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. 6,339,142
Issue Date: Jan. 15, 2002
Title: PROTEIN PURIFICATION

Inter Partes Review No. Unassigned

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,339,142 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. 6,339,142 to Basey, C. D. and Blank, G. S., *Protein Purification* ("'142 patent")
1002	Declaration of Drew N. Kelner, Ph.D. ("Kelner Decl.")
1003	File History excerpts for U.S. Appl. Ser. No. 09/679,397, which issued as the '142 patent ("'397 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")

Pfizer Exhibit Number	Description
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.

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	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")
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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 to 3 ("Challenged Claims") of U.S. Patent No. 6,339,142 ("'142 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 therefore 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 '142 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 '142 patent was filed on August 29, 2017. (IPR2017-02019.) The '142 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 ’142 patent is also related to U.S. Patent Nos. 6,417,335, 6,489,447, 7,074,404, 7,531,645, 9,249,218, and U.S. Appl. Ser. Nos. 14/988,657 and 15/494,362.

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 '142 patent is available for IPR, and that Petitioner is not barred or estopped from requesting IPR of any claim of the '142 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 to 3 of the '142 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 '142 patent:

Ground	Reference(s)	Statutory Basis	Claims
1	Andya (Ex. 1004)	§ 102(b)	1 to 3
2	Andya (Ex. 1004)	§ 103(a)	1 to 3
3	Waterside (Ex. 1005)	§ 102(b)	1
4	Waterside (Ex. 1005)	§ 103(a)	1 to 3

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 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 a certain level of acidic variants of the antibody. (Ex. 1002, ¶37.) An example of an acidic variant includes a variant wherein deamidation occurs at asparagine position 30 ("Asn30") to form an aspartate residue. (Ex. 1002, ¶¶90-103.) 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, ¶¶32-227.) Moreover, the prior art taught that deamidation of asparagine is a major degradation pathway for all antibodies, not just humMAb4D5-8. (Exs. 1002, ¶¶94-103; 1012.)

Claims 1 to 3 were anticipated by Andya (Ground 1) and claim 1 was anticipated Waterside (Ground 3). Andya disclosed aqueous pharmaceutical formulations of humMAb4D5-8 that have been reconstituted from lyophilized material. (Exs. 1002, ¶¶115-116, 127-141; 1004, 18:34-19:2.) Analysis of the reconstituted humMAb4D5-8 solutions shows that the compositions contain less than the claimed amounts of all acidic variants. (Exs. 1002, ¶¶127-141; 1004, Fig.

5.) Waterside also disclosed humMAb4D5-8 compositions wherein the amount of acidic variants was less the claimed amounts. (Exs. 1002, ¶¶117-118, 188-203; 1005, 4-6.) Accordingly, Andya *explicitly* anticipates claims 1 to 3, and Waterside *explicitly* anticipates claim 1 of the '142 patent. (Ex. 1002, ¶¶127-141, 188-203.)

To the extent the prior art is found not to explicitly disclose humMAb4D5-8 compositions having the claimed amount of acidic variants, such a disclosure is *inherently* present in the prior art compositions. (Ex. 1002, ¶¶142-159; 1004, Fig. 5; 1005, 4, 6; 1007, 132.) In order to confirm that acidic variants are 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, ¶¶142-147; 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, ¶¶144-154; 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, regardless of the source of the antibody. (Exs. 1002, ¶152; 1004; 1005; 1007; 1015, ¶¶47-67.) Thus, formation of acidic variants is the inherent and inevitable result of humMAb4D5-8 expressed in HEK cells (as in

Andya), or in CHO cells (as in Waterside and commercial trastuzumab). (Exs. 1002, ¶153; 1004; 1005; 1007.)

The Challenged Claims would also have been obvious over any one of Andya or Waterside in combination with the general knowledge of a POSA (Grounds 2 and 4). (Ex. 1002, ¶¶160-187, 204-223.) Andya and Waterside both 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; Ex. 1002, ¶¶116, 118, 30-131, 166-167, 200, 211.) 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; Exs. 1002, ¶¶160-223; 1006, Table 3, 72:17, 61:3-7, 68:25-28; 1008; 1021.) A POSA would have been motivated to obtain a humMAb4D5-8 composition having at least a level of acidic variants as low as that disclosed in the prior art because humMAb4D5-8 acidic variants were known to occur in the antibody recognition region, and were known to exhibit reduced activity. (§§VIII.B.1.c, VIII.D.1.c; Ex. 1002, ¶¶169-171, 211-212.)

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 Challenged Claims based on Andya and Waterside.

(Ex. 1002, ¶¶172-178, 213-214.) Andya and Waterside 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, ¶¶133-137, 168-179, 197-202; 210-215.) A POSA would have known that cation exchange chromatography ("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, ¶¶172-174, 213.)

A POSA would also have had a reasonable expectation of success in obtaining a humMAb4D5-8 composition in a pharmaceutically acceptable carrier based on their general knowledge and the state of the art. (Ex. 1002, ¶¶190, 219.) 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, ¶¶180-182, 216-218.) 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, ¶¶160-187, 204-223.)

B. The '142 Patent and Background

1. The '142 Patent

The '142 patent issued on January 15, 2002 from U.S. Appl. Ser. No. 09/679,397 ("'397 application"), which was filed on October 3, 2000. (Ex. 1002, ¶¶35-53.) The '397 application is a division of U.S. Appl. Ser. No. 09/304,465

("'465 application") filed May 3, 1999, which issued as U.S. Patent No. 6,489,447. The '142 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, also claim priority to the '459 provisional. (Ex. 1002, ¶¶54-79.)

The '142 patent has 3 claims, claim 1 being the sole independent claim. The '142 patent claims are directed to compositions comprising the humMAb4D5-8 anti-HER2 antibody comprising certain levels of "acidic variants" of humMAb4D5-8. Claim 1 requires "the amount of the acidic variant(s) is less than about 25%." Claim 2 requires that the composition comprise "a pharmaceutically acceptable carrier." Claim 3 requires "the anti-HER2 antibody is humMAb4D5-8."

The '142 patent acknowledges that the full length amino acid sequence of humMAb4D5-8 was known to the public, and that "humMAb4D5-8" was previously disclosed as "rhuMAb HER2." (Exs. 1001, 20:48-52; 1002, ¶¶50, 86.) The '142 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, 1:66-67; 1002, ¶¶46-47.) Thus, the fact that

ion-exchange chromatography resolves proteins based on charge was known in the art and acknowledged by the ’142 patent. (Ex. 1002, ¶¶46-47.)

The ’142 patent specification purports to disclose a novel ion exchange chromatographic method where:

> Following washing with the intermediate buffer, the cation exchange resin is washed or re-equilibrated with the wash buffer which has a conductivity or pH, or both, which is/are less than that of the intermediate buffer (i.e. *the conductivity, or pH, or both, is/are changed in an opposite, i.e.* ***reverse****, direction to the preceding step, unlike ion exchange chromatography steps in the literature*).

(Exs. 1001, 17:63-18:2 (emphasis added); 1002, ¶39.) This “reverse” wash step, however, is not claimed in the ’142 patent, and no methods limitations appear in the Challenged Claims. (Ex. 1002, ¶¶39-40.) Thus, the purported novelty disclosed by the ’142 patent is not present in the Challenged Claims. (Ex. 1002, ¶40.) Moreover, as discussed in more detail below, the POSA would have had no difficulty obtaining a humMAb4D5-8 composition having the requisite levels of acidic variants 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 '142 patent. (Ex. 1002, ¶41.)

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, ¶¶42-45.) Example 1, the sole example in the '142 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, 23:57-63; 1002, ¶42) Thus, the inventors obtained a humMAb4D5-8 composition having 25% acidic variants, without performing *any* CEX. (Ex. 1002, ¶42.)

2. Prosecution History and Related Proceedings

a. U.S. prosecution history

'905 Application Prosecution. The '397 application ('142 patent) and U.S. Appl. Ser. No. 12/418,905 ("'905 application) are both child applications of the '465 application and the '459 provisional. (Ex. 1002, ¶¶54-59.) The pending claims of the '905 application were directed to the same subject matter as the '142 patent. (Exs. 1002, ¶54; 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, ¶¶55, 56, 58; 1018, 20-26, 35-42, 71-80.)

In response, the Patent Owner argued that the claims are not directed to "non-native variants" as Andya disclosed, but rather to "acidic variants," and relied on a declaration by named inventor Dr. Greg Blank. (Exs. 1002, ¶57; 1018, 43-51.) The Patent Office maintained its rejection that Andya anticipated the pending claims. (Exs. 1002, ¶58; 1018, 71-80.) In an Examiner interview, the Patent Owner "urged that Andya et al does not disclose the precise nature of the variants produced." (Exs. 1002, ¶59; 1018, 81-82.) The Patent Owner did not respond to the Office Action and the application was abandoned. (Exs. 1002, ¶59; 1018, 84.)

'397 Application Prosecution. The '142 patent issued from the '397 application, which was filed on January 15, 2002. The pending claims 28-30 were identical to issued claims 1-3, respectively. (Exs. 1002, ¶52; 1003, 2-6.)

On July 9, 2001, the Patent Office required the applicant to provide a paper and CRF copy of the sequences, and make corrections to the specification. (Exs. 1002, ¶53; 1003, 7-11.) On August 7, 2001, the applicant made the amendment, and a notice of allowance was filed on August 22, 2001. (Exs. 1002, ¶53; 1003, 12-26.) The '142 patent issued on January 15, 2002 with claims 1-3. (Ex. 1001.)

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, ¶64; 1014.) Claim 1 of EP'455 is directed to the same subject matter as claim 1 of the '142 patent. (Ex. 1002, ¶65.)

EP'455 was challenged in *Hospira UK Limited v. Genentech Inc.*, HC12C03487 ("U.K. litigation," Ex. 1025.) (*Id.* at ¶66-68.) The U.K. Court found that a "case for anticipation by Andya is proved." (*Id.* at ¶67.) The U.K. Court further held that Andya is an enabling disclosure, comprising no more than 18% acidic variants." (*Id*.) The Court also found that all of the claims of EP '455 lacked inventive step over Waterside. (*Id.* at ¶68.)

EP '455 was also revoked in a European opposition proceeding (EP Appl. No. 02029008.6) (Ex. 1026) for lack of novelty over Andya, but reinstated on appeal. (Exs. 1002, ¶¶69-72; 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 V_L regions of humMAb4D5-8 converted to aspartate." (Exs. 1002, ¶¶70-71; 1027, ¶13.) However, unlike the EP '455 claims, the Challenged Claims in this Petition do not require that the acidic variants are "predominantly deamidated variants,

wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate," and therefore the TBA holding is not relevant. As discussed herein below, Andya both explicitly and inherently disclosed humMAb4D5-8 compositions meeting the Challenged Claims. (Ex. 1002, ¶¶127-159.)

CN '836, entitled "Protein Purification by Ion Exchange Chromatography," issued on June 21, 2006. (Ex. 1002, ¶¶73-76.) Claims 1-3 of CN '836, collectively, are nearly identical to claim 1 of the '142 patent. (Ex. 1002, ¶74.) The Intermediate Court in Beijing found that claims 1-3 of CN '836 were not novel or inventive over Andya. (Exs. 1002, ¶75; 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, ¶76; 1029, 12.)

3. State of the Art as of the '142 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, ¶¶94-103; 1011; 1024; 1012, 3-4.) Antibodies for therapeutic use were also known to be deamidated at asparagine to form acidic variants. (Exs. 1002, ¶¶96-103; 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 '142 patent. (Exs. 1002, ¶¶96-103; 1012, 3-4.)

A POSA would 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, ¶¶104-111.) Acidic variants are charge variants, meaning they have a different charge than the native protein. (Exs. 1002, ¶113; 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, ¶¶112-114; 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 '142 patent relates to the purification of a monoclonal antibody. (Ex. 1002, ¶30.) The POSA for the '142 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 '142 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 "composition"

The term "composition" in claim 1 of the '142 patent should be construed in accordance with its broadest reasonable construction to mean a composition appropriate for any use, 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, ¶80.) Support for this construction comes from the claim itself, which contains no requirement for any use or therapeutic effectiveness, nor does the claim contain limitations directed to a specific process or scale. (Ex. 1002, ¶81.) 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 supports Petitioner's proposed construction. The '142 patent specification disclosed that "[t]he 'composition' to be purified

herein comprises the polypeptide of interest and one or more contaminants." (Exs. 1001, 4:23-24; 1002, ¶82.) Moreover, the '142 patent disclosed the "polypeptide purified as disclosed herein or the composition comprising the polypeptide and a pharmaceutically acceptable carrier is then used for various diagnostic, therapeutic or other uses known for such polypeptides and compositions." (Exs. 1001, 20:35-39; 1002, ¶82.) The '142 patent does not disclose a specific dose amount or treatment regimen in relation to such uses. (Ex. 1002, ¶82.) Moreover, the '142 patent does explicitly or implicitly requires the composition to be made by any specific process, or manufactured at any scale. (Ex. 1002, ¶83-84.) Thus, a POSA would understand that the term "composition" is not limited to any specific dose amount, process, or scale of manufacture. (Ex. 1002, ¶85.)

2. 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, ¶90.) The '142 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, 5:46-49; 1002, ¶91.) The '142 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, 5:50-54; 1002, ¶92.)

Moreover, according to the '142 patent specification, the deamidated humMAb4D5 antibody from Example 1 has "Asn30 in CDR1 of either or both of the V_L regions thereof converted to aspartate." (Exs. 1001, 5:55-57; 1002, ¶93.) A POSA would understand that an aspartate has a more acidic side chain than asparagine. (Ex. 1002, ¶93.) Thus, the example uses the term "acidic variant" in a manner consistent with the definition provided by the specification. (*Id.*)

3. 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, ¶86.) The '142 patent disclosed "Full 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, 20:48-52 (emphasis added); 1002, ¶86.) Therefore, the '142 patent

[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, ¶87.)

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 '142 patent. (Ex. 1002, ¶86.)

"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 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 '142 patent is binding on the Patent Owner.

In addition, named inventor Dr. Gregory Blank submitted a declaration to the Patent Office during prosecution of the '905 application, which is in the same patent family as the '142 patent. (Exs. 1002, ¶88; 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, ¶88; 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 '142 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, 21:10-12; 21:32-36; 22:1-2; 22:15-18; 23:3-5; 23:10-24:40, Table 3; 1002, ¶89.) A POSA would therefore understand the term "rhuMAb HER2" to be synonymous with "humMAb4D5-8." (Ex. 1002, ¶89.)

E. Prior Art Relied On In Grounds

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 '142 patent, and is therefore prior art under 35 U.S.C. § 102(b). Andya was not before the Patent Office during prosecution of the '142 patent.

Andya disclosed reconstituted compositions "comprising full length humanized antibody humMAb4D5-8." (Exs. 1002, ¶¶115-116; 1004, 19:1-2.) Andya further taught that deamidation occurs at Asn30 of humMAb4D5-8. (§VIII.A.1.b; Ex. 1002, ¶116.) Moreover, Andya taught "the major degradation

route for rhuMAb HER2 in aqueous solutions is deamidation or succinimide formation." (§VIII.A.1.b; Ex. 1002, ¶116.) 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, ¶116.)

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 is a printed publication and was available to the public as of April 22 to 25, 1996 (Ex. 1020, Carson Decl.), which is more than one year before May 6, 1998, the earliest possible priority date of the '142 patent, and is therefore prior art under 35 U.S.C. § 102(b). Although Waterside was before the Patent Office during prosecution of the '142 patent, it was not relied upon in a rejection under § 102 or 103.

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.)

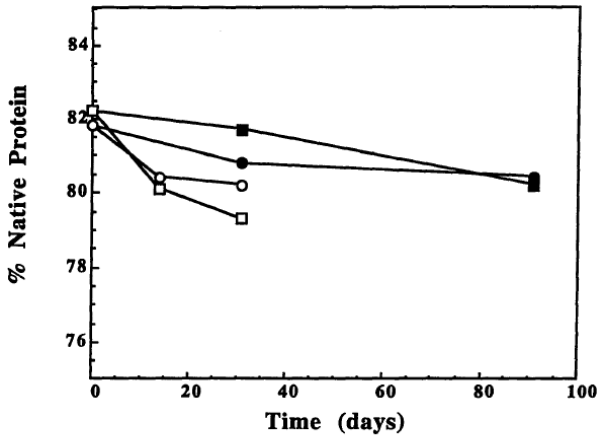
Waterside disclosed cation-exchange chromatograms of the rhuMAb HER2 (humMAb4D5-8) antibody having only two major "acidic variants." (§VIII.C.1.c; Exs. 1002, ¶¶117-118.) Waterside disclosed Peak IEX-1 ("peak 1") in the "acidic" region of the chromatogram, to contain a mutation where the asparagine at amino acid position 30 has been deamidated to aspartate. (§VIII.C.1.c; Exs. 1002, ¶118.) Waterside further disclosed that the deamidated Asn30 acidic variant of "peak 1" retains only 82% of the specific activity of the parent antibody. (§VIII.C.1.c; Exs. 1002, ¶118.)

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

A. Ground 1: Andya Anticipates Claims 1 to 3

Andya anticipates claims 1 to 3 as shown in the following chart and discussed below. (Ex. 1002, ¶¶127-159.)

Claim Limitations	Disclosed in Ex. 1004
1.[a] A 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

Claim Limitations	Disclosed in Ex. 1004
	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%.	"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.)  FIG. 5 (Ex. 1004, Fig. 5.)
2. The composition of claim 1 further comprising a pharmaceutically	"A stable lyophilized protein formulation is described which can be

Claim Limitations	Disclosed in Ex. 1004
acceptable carrier.	reconstituted with a suitable diluent to generate a high protein concentration reconstituted formulation which is suitable for subcutaneous 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.)
3. The composition of claim 1 wherein the anti-HER2 antibody is humMAb4D5-8.	See claim 1, element [a].

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). As Courts have

held, newly discovered results of "known processes directed to the same purpose are not patentable because such results are inherent." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001). "It matters not that those of ordinary skill heretofore may not have recognized the[ ] inherent characteristics of the [prior art]." *In re Montgomery*, 677 F.3d at 1381. (quoting *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1350 (Fed. Cir. 2002).)

1. Claims 1 to 3 were anticipated by Andya

a. Claim 1 element [a]

Claim 1 requires "A composition comprising a mixture of anti-HER2 antibody" (claim 1, element [a]). Andya disclosed "a lyophilized formulation comprising full length humanized antibody humMAb4D5-8 described in WO 92/22653." (Exs. 1002, ¶128; 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, ¶128; 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, ¶¶128-129.)

b. Claim 1 element [b]

Claim 1 also requires "one or more acidic variants thereof" (element [b]). Andya taught "[i]n the liquid state, rhuMAb HER2 was observed to degrade by deamidation (30Asn of light chain)." (Exs. 1002, ¶130; 1004, 19:13-14.)

Deamidation of asparagine (Asn) converts the amide-containing amino acid to aspartate (Asp), thus creating an "acidic variant." (Ex. 1002, ¶130.) Moreover, during prosecution of the '905 application, the Patent Owner admitted that "rhuMAb HER2" is the same antibody as humMAb4D5-8. (§VII.D.3; Ex. 1002, ¶131.) The term "rhuMAb HER2" is furthermore used throughout the '142 patent interchangeably with humMAb4D5-8. (Ex. 1002, ¶131.) 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, ¶¶130-132.)

c. Claim 1 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, ¶134.) Example 1 of Andya disclosed stability testing of liquid humMAb4D5-8 formulations, reconstituted from lyophilized formulations. (Exs. 1002, ¶134; 1004, 24:11-27:17.) Figures 5 to 8 report humMAb4D5-8 stability as "% Native Protein." (Exs. 1002, ¶134; 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, ¶134; 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, ¶135.)

The "% Native Protein" reported for the 4 mL humMAb4D5-8 composition in Figure 5 of Andya is 82% at time zero. (Exs. 1002, ¶¶135-136; 1004 at 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, ¶136.) 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.* at 133-137.)

d. Claim 2

Claim 2 depends from claim 1 and incorporates all of the limitations of claim 1. Claim 2 further requires that the composition comprise "a pharmaceutically acceptable carrier." Claim 2 was anticipated in view of Andya for the reasons described above for claim 1 and as set forth below. 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, ¶150; 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, ¶150; 1004, 9:19-22.) Thus, Andya disclosed claim 2. (Ex. 1002, ¶150.)

e. Claim 3

Claim 3 depends from claim 1 and incorporates all of the limitations of claim 1. Claim 3 further requires "wherein the anti-HER2 antibody is humMAb4D5-8." Claim 3 was anticipated in view of Andya for the reasons described above for claim 1 and as set forth below. Andya further taught that humMAb4D5-8 is a "full length humanized antibody." (Exs. 1002, ¶139; 1004, 19:1-2.) Example 1 of Andya disclosed an "ANTI-HER2 FORMULATION" comprising humMAb4D5-8, an anti-HER2 antibody. (Exs. 1002, ¶139; 1004, 18:34-19:2.) Therefore, Andya disclosed the anti-HER2 antibody humMAb4D5-8, as called for by claim 3. (Ex. 1002, ¶¶139-140.) Thus, Andya disclosed claim 3. (*Id.*)

Accordingly, Andya explicitly disclosed each and every element of claims 1 to 3 of the '142 patent. (*Id* at ¶141.)

2. Elements [b] and [c] of claim 1 were inherently present in humMAb4D5-8 compositions

As discussed above, Andya explicitly disclosed each and every element of claims 1 to 3 of the '142 patent. (Ex. 1002, ¶¶127-141.) To the extent it is found that Andya does not explicitly disclose elements [b] or [c] of claim 1, Andya inherently disclosed them. (Ex. 1002, ¶¶142-159.) In order to evaluate the

inherency of acidic variants in humMAb4D5-8 compositions, 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, ¶¶142-154; 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 elements [b] and [c] of claim 1. (Ex. 1002, ¶143.) Therefore, element [b] and [c] of claim 1 were also 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, ¶144-146; 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 '142 patent. (Exs. 1002, ¶144; 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, ¶145; 1015, ¶17-19), transfected the expression vector into HEK and CHO cells (Exs. 1002, ¶145; 1015, ¶20-22), and expressed the antibody. (Exs. 1002, ¶145; 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, ¶146-147; 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, ¶148; 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, ¶148; 1015 at ¶¶62-65, Figure G.) Dr. Buick also performed a peak analysis of commercial trastuzumab demonstrating the formation of an acidic variant in commercial trastuzumab. (Exs. 1002, ¶¶149-151; 1015, ¶¶59-61, Figures E and F.)

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, ¶152; 1015, ¶¶62-65; Figure G.) At least one acidic variant is inherently produced when the humMAb4D5-8 antibody is produced in either HEK or CHO cells. (Ex. 1002, ¶153.) Dr. Buick also identified the amount of acidic variant in a sample of commercial trastuzumab,

further confirming the inherency of acidic variants of the humMAb4D5-8 antibody. (Exs. 1002, ¶154-157; 1015, ¶¶59-61, 66-67.)

Andya further inherently disclosed "less than about 25% acidic variants," as required by element [c] of claim 1 because the composition of Figure 5 contained no less than 82% humMAb4D5-8, and therefore could not have contained more than 18% acidic variant. (*Id.*, ¶157.) Therefore, element [c] of claim 1 was inherently anticipated by Andya (§VIII.A.1.c; Ex. 1002, ¶157.)

The experiments performed by Dr. Buick were standard for a person of ordinary skill in the art as of the time the '142 patent was filed. (Ex. 1002, ¶158.) Any differences between the experiments performed by Dr. Buick and the prior art are not significant. (Ex. 1002, ¶147.) Subsequent disclosures in Harris 2001 further support Dr. Buick's findings. (Exs. 1002, ¶¶155-157; 1017, Figure 2, 238, Table 6, 243.) Thus, Dr. Buick's experiments, and subsequently published data, establish that Andya inherently disclosed elements [b] and [c] of claim 1, if not already disclosed explicitly. (Ex. 1002, ¶¶157-158.)

Therefore, Andya explicitly and/or inherently disclosed each and every element of claims 1 to 3 of the '142 patent. (Ex. 1002, ¶159.)

B. Ground 2: Andya and a POSA's General Knowledge Render Claims 1 to 3 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[2] 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.) The inventor's "own path itself never leads to a conclusion of

[2] The phrases "at the time" and "prior to the '142 patent" refer to May 6, 1998, the earliest priority date claimed by the '142 patent.

obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012).

Claims 1 to 3 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, ¶¶160-187.) As discussed above, Andya disclosed each and every element of claims 1 to 3 of the '142 patent. (§VIII.A; Ex. 1002, ¶¶ 127-159.)

1. Andya and the general knowledge of a POSA render claims 1 to 3 obvious

a. Claim 1 element [a]

As explained above, Andya disclosed element [a] of claim 1 (§VIII.A.1.a), which is incorporated by reference here. Element [a] 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, ¶¶161-163.) Claim 1 requires, "A composition comprising a mixture of anti-HER2 antibody" (claim 1, element [a]). As discussed above, Andya disclosed "a lyophilized formulation comprising full length humanized antibody humMAb4D5-8 described in WO 92/22653." (Exs. 1002, ¶161; 1004, 19:1-2.) Therefore, Andya disclosed the anti-HER2 antibody humMAb4D5-8, as called for by claim 1 elements [a]. (Ex. 1002, ¶161.)

A POSA would have known that humMAb4D5-8 was "the most potent" and "most preferred" humanized anti-HER2 antibody. (Exs. 1002, ¶162; 1006, 68:25-

26, 82:11-13; 1008, 4288.) A POSA would therefore have been motivated to use humMAb4D5-8 in an anti-HER2 antibody composition as taught by Andya. (Ex. 1002, ¶163.) Further, based on the teachings of Andya and their general knowledge, a POSA would have had a reasonable expectation of success in obtaining an anti-HER2 therapeutic composition. (*Id.*) Therefore, it would have been obvious to a POSA at the time the '142 patent was filed to use an anti-HER2 composition, as required by element [a] of claim 1. (*Id.* at ¶164.)

b. Claim 1 element [b]

As explained above, Andya disclosed element [b] of claim 1 (§VIII.A.1.b), which is incorporated by reference here. Element [b] 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, ¶¶165-167.) Claim 1 requires "one or more acidic variants thereof" (element [b]). Deamidation of asparagine was known to be a major degradation pathway for proteins in general, including antibodies. (Exs. 1002, ¶165; 1012, 3-4.) Thus, a POSA would have known that deamidation occurs and that CEX could purify such compositions. (Ex. 1002, ¶165.)

Andya taught "[i]n the liquid state, rhuMAb HER2 was observed to degrade by deamidation (30Asn of light chain)," thus creating an acidic variant. (§VIII.A.1; Exs. 1002, ¶166; 1004, 19:13-14.) A POSA would have known that

Asn30 is located in CDR1 of the humMAb4D5-8 V_L region, and V_L regions "are involved directly in binding the antibody to the antigen." (§VIII.A.1.c; Ex. 1002, ¶166.) Therefore, it would have been obvious to a POSA that humMAb4D5-8 compositions had one or more acidic variants as taught by Andya, and as required by element [b] of claim 1. (Ex. 1002, ¶167.)

c. Claim 1 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, ¶¶168-179.) Element [c] of claim 1 requires that *all* acidic variants in the composition comprise less than 25% of the total antibody present. (*Id.* at 168.) Obtaining a humMAb4D5-8 composition having less than 25% acidic variants would have been obvious to a POSA based on the disclosures of Andya and a POSA's general knowledge. (Ex. 1002, ¶168.)

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 the Andya. (Ex. 1002, ¶¶169-171.) 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, ¶169; 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, ¶166.)

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, ¶172.) Andya disclosed humMAb4D5-8 compositions having 18% acidic variant. (§VIII.A.1.c; Ex. 1002, ¶172.) 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, ¶172-174.) CEX was also known to be useful and scalable to manufacturing levels. (§VII.B.3; Ex. 1002, ¶174.)

A POSA would further have known that an antibody composition having the levels of acidic variants disclosed in Andya could have been obtained by employing known techniques such as optimizing load, wash and elution buffers, flow rate, gradient elution, and peak-cutting. (Ex. 1002, ¶175.) 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,

¶176-177; 1015, ¶¶8-15, 43-46.) Dr. Buick's chromatography procedure did not include the "reverse" wash step purported to be required by the '142 patent (Exs. 1002, ¶177; 1015, ¶¶43-46.), yet pure humMAb4D5-8 antibody was obtained and verified by subsequent CEX. (Exs. 1002, ¶177; 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, ¶177; 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 '142 patent. (Ex. 1002, ¶178.)

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, ¶178.) 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% in a composition comprising a mixture of anti-HER2 antibody and one or more acidic variants. (*Id*.) Therefore, claim 1 as a whole would have been obvious over Andya in combination with the general knowledge of a POSA. (*Id.*)

d. Claim 2

As explained above, Andya disclosed claim 2 (§VIII.A.1.d), which is incorporated by reference here. Claim 2 depends from claim 1 and incorporates all of the limitations of claim 1. Claim 2 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, ¶¶180-182.) Claim 2 requires that the composition comprise "a pharmaceutically acceptable carrier."

As discussed above, Andya disclosed a humMAb4D5-8 composition in a pharmaceutically acceptable carrier. (§VIII.A.1.d; Ex. 1002, ¶180.) Moreover, a POSA would have known that antibodies, such as humMAb4D5-8, were formulated for administration in pharmaceutically acceptable carriers. (Exs. 1002, ¶181; 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, ¶181.) 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 claim 2. (*Id.* at ¶182.)

e. Claim 3

As explained above, Andya disclosed claim 3 (§VIII.A.1.e), which is incorporated by reference here. Claim 3 depends from claim 1 and incorporates all

of the limitations of claim 1. Claim 3 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, ¶¶183-185.) Claim 3 depends on claim 1 and requires "wherein the anti-HER2 antibody is humMAb4D5-8." As discussed above, Andya taught a composition of humMAb4D5-8 having less than about 25% acidic variants. (§VIII.A; Ex. 1002, ¶183.) Moreover, a POSA would have known that humMAb4D5-8 was "the most potent" and "most preferred" humanized variant of the anti-HER2 antibodies evaluated. (Exs. 1002, ¶184; 1006, 68:25-26, 82:11-13; 1008.) A POSA would therefore have been motivated to use humMAb4D5-8 in an anti-HER2 antibody composition as taught by Andya. (Ex. 1002, ¶184.) Further, based on the teachings of Andya and the general knowledge of a POSA, 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 the '142 patent was filed to use humMAb4D5-8 in an anti-HER2 composition, as required by claim 3. (*Id.*, ¶185.)

Therefore, claims 1 to 3 would have been obvious over Andya and the general knowledge of a POSA. (Ex. 1002, ¶¶186-187.)

C. Ground 3: Waterside Anticipates Claim 1

Waterside anticipates claim 1 of the '142 patent as discussed below. (Ex. 1002, ¶¶188-203.)

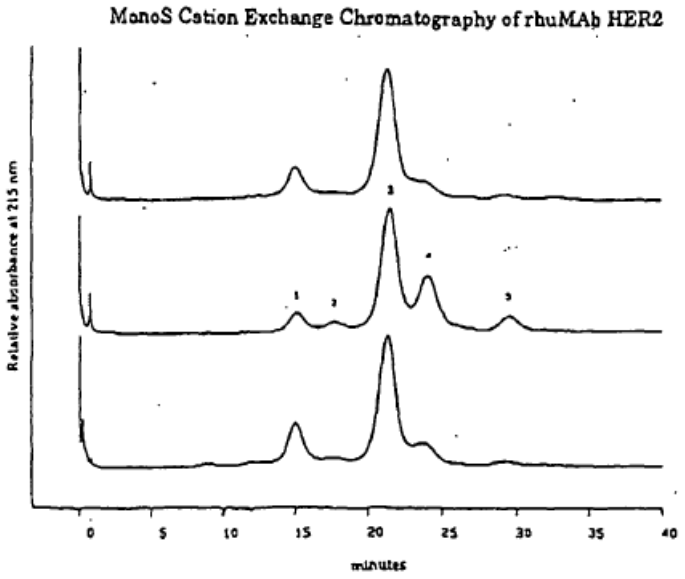
1. Claim 1 was anticipated by Waterside

a. Claim 1 element [a]

Claim 1 requires "A composition comprising a mixture of anti-HER2 antibody" (claim 1, element [a]). Waterside disclosed an antibody directed against the extracellular domain of the HER2 protein. (Exs. 1002, ¶189; 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, ¶189; 1005, 3.) Waterside also disclosed that the antibody is "in phase III clinical trials (breast cancer)." (Exs. 1002, ¶189; 1005, 3.) Waterside thus disclosed a composition comprising an anti-HER2 antibody. (Ex. 1002, ¶190.) Thus, Waterside disclosed element [a] of claim 1. (*Id.*)

b. Claim 1 element [b]

Claim 1 requires "one or more acidic variants thereof" (element [b]). Waterside disclosed three cation exchange chromatograms entitled "MonoS Cation Exchange Chromatography of rhuMAb HER2," as shown below:



(Exs. 1002, ¶191; 1005, 4.) "MonoS" is a type of cation exchange column, which was available at the time. (Ex. 1002, ¶191.) The middle chromatogram contains five peaks, labeled 1 to 5 from left to right. (Exs. 1002, ¶191; 1005, 4.) Each "peak" represents a different charged species. (Ex. 1002, ¶191.) 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.*, ¶192.)

Peak 3 of the MonoS chromatogram is the parent antibody peak, comprising humMAb4D5-8. (Exs. 1002, ¶193; 1005, 4.) 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.*) 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, ¶193.) 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.*)

Harris would have further confirmed to a POSA that Waterside disclosed a composition with at least one acidic variant. (Ex. 1002, ¶194.) Figure 2 of Harris disclosed the same three chromatograms as disclosed in Waterside. (Exs. 1002, ¶194; 1005, 4; 1007, 132.) Moreover, Harris described the chromatographic conditions for the data in Figure 2 as being performed on a "Pharmacia MonoS column," the same type of column as disclosed in Waterside. (Exs. 1002, ¶194; 1005, 4; 1007, 130.)

Harris confirms the disclosure of Waterside by disclosing the same set of three humMAb4D5-8 chromatograms (Ex. 1007, Fig. 2), and disclosing the peak assignments. Harris described the chromatogram in Figure 2 to have a main antibody peak (peak 3), two "basic" peaks having one (peak 4) and two (peak 5) lysine residues at the C-terminus of the antibody heavy chain, and "acidic" peaks deamidated at Asn30 having no lysine residues (peak 1) or one lysine residue (peak 2) at the C-Terminus of the heavy chain. (Exs. 1002, ¶195; 1007, 131.) Thus, Harris taught that ***both*** peaks 1 and 2 are "acidic variants" where Asn30 has been deamidated to aspartate, just as Waterside taught. (Ex. 1002, ¶195.) Thus, Harris

further confirms that Waterside disclosed "one or more acidic variants" of humMAb4D5-8, as required by element [b]. (Ex. 1002, ¶195-196.)

c. Claim 1 element [c]

Claim 1 requires "wherein the amount of the acidic variant(s) is less than about 25%" (element [c]). Element [c] of claim 1 requires that *all* acidic variants in the composition comprise less than 25% of the total antibody present. (Ex. 1002, ¶197.) A POSA would have known, based on their understanding of CEX and the definition of "acidic variant" in the '142 patent, that peaks 1 and 2 in the MonoS chromatograms are the *only* acidic variants in the chromatograms. (Exs. 1002, ¶198; 1005, 6.) The '142 patent defines acidic variant as "more acidic . . . than the polypeptide of interest." (§VII.D.3; Exs. 1001, 5:46-48; 1002, ¶198.) A POSA would have known that peak 3 represents native humMAb4D5-8, and therefore is "the polypeptide[s] of interest." (Ex. 1002, ¶198.) Peaks 1 and 2 would therefore have been understood by a POSA to be the acidic variants because they are the only peaks in the chromatogram that are "more acidic" than peak 3. (Exs. 1001, 5:46-48; 1002, ¶198.)

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, ¶199.) 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.*, ¶¶200-201.) Moreover, using the same analysis, the amount of acidic variants in the three chromatograms for the graph disclosed in Harris is 14.0% for the top, 8.5% for the middle, and 16.2% for the bottom, further confirming that the compositions disclosed in Waterside contain "less than about 25%" of acidic variants. (*Id*., ¶201) As these are the only acidic variants, the total amount of acidic variants is within the claimed concentrations. (*Id.*) Therefore, all three chromatograms disclosed in Waterside contain "less than about 25%" acidic variants, as called for by claim 1 element [c]. (*Id*.)

Accordingly, Waterside explicitly disclosed each and every element of claim 1 of the '142 patent. (*Id* at ¶202.)

2. Elements [b] and [c] of claim 1 were inherently present in humMAb4D5-8 compositions

As discussed above, Waterside explicitly disclosed each and every element of claim 1 of the '142 patent. (§VIII.C.1.) Waterside further inherently disclosed elements [b] and [c] of claim 1. As discussed above, 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] of claim

1. (§VIII.A.2.; Exs. 1002, ¶203; 1015, ¶¶5-69.) Waterside further inherently disclosed "less than about 25% acidic variants," as required by element [c] of claim 1, as all three chromatograms disclosed in Waterside were demonstrated to contain "less than about 25%" acidic variants. (Ex. 1002, ¶203.) Therefore, elements [b] and [c] of claim 1 were inherently anticipated by Waterside. (*Id.*) Accordingly, Waterside explicitly and/or inherently disclosed each and each and every element of claim 1 the '142 patent. (*Id.*)

D. Ground 4: Waterside and a POSA's General Knowledge Render Claims 1 to 3 Obvious

1. Waterside and a POSA's general knowledge render claims 1 to 3 obvious

a. Claim 1 element [a]

As explained above, Waterside disclosed element [a] of claim 1 (§VIII.C.1.a), which is incorporated by reference here. Element [a] would also have been obvious under 35 U.S.C. § 103 in view of Waterside and the general knowledge of a POSA, for the reasons set forth below. (Ex. 1002, ¶¶205-207.) Claim 1 requires "A composition comprising a mixture of anti-HER2 antibody" (claim 1, element [a]). As discussed above, Waterside disclosed a "composition comprising a mixture of anti-HER2 antibody," as required element [a] of claim 1. (§VIII.C; Ex. 1002, ¶205.)

A POSA would also have known that humMAb4D5-8 was "the most potent" and "most preferred" humanized variant of the anti-HER2 antibodies evaluated.

(Exs. 1002, ¶206; 1006, 68:25-26, 82:11-13; 1008.) A POSA would therefore have been motivated to use humMAb4D5-8 in an anti-HER2 therapeutic composition as taught by Waterside. (Ex. 1002, ¶206.) 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 an anti-HER2 therapeutic composition. (*Id.*) Therefore, it would have been obvious to a POSA at the time the '142 patent was filed to use an anti-HER2 composition, as required by element [a] of claim 1. (*Id.* at ¶207.)

b. Claim 1 element [b]

As explained above, Waterside disclosed element [b] of claim 1 (§VIII.C.1.b), which is incorporated by reference here. Element [b] would also have been obvious under 35 U.S.C. § 103 in view of Waterside and the general knowledge of a POSA, for the reasons set forth below. (Ex. 1002, ¶¶208-209.) Claim 1 element [b] requires "one or more acidic variants thereof." As discussed above, Waterside disclosed a composition having an anti-HER2 antibody having "one or more acidic variants," as called for by claim 1 element [b]. (§VIII.C.1.b.; Ex. 1002, ¶208.) Furthermore, Harris would have confirmed to a POSA that Waterside disclosed a composition with at least one acidic variant. (§VIII.C.1.b.; Ex. 1002, ¶208.) Therefore, humMAb4D5-8 compositions with one or more acidic

variants, as required by element [b] of claim 1, would have been obvious to a POSA at the time the '142 patent. (*Id.* at 209.)

c. Claim 1 element [c]

As explained above, Waterside disclosed element [c] of claim 1 (§VIII.C.1.c), which is incorporated by reference here. Element [c] would also have been obvious under 35 U.S.C. § 103 in view of Waterside and the general knowledge of a POSA, for the reasons set forth below. (Ex. 1002, ¶¶210-215.) Element [c] of claim 1 requires that *all* acidic variants in the composition comprise less than 25% of the total antibody present. Obtaining a composition wherein the amount of the acidic variant(s) is less than about 25% would have been obvious to a POSA based on the disclosures of Waterside and a POSA's general knowledge. (Ex. 1002, ¶210.) As discussed above, all three chromatograms disclosed in Waterside, as further confirmed by Harris, contain "less than about 25%" acidic variants, as called for by claim 1 element [c]. (§VIII.C.1.c.; Ex. 1002, ¶210.)

A POSA would have been motivated to obtain a humMAb4D5-8 composition having at least a level of acidic variants as low as that described in Waterside. (§VIII.B.1.c; Ex. 1002, ¶¶211-212.) 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, ¶211.) Waterside

taught that the deamidated Asn30 acidic variant exhibits only 82% specific activity compared to humMAb4D5-8. (Exs. 1002, ¶211; 1006, 7.) Thus, POSA would 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, ¶211-212.)

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, ¶213.) Waterside taught humMAb4D5-8 compositions having less than 25% acidic variants. (§VIII.C.1.c; Ex. 1002, ¶213.) 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, ¶213.) Thus, a POSA would have had a reasonable expectation of success in obtaining a humMAb4D5-8 composition within the scope of claim 1. (*Id.*, ¶214.)

Therefore, it would have been obvious to a POSA at the time the '142 patent was filed to reduce the amount of acidic variant(s) to an amount less than 25%, as required by claim 1 element [c]. (*Id.* at ¶215.) 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% in a composition comprising a mixture of anti-HER2 antibody and one or more acidic variants. (*Id*.) Therefore, claim 1 as a whole would have been obvious over Waterside in combination with the general knowledge of a POSA. (*Id.*)

d. Claim 2

Claim 2 depends from claim 1 and incorporates all of the limitations of claim 1. Claim 2 further requires that the composition comprise "a pharmaceutically acceptable carrier." Claim 2 would have been obvious for all the reasons outlined above for claim 1 (§VIII.D.1), and further over Waterside and the general knowledge of a POSA, for the reasons set forth below. (*Id.* at ¶¶216-218.) Claim 2 requires that the composition comprise "a pharmaceutically acceptable carrier."

Waterside disclosed that the rhuMAb HER2 antibody was "in phase III clinical trials (breast cancer)." (§VIII.C.1.a; Ex. 1002, ¶216.) 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, ¶216.) Moreover, a POSA would have known that antibodies, such as humMAb4D5-8, were formulated for administration in pharmaceutically acceptable carriers. (Exs. 1002, ¶216-217; 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, ¶217.) Therefore, it would have been obvious to a POSA at the time the '142 patent was filed to use humMAb4D5-8, as taught by Waterside, in a pharmaceutically acceptable carrier, as required by claim 2. (*Id.* at ¶218.)

e. Claim 3

Claim 3 depends from claim 1 and incorporates all of the limitations of claim 1. Claim 3 further requires "wherein the anti-HER2 antibody is humMAb4D5-8." Claim 3 would have been obvious for all the reasons outlined above for claim 1 (§VIII.D.1), and further over Waterside and the general knowledge of a POSA, for the reasons set forth below. (Ex. 1002, ¶¶219-221.) As discussed above, Waterside disclosed a composition comprising an anti-HER2 antibody, rhuMAb HER2. (§VIII.C.1.a, Ex. 1002, ¶219.) As discussed above, rhuMAb HER2 is the humMAb4D5-8 antibody. (§§VII.D.3, VIII.A.1.b; Ex. 1002, ¶219.) A POSA would therefore have understood that the "rhuMAb HER2" antibody disclosed by Waterside was the same antibody as "humMAb4D5-8," as called for by claim 3. (Ex. 1002, ¶219.)

A POSA would have known that humMAb4D5-8 was "the most potent" and "most preferred" humanized variant of the anti-HER2 antibodies evaluated. (Exs. 1002, ¶220; 1006, 68:25-26, 82:11-13; 1008.) A POSA would therefore have been

motivated to use humMAb4D5-8 in an anti-HER2 therapeutic composition as taught by Waterside. (Ex. 1002, ¶220.) 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 composition. (*Id.*) Therefore, it would have been obvious to a POSA at the time the '142 patent was filed to use humMAb4D5-8 in an anti-HER2 composition, as required by claim 3. (*Id.* at ¶221.)

Therefore, claims 1 to 3 would have been obvious over Waterside and the general knowledge of a POSA. (Ex. 1002, ¶¶222-223.)

IX. NO SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS

Secondary considerations, including long-felt need, failure of others, unexpected results, commercial success, copying, licensing, and industry praise, may assist a court in avoiding hindsight bias. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). However, 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 the claim. *In re Kao*, 639 F.3d 1057, 1068, 1072 (Fed. Cir. 2011) (emphasis in original) (finding that the only element not expressly disclosed in the prior art 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) for the Challenged Claims, as discussed above, and explained in the declaration of Dr. Drew Kelner. (Ex. 1002, ¶¶224-226.) 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 to 3 of the ’142 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 10,877 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. 6,339,142 and Exhibits 1001 to1029 were served via FEDERAL EXPRESS priority next day delivery, on December 18, 2017 to the below correspondence address listed for U.S. Patent No. 6,339,142 on the United States Patent and Trademark Office Patent Application Information Retrieval (PAIR) website.

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