], and [f] of claim 1. (*Id*.)

Therefore, it would have been obvious to a POSA that the humMAb4D5-8 acidic variants taught by Harris were predominantly deamidated acidic variants where Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 was converted to aspartate, as required by elements [b], [d], and [f] of claim 1. (Ex. 1002, ¶264.)

c. Element [c]

Claim 1 element [c] would have been obvious over Harris in combination with the general knowledge of a POSA. (Ex. 1002, ¶¶265-271.) Element [c] of claim 1 requires that *all* acidic variants in the composition comprise less than 25% of the total antibody present. (Exs. 1002, ¶265.) Figure 2 of Harris disclosed the same three chromatograms as disclosed in Waterside. (Exs. 1002, ¶266; 1005, 4; 1007, 132.) Using the same analysis as described in Ground 3, the amount of acidic variants in the three chromatograms is 14.0% for the top, 8.5% for the middle, and 16.2% for the bottom. (Ex. 1002, ¶¶267.) Therefore, all the three

chromatograms disclosed in Harris contain "less than about 25%" acidic variants, as called for by claim 1. (*Id.*) As these are the only acidic variants, the total amount of acidic variants is within the claimed concentrations. (*Id.*) Therefore, the amount of the Asn30 variant is also within the claimed concentrations. (*Id.*)

A POSA would have been motivated to obtain a humMAb4D5-8 composition having a level of acidic variants at least as low as that described in Harris. (*Id.*, ¶¶268-269.) A POSA would have known that at least one of the sites of deamidation in the humMAb4D5-8 acidic variant, Asn30, was located in CDR1 of the humMAb4D5-8 V_L region, and thus "involved directly in binding the antibody to the antigen." (§VIII.B.1.c; Ex. 1002, ¶268.) This understanding is confirmed by the disclosure in Waterside that the deamidated Asn30 acidic variant exhibited only 82% of the activity of humMAb4D5-8. (§VIII.B.1.c; Ex. 1002, ¶269.)

A POSA would further have had a reasonable expectation of success in obtaining a humMAb4D5-8 composition having less than about 25% acidic variants, as called for by claim 1, based on the disclosures in Harris and a POSA's general knowledge at the time. (*Id.*, ¶270.) Harris taught that humMAb4D5-8 compositions having less than 25% acidic variants. (§VIII.A.1c; Ex. 1002, ¶270.) Further, a POSA would have known that CEX was the method of choice for reducing the amount of acidic variants in protein compositions, because CEX was

known to be able to separate proteins based on charge difference. (§VIII.B.1.c; Ex. 1002, ¶270.) Thus, a POSA would have had a reasonable expectation of success in obtaining a humMAb4D5-8 composition having less than the level of acidic variants called for by element [c] of claim 1 of the '218 patent. (Ex. 1002, ¶270.)

Therefore, it would have been obvious to a POSA at the time to reduce the amount of acidic variant(s) to an amount less than 25%, as required by claim 1 element [c]. (*Id.*, ¶271.)

d. Element [g]

Claim 1 element [g] would have been obvious over Harris in combination with the general knowledge of a POSA. (*Id.*, ¶272-274.) Claim 1 requires that the composition comprise "a pharmaceutically acceptable carrier" (element [g]).

A POSA would have known that antibodies, such as humMAb4D5-8, were formulated for administration in pharmaceutically acceptable carriers. (Exs. 1002, ¶273; 1004, Abstract, 9:19-22; 1006, 61:3-7.) Thus, a POSA would have been motivated to obtain a humMAb4D5-8 composition in a pharmaceutically acceptable carrier and would have had a reasonable expectation of success. (Ex. 1002, ¶273.) Therefore, it would have been obvious to a POSA at the time to use humMAb4D5-8, as taught by Harris, in a pharmaceutically acceptable carrier, as required by element [g] of claim 1. (*Id.*, ¶274.)

For all of the reasons described above, it would have been obvious to a POSA to reduce the amount of acidic variant(s) to an amount less than about 25%, where the acidic variant(s) are predominantly deamidated variants where one or more acidic variants of the anti-HER2 antibody have been deamidated, and where the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate. (*Id.*, ¶280-282.) Therefore, claim 1 as a whole would have been obvious over Harris in combination with the general knowledge of a POSA. (*Id.*)

2. Harris and a POSA's general knowledge render claim 5 obvious

Claim 5 depends from any one of claims 1 to 4 and requires the anti-HER2 antibody comprise "the light chain amino acid sequence of SEQ ID NO 1 and the heavy chain amino acid sequence of SEQ ID NO: 2." Claim 5 would have been obvious for all the reasons outlined above for claim 1 (§VIII.D.1), and further over Harris in combination with the general knowledge of a POSA, for the reasons set forth below. (Ex. 1002, ¶¶275-277.)

A POSA would have known the humAb4D5-8 amino acid sequence. (Exs. 1002, ¶175; 1006, Table 3, 72.) A POSA would also have known that humAb4D5-8 was "the most potent" and "most preferred" humanized anti-HER2 antibody. (§VIII.B.1.a; Ex. 1002, ¶276.) Therefore, it would have been obvious to a POSA

at the time to use humAb4D5-8, which is encoded by SEQ ID NOS 1 and 2, in an anti-HER2 composition, as required by claim 5. (Ex. 1002, ¶¶277.)

3. Harris and a POSA's general knowledge render claims 6 and 7 obvious

Claim 6 depends from any one of claims 1 to 4, and claim 7 depends from claim 5. Claims 6 and 7 require the composition "is in the form of a lyophilized formulation or an aqueous solution." Claims 6 and 7 would have been obvious for all the reasons outlined above for claims 1 and 5 (§VIII.D.1), and further over Harris in combination with the general knowledge of a POSA, for the reasons set forth below. (Ex. 1002, ¶¶278-279.)

Harris disclosed therapeutic antibody compositions as called for by claim 1. (§VIII.D.1.) A POSA would have known that water is a pharmaceutically acceptable carrier, which forms an "aqueous solution." (§VIII.B.1.d; Ex. 1002, ¶278.) Therefore, it would have been obvious to a POSA at the time to use the therapeutic antibody composition disclosed by Harris in a pharmaceutically acceptable carrier such as water, as required by claims 6 and 7. (Ex. 1002, ¶¶279.)

For all the reasons described above, claims 1 and 5-7 would have been obvious over Harris in combination with the general knowledge of a POSA. (*Id.*, ¶280-282.)

IX. NO SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS

Secondary considerations, including long-felt need, failure of others, unexpected results, commercial success, copying, and industry praise, may assist a court in avoiding hindsight bias. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). A showing of secondary considerations must be commensurate with the showing of obviousness—a weak showing of secondary considerations cannot overcome a strong prima facie case of obviousness. *Wyers v. Master Lock Co*., 616 F.3d 1231, 1246 (Fed. Cir. 2010). In addition, the patentee must establish a nexus between the secondary considerations and the claimed invention. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). No nexus exists unless the offered secondary consideration results from element that is both claimed and *novel.* *In re Kao*, 639 F.3d 1057, 1068, 1072 (Fed. Cir. 2011) (emphasis in original) (finding the only element not expressly disclosed was an inherent property, and concluding that evidence of secondary considerations did not outweigh the strong showing of obviousness).

Here, there is no evidence of any of secondary factors that could outweigh the strong case of prima facie obviousness under Section 103(a), as discussed herein and explained in the declaration of Dr. Drew Kelner. (Ex. 1002, ¶¶283-285.) Accordingly, there is no nexus between any secondary consideration and the elements recited in the claims.

X. CONCLUSION

For the reasons described above and in the concurrently filed declarations of Dr. Kelner, Dr. Buick, and Mr. Carson, this Petition demonstrates a reasonable likelihood that Petitioner will prevail with respect to at least one of the Challenged Claims pursuant to 35 U.S.C. § 314(a). Moreover, claims 1 and 5-7 of the '218 patent are invalid and should be cancelled.

Dated: December 18, 2017

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE PURSUANT TO 37 C.F.R. § 42

The undersigned certifies that this Petition complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). This Petition contains 13,908 words as counted by the word processing program Microsoft Word 2013, on which it was prepared, excluding the cover page, signature block, and those portions of the Petition exempted under 37 C.F.R. § 42.24(a)(1).

The undersigned further certifies that this brief complies with the typeface requirements of 37 C.F.R. § 42.6(a)(2)(ii) and typestyle requirements of 37 C.F.R. § 42.6(a)(2)(iii). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2013 in Times New Roman 14 point font.

Dated: December 18, 2017

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CERTIFICATE OF SERVICE

The undersigned certifies that, pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), a true and correct copy of this Petition for *Inter Partes* Review of U.S. Patent No. 9,249,218 and Exhibits 1001 to 1029 were served via FEDERAL EXPRESS priority next day delivery, on December 18, 2017 to the below correspondence address listed for U.S. Patent No. 9,249,218 on the United States Patent and Trademark Office Patent Application Information Retrieval (PAIR) website.

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