IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the *Inter Partes* Review of: Trial Number: To Be Assigned

U.S. Patent No. 9,249,218

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Inventor(s): Carol D. Basey; Greg S. Blank

Assignee: Genentech, Inc.

Title: Protein Purification Panel: To Be Assigned

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PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 9,249,218
UNDER 35 U.S.C. § 311 AND 37 C.F.R. § 42.100

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1001	U.S. Patent No. 9,249,218 (the "'218 patent")
1002	Application No. 13/313,931 (the "'931 application") File History
1003	Declaration of Dr. Carl Scandella
1004	International PCT Application No. WO 97/04801 to Andya *et al*. ("Andya")
1005	Reed J. Harris, *Processing of C-terminal Lysine and Arginine Residues of Proteins Isolated from Mammalian Cell Culture*, 705 J. CHROMATOGRAPHY A 129 (1995) ("Harris")
1006	Reed J. Harris, *Chromatographic Techniques for the Characterization of Human MAbs* (Slides presented at the Waterside Monoclonal Conference held at the Omni Waterside Hotel in Harborside-Norfolk, Virginia on Apr. 22–25, 1996) ("Waterside")
1007	U.S. Patent No. 6,489,447 (the "'447 patent")
1008	Application No. 12/418,905 (the "'905 application) File History
1009	Application No. 10/949,683 (the "'683 application") File History
1010	Application No. 10/253,366 (the "'366 application") File History
1011	U.S. Patent No. 6,267,958 (the "'958 patent")
1012	Application No. 08/615,369 File History
1013	Baselga *et al*., *Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer*, 14(3) J. CLIN. ONCOL. 737–44 (1996)
1014	1998 FDA Approved Label for Herceptin®
1015	Press Release, Genentech, Inc. Biotechnology Breakthrough In Breast Cancer Wins FDA Approval (Sept. 25, 1998) (on file at Genentech company website)
1016	Hudziak *et al*., *p185^{HER2} Monoclonal Antibody Has Antiproliferative Effects In Vitro and Sensitizes Human Breast Tumor Cells to Tumor Necrosis Factor*, 9(3) MOLECULAR CELLULAR BIOLOGY 1165–72 (1989)

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1017	Manning *et al*., *Stability of Protein Pharmaceuticals*, 6 PHARM. RESEARCH 11 (1989)
1018	Genentech, Inc. Annual Report (Form 10-K) (Jan. 22, 1999)
1019	U.S. Patent No. 5,821,337 (the "'337 patent")
1020	USPTO Assignment Record for Application No. 09/304,465
1021	European Patent Number EP 1 308 455 (the "EP '455 patent")
1022	European Patent Office Opposition Division Decision for European Patent No. 1 308 455 (October 5, 2010)
1023	Boards of Appeal of the European Patent Office Decision for European Patent No. 1 308 455 (April 16, 2015)
1024	Approved Judgment from *Hospira UK Ltd. v. Genentech Inc*., Case No. HC12 C03487, High Court of Justice, Chancery Division, Patents Court (April 10, 2014)
1025	Declaration of Simon Charles Cohen
1026	Hospira's Re-Amended Grounds of Invalidity from *Hospira UK Ltd. v. Genentech Inc*., Case No. HC12 C03487, High Court of Justice, Chancery Division, Patents Court (December 13, 2013)
1027	Genentech's Re-Amended Defence from *Hospira UK Ltd. v. Genentech Inc*., Case No. HC12 C03487, High Court of Justice, Chancery Division, Patents Court (January 10, 2014)
1028	2017 FDA Approved Label for Herceptin®
1029	Carter, *Targeting The Product Of The HER2/neu Protooncogene For Therapy*, Breast Cancer Advances in Biology and Therapeutics, 21st Meeting of the International Association for Breast Cancer Research, July 3–5, 1996
1030	Paul Carter *et al*., *Humanization of an Anti-p185^{HER2} Antibody for Human Cancer Therapy*, 89 PROC. NAT'L ACAD. SCI. USA 4285–89 (1992)
1031	Pete Gagnon, PURIFICATION TOOLS FOR MONOCLONAL ANTIBODIES (Validated Biosystems, Inc., 1996)
1032	U.S. Patent No. 5,821,337 File History

PETITIONER'S EXHIBIT LIST	
Exhibit No.	**Description**
1033	Lubert Stryer, BIOCHEMISTRY (4th ed., W.H. Freeman & Co., 1995)
1034	Reed J. Harris *et al*., *Identification of Multiple Sources of Charge Heterogeneity in a Recombinant Antibody*, 752 J. CHROMATOGRAPHY B 233 (March, 2001) ("Harris 2001")
1035	L.A. Sorbera *et al*., Herceptin®, 23(10) DRUGS OF THE FUTURE 1078–82 (1998)
1036	Declaration of Karen Younkins
1037	Declaration of Christopher Lowden
1038	Library of Congress Record for Exhibit 1013
1039	Library of Congress Record for Exhibit 1030
1040	Library of Congress Record for Exhibit 1033
1041	Declaration of Keith Carson
1042	Declaration of Richard Buick
1043	International PCT Application No. WO 92/22653 to Carter *et al*.
1044	Martin Jordan *et. al., Transfecting mammalian cells: optimization of critical parameters affecting calcium-phosphate precipitate formation,* 24(4) NUCLEIC ACIDS RESEARCH 596–601 (1996)
1045	Instructions (71-7090-00) for Protein A Sepharose™ CL-4B, GE Healthcare Life Sciences (May 2011)
1046	Instructions (71-7090-00) for Protein A Sepharose™ CL-4B, Pharmacia BioTech (Feb. 1994)
1047	Frederick M. Ausubel, *et al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (1994)

I. INTRODUCTION

Pfizer, Inc. ("Petitioner" or "Pfizer") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42 *et seq*. of Claims 1 and 5–7 ("Challenged Claims") of U.S. Patent No. 9,249,218 ("'218 patent," Ex. 1001). USPTO assignment records state the '218 patent is assigned to Genentech, Inc. ("Genentech"). *See* Ex. 1020 at 1.

The '218 patent, a distant child of a provisional application filed the same year Genentech's Herceptin® product received FDA approval, is an improper attempt to prolong patent protection for that drug without contributing anything inventive to the public in return. Its claims are directed to a "mixture" of Herceptin®'s active ingredient—the anti-HER2 antibody humMAb4D5-8—and certain "acidic variants" thereof. Nothing about the claimed invention was novel or non-obvious by May 6, 1998—the '218 patent's alleged priority date. By then, the recited antibody had been widely published and promoted as "a unique new approach for treating one type of metastatic breast cancer" (Ex. 1015 at 1), and the claimed acidic variants were merely known "contaminants" that naturally form when the antibody degrades (Ex. 1001 at 5:29–33).

The claims require "less than about 25%" of these variants, but that does not render them patentable. Acidic variant levels within this range are expressly taught multiple times by prior art cited in this Petition. And the '218 patent itself

acknowledges that a known technique (production of anti-HER2 antibody through recombinant DNA) achieved "about 25%" acidic variants and identifies nothing critical or unexpected about the claimed range immediately below. Ex. 1001 at 6:14–19. This alone renders the range unpatentable. *See* MPEP 2131.05. That is especially true given that humMAb4D5-8 was a known breast cancer treatment, acidic variants were known impurities, and "there is always in such cases a motivation to aim for obtaining a pure, resolved material." *Spectrum Pharms., Inc. et al. v. Sandoz Inc.*, 802 F.3d 1326, 1334 (Fed. Cir. 2015).

The '218 patent does not even say the claimed mixtures were anything new. Its described "invention" was something different—a method for purifying antibodies. Using essentially the same specification as the '218 patent, Genentech filed for and obtained another patent on its allegedly inventive purification method. In pursuing the '218 patent, however, it lost sight of the original invention and reached too far. Petitioner shows below that three of Genentech's own prior publications independently invalidate its claims.

II. MANDATORY NOTICES

A. Real Parties-In-Interest (37 C.F.R. § 42.8(B)(1))

Pfizer, Inc. is the real party-in-interest for Petitioner.

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

Petitioner concurrently files IPR petitions for claims of the '218 patent and U.S. Patent No. 6,339,142 (the "'142 patent"). A European counterpart to the '142

and ’218 patents, European Patent Number EP 1 308 455 (the “EP ’455 patent”) (Ex. 1021, has been the subject of several proceedings in Europe. *See* Section VIII; Case Number A/16/04171 in Belgium, File Number DE 699 30 424.5 in Germany, Application Number 02029008.6 - 2406 in the European Patent Office, and Case Number HC12 C03487 in the United Kingdom. A Canadian counterpart to the ’218 patents, Canadian Patent No. 2,329,829 (the “Canada ’829 patent”), is also the subject of a proceeding in Canada (File Number T-1239-17). The EP ’455 patent, Canada ’829 patent, and the ’218 patent purport to claim priority to U.S. Provisional Application No. 60/084,459 (“’459 provisional application”), filed May 6, 1998. *See* Exs. 1001; 1021 at 1.

Petitioner is not aware of any other judicial or administrative matters that would affect, or be affected by, a decision in the proceeding.

C. Lead and Back-up Counsel (37 C.F.R. § 42.8(B)(3))

Petitioner designates the following counsel:

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

Please address all correspondence to lead counsel at the contact information above. Petitioner consents to service by electronic mail at Pfizer_Genentech_IPRs@kirkland.com. A Power of Attorney is being filed concurrently herewith. 37 C.F.R. § 42.10(b).

III. CERTIFICATION OF GROUNDS FOR STANDING

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies the '218 patent is available for IPR and Petitioner is not barred or estopped from requesting IPR challenging the patent claims on the grounds identified in this petition.

IV. FEES

The USPTO is authorized to charge the fee set forth in 37 C.F.R. § 42.15(a) for this Petition and any other fees that may be due in connection with this Petition to Deposit Account No. 506092.

V. OVERVIEW OF CHALLENGE AND RELIEF REQUESTED

The '218 patent purports to claim priority to the '459 provisional application, filed May 6, 1998. Because the '459 provisional application was filed before March 16, 2013, this Petition is governed by pre-AIA 35 U.S.C. §§ 102 and 103.[1] MPEP 2159.01. Petitioner requests review of the Challenged Claims as follows:

[1] References to 35 U.S.C. §§ 102 and 103 are to the pre-AIA versions.

Ground	Proposed Statutory Rejections
1	Claims 1 and 5–7 are invalid under 35 U.S.C. § 102(b) as anticipated by **Andya**[2] (published February 13, 1997), or in the alternative, are invalid under 35 U.S.C. § 103(a) as obvious over **Andya**.
2	Claims 1 and 5–7 are invalid under 35 U.S.C. § 103(a) as obvious over **Waterside**[3] (published April 1996) and the knowledge of a person of ordinary skill in the art ("POSITA").
3	Claims 1 and 5–7 are invalid under 35 U.S.C. § 103(a) as obvious over **Harris**[4] (published June 23, 1995) and the knowledge of a POSITA.

[2] International PCT Application No. WO 97/04801 to Andya *et al*. ("Andya") (Ex. 1004).

[3] Reed J. Harris, *Chromatographic Techniques for the Characterization of Human MAbs* (Slides presented at the Waterside Monoclonal Conference at the Omni Waterside Hotel in Harborside-Norfolk, Virginia on Apr. 22–25, 1996) ("Waterside") (Ex. 1006).

[4] Reed J. Harris, *Processing of C-terminal Lysine and Arginine Residues of Proteins Isolated from Mammalian Cell Culture*, 705 J. CHROMATOGRAPHY A 129 (1995) ("Harris") (Ex. 1005).

The cited prior art is as follows:

- **Andya** is a PCT application and a printed publication that was accessible to the relevant public on February 13, 1997, more than one year prior to the earliest possible priority date (May 6, 1998). Ex. 1004. Thus, Andya is prior art under 35 U.S.C. § 102(b).
- **Waterside** is a printed publication published during the April 22–25, 1996 Waterside Monoclonal Conference. The publication includes slides for a presentation by Reed Harris from Genentech's Analytical Chemistry Department on "Chromatographic Techniques for the Characterization of Human Monoclonal Antibodies: rhuMAb HER2." Ex. 1006 at 3. These slides were accessible to the public by April 22, 1996. Exs. 1041, ¶3; 1006 at 2. The Waterside Monoclonal Conference was a popular conference attended by scientists interested in and working on monoclonal antibodies, such as the anti-HER2 antibody of the '218 patent. Exs. 1041, ¶2; 1003, ¶61. Copies of all presentations to be given at the conference, including Waterside, were printed and distributed to attendees, speakers, and sponsors. Ex. 1041, ¶3. Over 200 people received a copy of Waterside at the 1996 Waterside Monoclonal Conference. *Id.* In addition, Genentech provided a copy of Waterside to the USPTO in an Information Disclosure Statement during prosecution of the '218 patent and confirmed these slides were in fact "presented at the Waterside

Monoclonal Conference held at the Omni Waterside Hotel in Harborside-Norfolk, Virginia on April 22–25, 1996." Ex. 1002 at 81. In the UK litigation discussed below (Section VIII), Genentech likewise represented that Waterside was "made available to the public before the priority date of" the EP '455 patent, which allegedly claims priority to the same '459 provisional application. Ex. 1027 at 1 (referring to Waterside as the document relied on in ¶7(b) of Exhibit 1026); Ex. 1026 at 5 (showing Waterside is the document in ¶7(b)). Waterside therefore is a printed publication that was accessible to the public more than one year prior to May 6, 1998 and is prior art under 35 U.S.C. § 102(b).

- **Harris** is an article published on June 23, 1995, in the well-known scientific journal, Journal of Chromatography A. Exs. 1005 at 1; 1003, ¶50. Additionally, Harris was accessible at the University of Illinois at Chicago ("U.I.C.") library as early as July 7, 1995. Ex. 1005 at 1. Harris therefore is a printed publication that was accessible to the public more than one year prior to May 6, 1998 and is prior art under 35 U.S.C. § 102(b).

Section XII details the statutory grounds for the unpatentability of each of the Challenged Claims and identifies where each element is found in the cited prior art and the relevance of that prior art.

Additional evidence is provided in the accompanying Declarations of Dr. Carl Scandella (Ex. 1003), Dr. Richard Buick (Ex. 1042), and other supporting exhibits,

including authenticating declarations (Exs. 1025; 1036; 1037). Dr. Scandella has over 40 years of experience in protein analysis, purification, and manufacturing. Ex. 1003, ¶¶3–12, 16–17. Dr. Buick has over a decade of experience in preparing and analyzing recombinant antibodies, including humanized monoclonal antibodies. Ex. 1042, ¶¶2–5.

VI. LEVEL OF ORDINARY SKILL

A POSITA would be a person or a team of persons with a Ph.D. in chemistry, biochemistry, or a closely related field or the equivalent knowledge gained through, for example, an M.S. in chemistry, biochemistry, or a closely related field and 3–5 years of relevant work experience. Ex. 1003, ¶16. A POSITA would have knowledge of and experience regarding protein analysis and protein chemistry, including protein preparation and purification, and formulation of therapeutic proteins for human use. *Id*.

VII. BACKGROUND

A. HumMAb4D5-8

The ’218 patent purports to describe “[a] method for purifying a polypeptide by ion exchange chromatography.” Ex. 1001 at Abstract. The Challenged Claims, however, recite a “therapeutic composition comprising” a mixture of anti-HER2 antibody and one or more acidic variants thereof.” Claim 1 (the only independent claim) is copied below:

1. A therapeutic composition comprising a mixture of anti-HER2 antibody and one or more acidic variants thereof,

wherein the amount of the acidic variant(s) is less than about 25%,

and wherein the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated,

and wherein the anti-HER2 antibody is humMAb4D5-8,

and wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate,

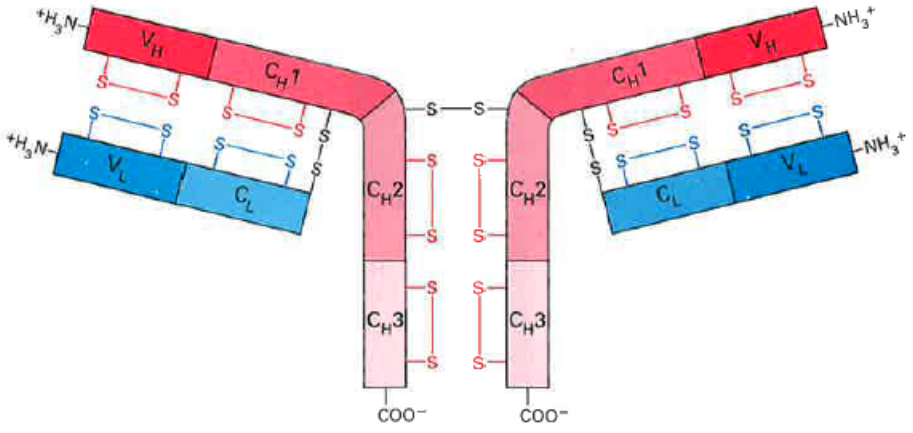
and a pharmaceutically acceptable carrier.

The "anti-HER2 antibody" "humMAb4D5-8" is also known as rhuMAb HER2. *Id.* 20:39–43; Ex. 1003, ¶32. In the art, "hu" or "hum" is used to denote something that has been "humanized," while "MAb" means monoclonal antibody. Ex. 1003, ¶32. Thus, "humAb4D5-8" or "humMAb4D5-8" is a humanized monoclonal antibody named 4D5-8. *Id.* Other naming conventions could be used to describe this antibody. For example, rhuMAb of a particular target (*e.g.*, rhuMAb HER2) means recombinant humanized monoclonal antibody against the particular target. *Id.*

HER2 is a gene that "encodes a 185-kd transmembrane glycoprotein receptor

(p185^{HER2})."[5] Ex. 1013 at 9. By the 1980s, it was known that HER2 overexpression was correlated with aggressive breast cancer, that targeting HER2 could have clinical benefit, and that antibodies could be developed to target particular receptors. Exs. 1003, ¶34; 1016 at 8.

Antibodies are proteins derived from the immune system that selectively target receptors. Ex. 1003, ¶35. Like all proteins, antibodies comprise chains of amino acid "residues." Ex. 1033, Vol. 3 at 396–97. The typical structure of an antibody—a Y-shape made up of two identical heavy ("H") and two identical light ("L") chains—is shown below. *Id.* at 401. Each heavy chain comprises three constant regions (C_H1, C_H2, and C_H3) and one variable region (V_H), while each light chain has one constant (C_L) and one variable region (V_L). *Id.* at 402.



[5] p185^{HER2} is also known as the HER2 receptor. Ex. 1003, ¶34.

Id. (Figure 14-11). It is the "[h]ypervariable regions" or "complementarity determining regions" ("CDRs") within V_H and V_L which bind to and confer specificity against the target (or "antigen"). *Id.*; Ex. 1003, ¶37.

By 1989, mouse (murine) monoclonal antibodies against HER2 had shown efficacy against cancer cell-lines in *in vitro* and animal tests. Exs. 1016 (describing preparation of mouse monoclonal antibody ("MAb") 4D5); 1013 at 9 (4D5 "is a potent inhibitor of growth, *in vitro* and in xenograft models, of human breast cancer cells that overexpress HER2."). By the early 1990s, humanized versions of 4D5 had been developed for human use. Exs. 1013 at 9 ("[M]urine antibodies are limited clinically because they are immunogenic. To facilitate further clinical investigations, therefore, MAb 4D5 was humanized."); 1030 ("Carter") at 12. Out of several humanized variants created, Carter identified one of these, humMAb4D5-8, as the preferred variant as using humMAb4D5-8 "augurs well for the ongoing treatment of human cancers overexpressing $p185^{HER2}$…." Exs. 1030 at 12, 14; 1001 at 8:13–16 (citing Ex. 1030).

B. Protein Purity and Degradation

It was well-known by May 6, 1998 that proteins undergo changes to their structure after synthesis, resulting in a mixture of native and modified protein. Such changes include post-translational modifications and protein degradation. Exs. 1003, ¶40; 1017 at 5–6; 1005 at 4–5. Protein degradation may be caused by physical

or chemical changes to the protein. Ex. 1017 at 5–6. Two well-known degradants result from deamidation or isomerization.

Deamidation is a type of protein degradation in which an amine group (-NH_2) is hydrolyzed and removed from the side-chain of either an asparagine (Asn) or glutamine (Gln) residue and replaced by an -OH. *Id.* at 5; Ex. 1003, ¶41. Deamidation at asparagine may proceed through a cyclic imide intermediate, succinimide, which then hydrolyzes to form either aspartate (Asp) or iso-aspartate (isoAsp). Ex. 1017 at 6. Deamidation at asparagine is one of the most common routes of protein degradation. Exs. 1003, ¶41; 1004 at 3; 1017 at 5–7. Due to carboxylic acid formation, the resulting protein variant is more acidic than the native protein. Ex. 1003, ¶42. Such a variant, resulting from either aspartate or iso-aspartate, is commonly called an "acidic variant." *Id.*; Ex. 1001 at 6:14–19.

Isomerization of aspartate is another mechanism of protein degradation. Exs. 1003, ¶43; 1034 at 5 (Abstract), 15–16. Isomerization, or "succinimide formation," is an intra-molecular reaction in which aspartate is converted to iso-aspartate via succinimide. Ex. 1003, ¶43. The change from aspartate (acidic) to iso-aspartate (acidic) is a neutral change relative to the native protein. Thus, the resulting protein variant (isoAsp) is not an acidic variant. *Id.*; Ex. 1034 at 5 (Abstract), 11. Although deamidation and isomerization may both proceed through a succinimide intermediate, they degrade from different starting amino acid residues (asparagine

versus aspartate) and result in different surface charges—deamidation results in acidic variants and isomerization results in neutral variants compared to the native protein. Ex. 1003, ¶43.

It was known by May 6, 1998 that acidic variants, like other forms of protein degradation, could negatively influence a protein's activity and efficacy. *Id.*, ¶44; Ex. 1017 at 7. It was also known that acidic variants and other impurities should be identified and reduced to ensure an acceptable level of purity and potency. Ex. 1003, ¶45. Indeed, FDA regulations then (and now) required showing biological products are "safe, pure, and potent" before approval. 42 U.S.C § 262 (1997).

Several methods for achieving this goal were available to POSITAs. Ex. 1003, ¶46; *see generally* Ex. 1031. For instance, ion-exchange chromatography, a long-established purification technique, can be used to separate even closely-related molecules on the basis of their surface charge. Exs. 1003, ¶46; 1031 at 73–102. Indeed, cation-exchange chromatography, a type of ion-exchange chromatography, was known and used to analyze antibodies, including humMAb4D5-8, and acidic variants thereof before May 6, 1998. Exs. 1003, ¶¶47–48; 1004 at 6, 28; 1005 at 5–7; 1006 at 4, 6; Sections VII.C.1–VII.C.3.

C. Genentech's Public Disclosures Prior to May 6, 1998

Genentech has publicly referred to humMAb4D5-8 as "Herceptin®," "trastuzumab," and "rhuMAb HER2." *See, e.g.*, Exs. 1004 at 1, 6, 21, 23, 26 (using

"huMAb4D5-8" and "rhuMAb HER2"); 1001 at 20:39–40 (using "humMAb4D5-8" and "rhuMAb HER2"); 1014 at 1 (using "trastuzumab" and "Herceptin®"); 1035 at 5 (using "rhuMAb HER2", "Herceptin®," and "trastuzumab"); IPR2017-00804, Paper 6 at 1, n.1 ("Trastuzumab is the antibody molecule in Herceptin. Trastuzumab is also known as 'rhuMAb HER2' or 'rhuMAb4D5-8.'").

Herceptin® clinical trials were underway by the mid-1990s. Exs. 1013 at 9–15 (Phase II clinical trial data); 1015 at 4 ("By 1996, 900 women were involved in Phase III clinical trials…."). In September 1998, Herceptin® was approved as a treatment for HER2 positive breast cancer. Exs. 1014 at 2; 1015 at 1. Shortly after receiving FDA approval, Genentech began commercializing and selling Herceptin®. Exs. 1018 at 36; 1028 at 1.

Genentech has already enjoyed almost two decades of worldwide patent protection for Herceptin®. Its U.S. base patent for this product, U.S. Patent No. 5,821,337, issued in 1998. Ex. 1019 at 4:34–35; Claim 1. This patent was not challenged by Petitioner and expired in 2015. *See generally* Ex. 1032.

Genentech filed a series of follow-on U.S. patent applications that did not aim to protect Herceptin® but attempted to claim known manufacturing processes and—in the '218 patent—compositions with properties that necessarily result from performing those processes. As detailed below, however, all of those properties—

including the nature and quantity of the "acidic variants" claimed by the '218 patent—were public and known in the art well before May 6, 1998.

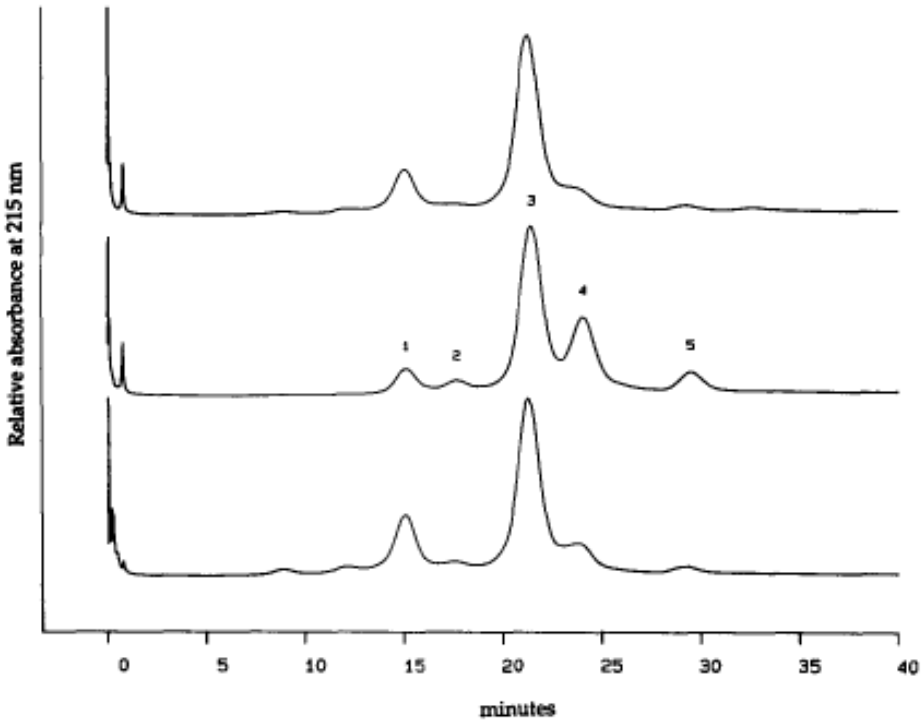
1. Harris

Reed J. Harris published an article on purifying "proteins isolated from mammalian cell culture" on June 23, 1995. Ex. 1005. In Harris, Genentech taught "[v]ariants [of a recombinant protein] may result from either known or novel types of in vivo (posttranslational) modification…or from spontaneous (non-enzymatic) protein degradation, such as…***aspartate isomerization*** and ***deamidation of asparagine residues***," and "successful approaches for identifying such variants…." *Id.* at 4–5 (emphases added).

Genentech described resolving (separating) "charge[d] variants" from native rhuMAb HER2 in "three lots of rhuMAB HER2" using cation-exchange chromatography. *Id.* at 5–7; Ex. 1003, ¶52. A POSITA would have understood the rhuMAb HER2 in Harris was humMAb4D5-8.[6] Ex. 1003, ¶52.

The results of using cation-exchange chromatography to resolve the three lots are shown in the following chromatograms:

[6] All references to what a POSITA would have known or understood are as of May 6, 1998 unless otherwise specified.



Ex. 1005 at 7 (Figure 2). Each peak was identified by peptide mapping with amino acid analysis, N-terminal sequencing, and mass spectrometry:

> rhuMAb HER2 shows five [*sic*] charge species (Fig. 2). The main peak (peak 3) has no Lys^{450} residues, while the more basic peaks 4 and 5 have one or two Lys^{450} residues, respectively (data not shown). ***The more acidic peaks 1 and 2 are deamidated at Asn^{30} in one light chain***; peak 1 has no Lys^{450} residues, while peak 2 has one Lys^{450} residue.

Id. at 6 (emphases added). A POSITA would have known all rhuMAb HER2 acidic variants present could be separated from native rhuMAb HER2 by cation-exchange chromatography. Ex. 1003, ¶54. A POSITA would expect the peaks in the top and bottom chromatograms that eluted at the same time as the numbered peaks in the middle chromatogram to have the same content. *Id.*, ¶55.

Harris expressly and inherently taught that the acidic variants, which are "deamidated at Asn30 in one light chain," were present in amounts less than about 25%. Ex. 1005 at 6. This is expressly taught because a POSITA reading the chromatograms and associated descriptions would have known from inspection of the relative area under each of the peaks alone the approximate percentage of each charged species. Ex. 1003, ¶56. As Dr. Scandella sets forth in his declaration, the area under peaks 1 and 2 disclosed in Figure 2 (and therefore, the amount of acidic variants in the compositions) was less than approximately 25% of the total area under the curve for peaks 1–5. *Id.* This would have been apparent to a POSITA reading Harris. *Id.*

The acidic variants in Harris also were inherently present in an amount less than about 25%. This can be proven mathematically using the information disclosed. *See Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). As explained by Dr. Scandella, this can be proven using a software program such as Data Thief to convert the chromatograms to digital files and then using software such as MATLAB™ and Excel to integrate the data and calculate the percent area under the curve for each peak.[7] Ex. 1003, ¶¶57–59.

[7] Data Thief, MATLAB™, and Excel were available by May 6, 1998 and have since been periodically updated.

Dr. Scandella performed these calculations for the rhuMAb HER2 compositions disclosed in Figure 2 and determined that they inherently contained less than about 25% acidic variants:

Chromatogram	Peak 1	Peak 2	Total Acidic Variants (Peak 1 + Peak 2)
Top	15%	5%	20%
Middle	8%	5%	13%
Bottom	18%	5%	24%

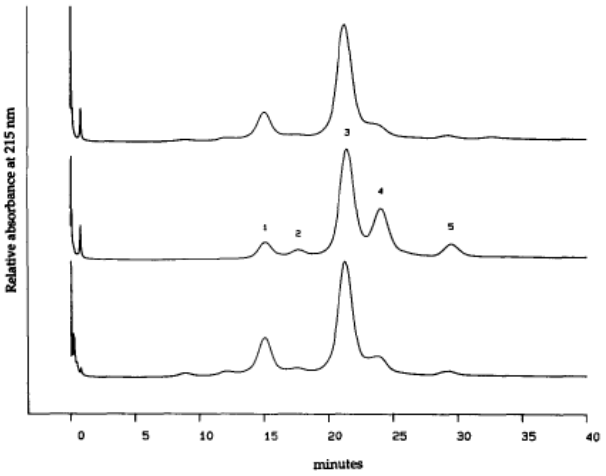
Id. ¶60; *see Schering Corp.*, 339 F.3d at 1377.

2. Waterside

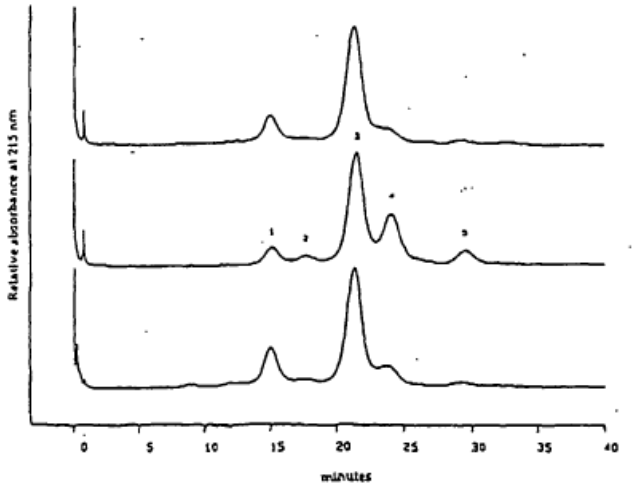
Approximately a year after Harris, Genentech presented that work at the Waterside Monoclonal Conference. Exs. 1006 at 1; 1002 at 81. At Waterside, Genentech disclosed rhuMAb HER2 targets the HER2 receptor and HER2 overexpression was correlated with breast cancer. Ex. 1006 at 3. Genentech further disclosed rhuMAb HER2 was in Phase III clinical trials for the treatment of breast cancer, had been made at a 12,000 L production scale, and had undergone detailed structural characterization by chromatography. *Id.* at 3–4.

A POSITA would have understood the rhuMAb HER2 referenced in Waterside was humMAb4D5-8. Ex. 1003, ¶63. As the below comparison demonstrates, Genentech presented what appear to be the same cation-exchange chromatograms of rhuMAb HER2 published in Harris:

Harris (June 23, 1995)



Waterside (April 1996)



Exs. 1005 at 7; 1006 at 4.

A POSITA would have understood that, when cation-exchange chromatography is used, acidic variants elute before the main peak (native protein) and basic variants elute after the main peak. Ex. 1003, ¶66. Accordingly, peaks 1 and 2 above represent acidic variants of rhuMAb HER2, peak 3 represents native rhuMAb HER2, and peaks 4 and 5 represent basic variants of rhuMAb HER2. *See id.*; Ex. 1006 at 5–6. This is consistent with Genentech's description of the same chromatogram in Harris. Ex. 1005 at 6. Just as for Harris, a POSITA would expect the peaks in the top and bottom chromatograms that eluted at the same time as the numbered peaks in the middle chromatogram to have the same content. Ex. 1003, ¶66.

As with Harris, Waterside expressly and inherently taught that rhuMAb HER2 acidic variants were present in amounts less than about 25%. Section VII.C.1. This is expressly taught because a POSITA reading the chromatograms and associated

descriptions would have known the approximate amount of each charged species by inspection of the relative area under each of the peaks. Ex. 1003, ¶67. As Dr. Scandella explains in his declaration, inspection reveals that the area under peaks 1 and 2 (and therefore, the amount of acidic variants in the composition) was less than 25% of the total area under the curve for peaks 1–5. *Id.* This would have been apparent to a POSITA reading Waterside. *Id.*

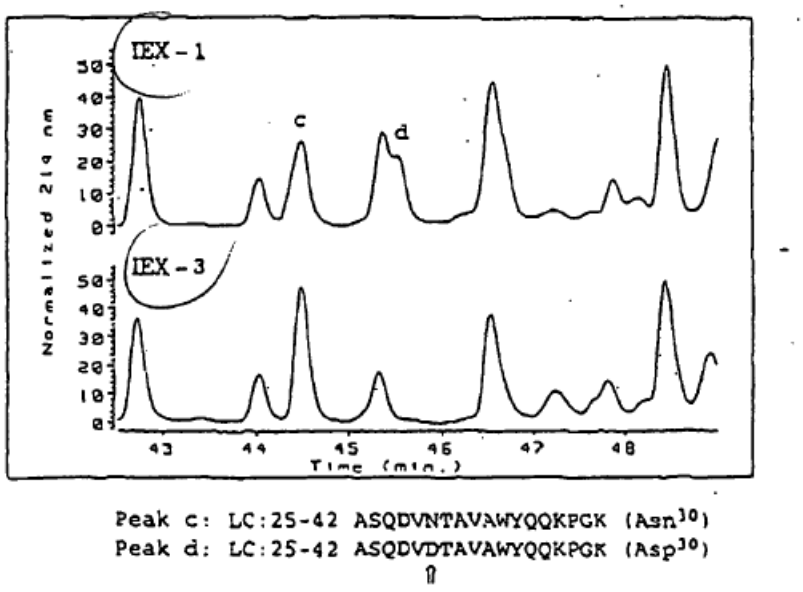
This characteristic also is necessarily present, or inherent, in Waterside because, like Harris, it can be proven mathematically using the information given. *See Schering Corp.*, 339 F.3d at 1377. Dr. Scandella performed these calculations using Data Thief, Excel, and MATLAB™ and determined the rhuMAb HER2 compositions necessarily contained less than about 25% acidic variants:

Chromatogram	**Peak 1**	**Peak 2**	**Total Acidic Variants (Peak 1 + Peak 2)**
Top	15%	7%	22%
Middle	8%	6%	14%
Bottom	18%	6%	24%

Ex. 1003, ¶¶68–71.

Additionally, Waterside taught that deamidation increases when harvest cell culture fluid ("HCCF") is held. Ex. 1006 at 7. This means the amount of acidic variants in the compositions may have been even lower than the amounts shown in the chromatograms at an earlier time. Ex. 1003, ¶72.

Genentech further disclosed additional chromatographic analysis confirming peak 1 was deamidated at Asn30 (a rhuMAb HER2 acidic variant):



Exs. 1006 at 6; 1003, ¶73. As explained by Dr. Scandella, Genentech disclosed "peak c" had intact asparagine at position 30 ("Asn30") in the light chain and "peak d" had Asn30 that had been deamidated to aspartate ("Asp30"). *Id.*, ¶73; Ex. 1006 at 6. This confirmed that when Asn30 in rhuMAb HER2 is deamidated, it converts to aspartate. Exs. 1003, ¶73; 1006 at 6. Genentech further disclosed peak 1 ("IEX-1") contained "peak d," (deamidated Asn30), whereas peak 3 ("IEX-3") did not. Exs. 1003, ¶73; 1006 at 6. Accordingly, peak 1 was an acidic variant of rhuMAb HER2, wherein Asn30 in the light chain had deamidated to aspartate. Exs. 1003, ¶73; 1006 at 4, 6.

Furthermore, peak 2 is inherently deamidated at Asn30. *See Schering Corp.*, 339 F.3d at 1377. Harris disclosed nearly (if not) identical chromatograms and

taught both peaks 1 and 2 contain deamidated Asn30. Ex. 1005 at 6, 7 (Fig. 2); *see* Exs. 1034 at 10 (Fig. 2), 12–13, 15 (Table 6); 1003, ¶73; Section VII.C.1.

3. Andya

A few months after the 1996 Waterside Monoclonal Conference, Genentech filed Andya, an International PCT Application, which published February 13, 1997. Ex. 1004. Andya discloses a "stable isotonic lyophilized protein formulation" in which humMAb4D5-8 is disclosed in four compositions. *Id.* at 20–21. Genentech again disclosed humMAb4D5-8 "degrade[s] by deamidation at 30Asn of light chain" or isomerization of "102Asp of heavy chain" formed by succinimide. *Id.* at 6, 21, 28; Ex. 1003, ¶75. As discussed above, deamidation at Asn30 results in acidic variants and isomerization at Asp102 results in non-acidic variants. Section VII.B.

Further, Genentech assessed the "loss of native protein due to deamidation or succinimide formation" for lyophilized (freeze dried) and then reconstituted humMAb4D5-8 compositions using cation-exchange chromatography. Ex. 1004 at 28. Figures 5–8 disclose the "% native protein," "(not degraded) protein," for each of these four compositions as a function of time after reconstitution and chromatography. *Id.* at 6; 39–40 (Figs. 5–8).

For example, Figure 5 reflects a composition tested under four conditions where the amount of native humMAb4D5-8, which was separated from the degraded protein by cation-exchange chromatography, was approximately 81–82%:

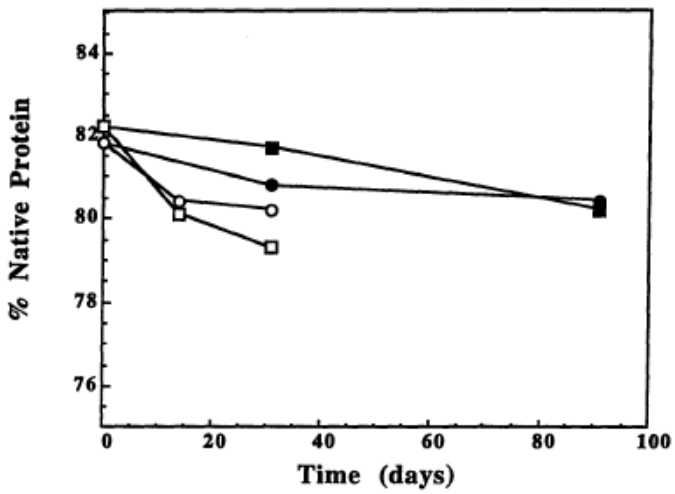


FIG. 5

Id. at 39. The remaining 18–19% included the sum total of all degraded protein resulting from deamidation at Asn30 (acidic variants) and succinimide formation Asp102 (non-acidic variants). Exs. 1003, ¶77; 1004 at 39 (Fig. 5).

Accordingly, a POSITA would understand Figure 5 disclosed humMAb4D5-8 compositions with at most 18–19% acidic variants, where those acidic variants are mainly (if not entirely) deamidated at Asn30. *See id.* at 28; Ex. 1003, ¶77. Applying the same analysis to Figures 6–8, a POSITA would understand those figures disclosed humMAb4D5-8 compositions with 78–82% native protein and, at most, 18–22% acidic variants mainly (if not entirely) deamidated at Asn30. Exs., 1003 ¶¶78–82; 1004 at 39–40 (Figs. 6–8).

As set forth below, the Challenged Claims are anticipated, or at least obvious, based on Andya, Waterside, and Harris.

VIII. RELATED FOREIGN PROCEEDINGS

As mentioned above, the EP '455 patent has been the subject of proceedings in Europe. On October 4, 2014, the UK High Court of Justice, Patents Court found claims of EP '455 invalid as anticipated by Andya. Ex. 1024, ¶217 ("The composition enabled by Andya will comprise acidic variants of trastuzumab of the relevant kind but will contain no more than 18% acidic variants."). The Court also found all claims of the EP '455 patent invalid as lacking inventive step over Waterside. *Id*., ¶242. Regarding Waterside:

> [i]t would not be inventive to specify a level of acidic variants which was at any level within the range of numbers considered in this case. Assuming…the level of acidic variants in the material after Protein A affinity chromatography was higher than 25%, it would not be inventive to decide to reduce the concentration of acidic variants below that level.

Id., ¶ 233. Genentech did not appeal this decision.

Finding the claims of EP '455 lacked novelty over Andya, the European Patent Office's Opposition Division revoked the EP '455 patent on May 10, 2010, but the decision was later set aside on appeal. Exs. 1022 at 1, 16, 19; 1023 at 28 (finding "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…not directly and unambiguously disclosed"). This Petition, however, establishes this feature is both explicitly

disclosed and inherent in Andya by at least a preponderance of evidence.[8]

Pfizer has also filed proceedings challenging the EP '455 Patent in Germany and Belgium and filed proceedings challenging the Canada '829 patent. Section II.B. These proceedings are ongoing.

IX. THE '218 PATENT AND PROSECUTION HISTORY

A. '218 Patent

The '218 patent has seven claims. As explained above, Claim 1 is the only independent claim and claims a "therapeutic composition." *See* Section VII.A. Challenged Claim 5 recites the "therapeutic composition of any one of Claims 1 to 4, wherein the anti-HER2 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." Challenged Claim 6 recites the "therapeutic composition of any one of Claims 1 to 4, which is in the form of a lyophilized formulation or an aqueous solution." Challenged Claim 7 depends on Claim 5 and also recites a "therapeutic composition…which is in the form of a lyophilized formulation or an aqueous solution."

[8] The remaining ground for reinstating EP '455 relates to a position Petitioner does not advance.

These claims do not align with the alleged "invention" of the '218 patent. The "invention" is described as a particular purification "***method***" using "ion exchange chromatography."[9] Ex. 1001 at Abstract, 1:22–27, 2:25–3:36, 20:39–21:6 (emphasis added). Although the '218 patent says this invention "***provides***" a mixture having less than about 25% acidic variant(s), it never describes the claimed "mixtures" or percentages as themselves inventive or something the named inventors were the first to conceive or achieve. Indeed, the specification repeatedly describes the claimed acidic variants as "***contaminants***," and teaches that mixtures containing them (like the ones claimed) are undesirable and in need of purification. Ex. 1001 at 5:29–33, 5:60–3.

The '218 patent also notes performing "Protein A" chromatography on rhuMAb HER2 made through recombinant DNA results in mixtures having "deamidated and other acidic variants [that] constituted ***about 25%***…of the composition." Ex. 1001 at 22:60–63 (emphasis added). "Protein A" is not described as the inventors' invention. Nor could it, as such technique was already known. *See*

[9] This allegedly "novel" purification method appears to be the subject of another Genentech patent with the same specification stemming from the '459 provisional application. *See* Exs. 1001 ("Related U.S. Application Data"); 1007 (claiming purification method).

Ex. 1031 at 169. To the contrary, the specification describes this 25% acidic variant composition as in need of purification by its allegedly inventive method:

> ***The deamidated and other acidic variants constituted about 25%...of the composition obtained from the initial Protein A chromatography step***. It was discovered that the ion exchange method described herein could be used to substantially reduce the amount of deamidated and other acidic variants in the anti-HER2 composition, i.e. to about 13% or less….

Ex. 1001 at 6:16–19, 22:57–23:3. In other words, Genentech claimed essentially ***the very problem in the art that its patent said its alleged invention solved***. Genentech wrote "***less than about 25%***" in its claims, but nothing in the specification indicates there is anything critical or novel about that difference. *Id.* at Claim 1.

B. Prosecution History

The '218 patent issued from Application No. 13/313,931 (the "'931 application"), filed December 7, 2011. Through a chain of continuation and divisional applications, Nos. 12/418,905 (the "'905 application"), 11/398,447, 10/949,683 (the "'683 application"), 10/253,366 (the "'366 application"), and 09/304,465, the '218 patent purports to claim priority to the '459 provisional application, filed May 6, 1998. Ex. 1001.

1. The USPTO Repeatedly Rejected Related Applications Based On Andya

In each of the '366, '683, and '905 applications, Genentech was forced to

abandon or amend its claims in order to overcome rejections based on the same Andya reference asserted in this Petition. *See* Exs. 1010 at 372; 1009 at 92–92; 1008 at 123–24, 160, 223–29. For instance, in the '366 application, Genentech attempted to claim a composition of anti-HER2 antibody with less than about 25% acidic variants. Ex. 1010 at 128. The Examiner found Andya disclosed the "preparation of rhuMAb 4D5-8 in Example 1" and "analysis of deamidated (i.e. acidic) variants by CSx chromatography." *Id.* at 372–73 (citing Ex. 1004 at 28, Figs. 5–8). The Examiner further found Andya's Figures 5–8 disclosed "81–82% native protein at the start of each stabilization experiment[,] mean[ing] there is 18–19% non-native variants; this range is clearly 'less than about 25%.'" *Id.* at 373. Genentech only overcame this rejection by amending the claims to require an intermediate wash step. *Id.* at 380. The Challenged Claims contain no such limitation.

Claims of the '683 application were likewise rejected as anticipated by Andya. Ex. 1009 at 91–92. The rejected product-by-process claims of the '683 application were directed to a composition of anti-HER2 antibody with less than about 25% acidic variants, which has been subjected to cation-exchange chromatography. *Id.* at 51. According to the Examiner, Andya disclosed preparation of rhuMAb 4D5-8 with less than about 25% acidic variants. *Id.* at 91. Further, "[w]hile Andya…d[id] not disclose the instant [*sic*] unification method, a preparation of an antibody having a recited antigen combining specificity and degree of purity is what it is per se,

irrespective of any method employed to obtain it." *Id.* Genentech overcame this rejection by reducing the percentage of acidic variants to less than about 13%. *See id.* at 154–55, 164. The Challenged Claims contain no such limitation.

During prosecution of the '905 application, the Examiner rejected claims directed to a composition of humMAb4D5-8 with less than about 25% acidic variants, wherein the acidic variants are predominantly deamidated variants and where the deamidated variants are deamidated at a specified residue—asparagine at position 30 in CDR1 of either or both of the light chains of the anti-HER2 antibody—and converted to aspartate based on Andya. *See* Ex. 1008 at 112, 123, 147–48, 160–61, 224–29. According to the Examiner, Andya's Figures 5–8 "show 81–82% native protein at the start of each stabilization experiment[,] mean[ing] there are 18–19% non-native variants; this range is clearly 'less than about 25%'…." *Id.* at 123. Further, the Examiner found the limitations "wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate" and "wherein the anti-HER2 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" inherent in the humMAb4D5-8 of Andya. *See id.* at 112, 124. Genentech tried repeatedly, and unsuccessfully, to overcome the Examiner's rejections, ultimately abandoning its claims. *Id.* at 242.

2. '931 Application

After abandoning the '905 application, Genentech proceeded to file essentially the same rejected claims of that application in the '931 application, which led to the '218 patent. Indeed, only the word "therapeutic" was added in the preamble. As discussed below, however, the preamble of the Challenged Claims is not limiting and, even if it were, does not add any subject matter that would render those claims patentable. Section X.A. Nonetheless, the Examiner for the '931 application (a different Examiner than the Examiner who considered the '905, '366, and '683 applications) allowed the Challenged Claims without providing any guidance as to why the claims should be allowable over Andya or any other prior art, much less attempt to reconcile the allowance with the prior Examiner's claim rejections over Andya. In fact, the '931 application's file history is devoid of any mention of Andya. *See generally* Ex. 1002. The '218 patent issued from the '931 application on February 2, 2016. Ex. 1001.

This apparent inconsistency between Examiners is relevant to this Petition, and the Board should reconsider Andya in light of the prosecution history of the related applications, particularly where the Examiner in the '905 application found almost identical claims as in the '218 patent anticipated by Andya. *See Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1382–84 (Fed. Cir. 2005) (remanding to the district court to "review the file history as part of its assessment of whether

the invention claimed" is nonobvious and stating "[w]hether the second examiner was aware of the earlier rejection of [Applicant's] claims is unknown[,] [b]ut the relevance of the inconsistency between the views of two examiners is not insignificant").

X. CLAIM CONSTRUCTION

The Challenged Claims should be given their broadest reasonable interpretation ("BRI") in light of the patent specification. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs. LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016). It is improper to read limitations from the specification into the claims "absent a clear indication in the intrinsic record that the patentee intended the claims to be so limited." *GE Lighting Solns, LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1309 (Fed. Cir. 2014) (quoting *Liebel–Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 913 (Fed. Cir. 2004)).

"If the preamble adds no limitations to those in the body of the claim" and merely describes or gives context to the limitations in the claim, the preamble is not limiting. *IMS Tech., Inc. v. Haas Automation, Inc.*, 206 F.3d 1422, 1434 (Fed. Cir. 2000). Additionally, a preamble is not limiting "when the claim body describes a structurally complete invention." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002).

A. Preamble Is Not Limiting

The preamble of each claim—"[a] therapeutic composition"—is not limiting

because it adds no structural limitations to those in the body of the claim, and instead merely "gives a descriptive name" to the claimed elements. *See IMS Tech.*, 206 F.3d at 1434; Ex. 1003, ¶¶26–27.[10] Accordingly, the preamble does not distinguish the claims from the prior art.

To the extent the preamble is found to be limiting, the BRI of "[a] therapeutic composition" is an anti-HER2 antibody with the claimed degree of purity. This construction is supported by the patent specification. The term "therapeutic composition" does not appear in the specification; however, Genentech defined "[a] therapeutic formulation" as a mixture of "the polypeptide having the ***desired degree of purity*** with optional pharmaceutically acceptable carriers, excipients or stabilizers…in the form of lyophilized formulations or aqueous solutions." Ex. 1001 at 19:27–33 (emphasis added). This is consistent with what a POSITA would have understood "therapeutic formulation" to mean at the time of the alleged invention, *i.e.*, a purified protein that has been put in a form with pharmaceutically acceptable carriers, excipients and/or stabilizers, which help make the antibody stable and suitable for delivery and storage. Ex. 1003, ¶¶28–29.

The "polypeptide having the desired degree of purity," would have been

[10] Even if the preamble were limiting, the prior art still discloses this additional limitation. *See infra* Sections XII.A.1(a)i, XII.A.2(a)i, XII.A.3(a)i.

understood by a POSITA to be a "therapeutic composition." *Id.*, ¶30. In the context of the claims and the specification, a POSITA would understand the "desired degree of purity" refers to the claimed amount of acidic variants. *Id.* For example, the specification refers to "deamidated variants" such as those recited by the Challenged Claims as "contaminants." Ex. 1001 at 5:29–33. Therefore, the BRI of "therapeutic composition" to a POSITA in light of the specification is an anti-HER2 antibody with the claimed degree of purity. Ex. 1003, ¶30. This BRI is further proof of the non-limiting nature of the preamble because the bodies of the Challenged Claims already require an anti-HER2 antibody having a specified amount of acidic variants.

Any attempt to argue, as Genentech has previously done, that "[a] therapeutic composition" should require the composition to have "been made on a full manufacturing scale" should be rejected. *See* Ex. 1024, ¶188 (High Court of Justice, Chancery Division, Patents Court rejecting this argument). Importing a particular method of manufacturing or purification into the claims of the '218 patent is improper, particularly under the BRI standard. *See Vanguard Products Corp. v. Parker Hannifin Corp.*, 234 F.3d 1370, 1372 (Fed. Cir. 2000) ("The method of manufacture, even when cited as advantageous, does not of itself convert product claims into claims limited to a particular process."). Further, doing so would treat the preamble as limiting, which is improper for the reasons above.

B. "Pharmaceutically Acceptable Carrier" (Claim 1)

Pfizer submits the BRI of "pharmaceutically acceptable carrier" is a non-toxic carrier to recipients at the dosages and concentrations employed, and may include the carriers, excipients, and stabilizers identified in the specification. *See* Ex. 1001 at 19:27–53. This construction is supported by the patent specification, which states "'[p]harmaceutically acceptable' carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed." *Id.*; Ex. 1003, ¶31. Again, any attempt to argue that "pharmaceutically acceptable carrier" should be construed as requiring "full manufacturing scale" should be rejected. *See* Ex. 1024, ¶188; *Vanguard Products Corp.*, 234 F.3d at 1372; Section X.A.

XI. STATEMENT OF THE LAW

A patent claim is anticipated under 35 U.S.C. § 102(b) if each and every limitation recited in a claim is found, either expressly or inherently, in one prior art reference. *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374 (Fed. Cir. 2001). A prior art reference may anticipate a claim when the limitation(s) not expressly found in that reference are nonetheless inherent in it, regardless of whether a POSITA knew of or appreciated the inherent characteristics or the functioning of the prior art. *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999). A reference is enabling for the purposes of § 102(b) if it "sufficiently describe(s) the claimed invention to have placed the public in

possession of it." *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985). Such possession is effected if a POSITA could have combined the reference with their own knowledge to make the claimed invention. *See id*.

A patent claim is invalid under 35 U.S.C. § 103(a) if the differences between the patented subject matter and the prior art are such that the subject matter as a whole would have been obvious to a POSITA at the time the invention was made. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007). Further, where "general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295–96 (Fed. Cir. 2012) (internal citation omitted). Merely purifying a compound is generally not novel or non-obvious. *See, e.g.*, *Spectrum Pharms., Inc.*, 802 F.3d at 1334 ("A physician would not likely want to administer a contaminant or a less pure material to a patient if one could use a pure material. Thus, there is always in such cases a motivation to aim for obtaining a pure, resolved material.").

Additionally, "a prima facie case of obviousness exists where the claimed ranges or amounts" overlap or are "close" to the prior art. MPEP 2144.05; *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 783 (Fed. Cir. 1985) ("The proportions are so close that prima facie one skilled in the art would have expected them to have the same properties."). "Generally, differences in concentration or

temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." MPEP 2144.05 (citing cases).

Inherency may supply claim limitations in an obviousness analysis. *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012). Indeed, "[p]atentability cannot rest on the fact that" a claimed limitation "that would have been obvious for the reasons taught by the prior art has additionally claimed properties that were not recognized in the art at the time of the invention....to hold otherwise would allow an obvious product to be patented over and over again merely by claiming a different property of otherwise identical products." *Ex Parte Takamiya*, 2017 WL 1091179, at *4 (P.T.A.B. Mar. 20, 2017).

XII. THE CHALLENGED CLAIMS ARE UNPATENTABLE

As detailed below, the Board should declare the Challenged Claims unpatentable.

A. Claim-By-Claim Explanation of Grounds of Unpatentability

1. Ground 1: Claims 1 and 5–7 Are Invalid under 35 U.S.C. § 102(b) as Anticipated by Andya, or in the Alternative, Are Invalid under 35 U.S.C. § 103(a) as Obvious over Andya [11]

(a) Claim 1

i. Preamble: "A therapeutic composition"

The preamble is not limiting. Section X.A. Nonetheless, Andya teaches "[a] therapeutic composition" because, as set forth below, it discloses compositions of rhuMAb HER2, an anti-HER2 antibody, with the claimed degree of purity. Section XII.A.1(a)iii; Ex. 1003, ¶85. Andya also teaches throughout that its "invention is directed to a lyophilized protein formulation…suitable for" human administration and therapeutic uses. Ex. 1004 at 3.

ii. Element [a]: "comprising a mixture of anti-HER2 antibody and one or more acidic variants thereof,"

Andya teaches an anti-HER2 composition. Example 1 of Andya, entitled

[11] During prosecution of applications leading to the '218 patent, Genentech did not dispute that Andya disclosed many elements in its claims, including "wherein the anti-HER2 antibody is humMAb4D5-8" and "a pharmaceutically acceptable carrier." Exs. 1008 at 123–24, 147–50, 161–62, 175–80, 223–27; 1009 at 91, 154–56; 1010 at 372–73, 380–81. This is further evidence that Andya anticipates the claims.

"ANTI-HER2 FORMULATION," "describes the development of a lyophilized formulation comprising full length humanized antibody huMAb4D5-8…." Ex. 1004 at 20–21. As discussed above, humMAb4D5-8 is an anti-HER2 antibody. Section VII.A.

The compositions of Example 1 are mixtures of humMAb4D5-8 and acidic variant(s) thereof. Andya teaches that "[i]n the liquid state, rhuMAb HER2 was observed to degrade by deamidation (30Asn of light chain) and isoaspartate formation via a cyclic imide intermediate, succinimide (102Asp of heavy chain)." *Id*. at 21. The "loss of native protein due to deamidation or succinimide formation" was assessed for the reconstituted humMAb4D5-8 compositions using cation-exchange chromatography. *Id.* at 28. The results are depicted in Figures 5–8. *Id.* at 6.

As discussed above in Section VII.C.3, Figures 5–8 show the percentage of "native (not degraded) protein" is 78–82% and the percentage of degraded protein is 18–22%. As Andya explicitly teaches, a "major degradation route for rhuMAb HER2" is deamidation. *Id.* at 28. A POSITA would understand that such deamidated variants are acidic. Ex. 1003, ¶88. Accordingly, Figures 5–8 disclose a

"mixture of anti-HER2 antibody and one or more acidic variants thereof."[12] *Id.* This limitation is at minimum obvious in light of these disclosures.

iii. Element [b]: "wherein the amount of the acidic variant(s) is less than about 25%,"

Each of the compositions described by Figures 5–8 of Andya contains less than 25% acidic variants. As discussed above, Figures 5–8 of Andya teach compositions of humMAb4D5-8 with 78–82% "native (not degraded) protein" and 18–22% degraded protein. Exs. 1004 at 6, 39–40 (Figs. 5–8) ("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."); 1003, ¶89. A POSITA would understand that all acidic variants are contained within the 18–22% degraded protein, and therefore comprise no more than 25% of the total amount. Ex. 1003, ¶89.

Figure 5 shows the amount of "native (not degraded)" humMAb4D5-8 separated from the degraded protein by cation-exchange chromatography is 81–82%:

[12] The USPTO found this limitation anticipated by Andya in the related applications. Ex. 1008 at 123–24, 161–62, 223–27; 1009 at 91; 1010 at 372–73.

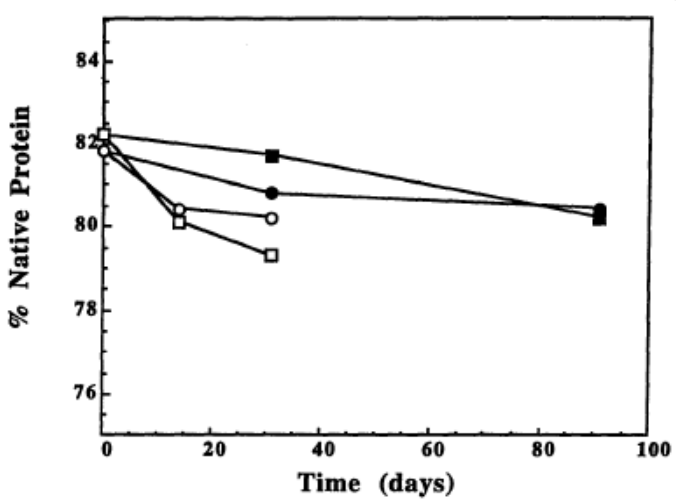


FIG. 5

Exs. 1004 at 39 (Fig. 5); 1003, ¶90. Andya teaches the 18–19% degraded protein depicted in Figure 5 is primarily the result of: (1) deamidation at Asn30 in the light chain; and (2) isomerization of Asp102 in the heavy chain (*i.e.*, formation isoAsp102 in the heavy chain via a cyclic succinimide intermediate). Ex. 1004 at 21, 28 ("The loss of native protein due to deamidation or succinimide formation was assessed for the four reconstituted rhuMAb HER2 formulations."). A POSITA would therefore understand that at least some of the 18–19% degraded protein is formed by deamidation and therefore acidic in nature. Ex. 1003, ¶90. Accordingly, Andya teaches acidic variants (deamidated variants) comprise no more than 18–19% of the composition. Section VII.B.

Figures 6–8 likewise teach compositions of humMAb4D5-8 and acidic variants thereof wherein the acidic variants comprise no more than 18–22% of the total composition. Section VII.C.3; Exs. 1003, ¶¶78–82, 91; 1004 at 39–40 (Figs.

6–8). Accordingly, Andya teaches compositions of humMAb4D5-8 "wherein the amount of the acidic variant(s) is less than about 25%."[13] This limitation is at minimum obvious in light of these disclosures.

iv. Element [c]: "and wherein the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated,"

Andya discloses the acidic variants in the compositions described by Figures 5–8 are predominantly deamidated variants that have been deamidated at a specific residue—Asn30. Andya says "[t]he major degradation route for rhuMAb HER2 in aqueous solutions is deamidation or succinimide formation," and that rhuMAb HER2 "was observed to degrade by deamidation (30Asn of light chain)." Ex. 1004 at 21, 28. As shown in Section VII.B, degraded protein formed by deamidation (*e.g.*, deamidation at Asn30, which is converted into aspartate) are acidic variants of the native protein while degraded protein formed by isomerization are non-acidic variants. Ex. 1003, ¶¶43–44, 94. Indeed, the only form of acidic variants Andya discloses are those which are formed via deamidation at Asn30. Thus, Andya

[13] The USPTO found this limitation anticipated by Andya in the related applications. *See* Ex. 1008 at 123–24, 161–62, 223–27; 1009 at 91; 1010 at 372–73.

teaches "the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated."[14] *Id.*, ¶94. This limitation is at minimum obvious in light of these disclosures.

v. Element [d]: "and wherein the anti-HER2 antibody is humMAb4D5-8,"

As discussed in Section XII.A.1(a)ii, Andya teaches the antibody described by Figures 5–8 is humMAb4D5-8. Ex. 1004 at 21 ("This example describes the development of a lyophilized formulation comprising full length humanized antibody huMAbD5-8….").[15] This limitation is at minimum obvious in light of this disclosure as well as Andya's disclosure of formulations of "rhuMAb HER2…as a therapeutic for the treatment of breast cancer." Ex. 1004 at 22, 20.

vi. Element [e]: "and wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate,"

As set forth in Section XII.A.1(a)iv, Andya teaches that Asn30 in the light

[14] The USPTO found this limitation anticipated by Andya in the related '905 application. *See* Ex. 1008 at 123–24, 161–62, 223–27.

[15] The USPTO found this limitation anticipated by Andya in the related applications, and Genentech did not dispute this. *See* Exs. 1008 at 123–24, 147–50, 161–62, 175–80, 223–27; 1009 at 91, 154–56; 1010 at 372–73, 380–81.

chain of humMAb4D5-8 is deamidated. *Id.* at 21, 28; Ex. 1003, ¶96. Andya's humMAb4D5-8 deamidated variants inherently have Asn30 in CDR1 of one or both light chains converted to aspartate because asparagine necessarily converts to aspartate when humMAb4D5-8 deamidates at Asn30.[16] *See* Ex. 1003, ¶96. This inherent property is confirmed by other Genentech publications, as well as the '218 patent itself. *See* Exs. 1001 at 6:1–3 ("[d]eamidated humMAb4D5 antibody…has Asn30 in CDR1 of either or both of the V_L regions thereof converted to aspartate"); 1006 at 6 (showing when Asn30 deamidates, it converts to Asp 30); 1034 at 9 ("[t]he Asn30 deamidation product is aspartate"). Testing completed at Dr. Buick's direction and under his supervision further supports that this is an inherent characteristic of Andya's humMAb4D5-8. Exs. 1042, ¶¶19–20, 22; 1003, ¶98.

At best, this limitation is nothing but a purported discovery of a property of humMAb4D5-8, which was known and in the prior art. *See* Ex. 1003, ¶99. This, however, would not make the claimed invention novel. *See Schering Corp.*, 339 F.3d at 1377–78 (affirming determination that claims directed to a metabolite of loratadine ("DCL") were inherently anticipated because DCL ***necessarily and inevitably forms*** from loratadine, an antihistamine disclosed in the prior art, under

[16] The USPTO found this limitation anticipated by Andya in the related '905 application. *See* Ex. 1008 at 123–24, 162.

normal conditions); *Atlas*, 190 F.3d at 1347 (affirming determination that "sufficient aeration" was inherent in prior art compositions that necessarily also contained air as claimed, even though the benefits of air were not recognized). This limitation is at minimum obvious in light of these disclosures.

vii. Element [f]: "and a pharmaceutically acceptable carrier."

Andya discloses one "object" of the invention is "to provide a stable reconstituted protein formulation which is suitable for subcutaneous administration."[17] Ex. 1004 at 3. Accordingly, the humMAb4D5-8 compositions described by Figures 5–8 are formulated with pharmaceutically acceptable carriers, including those explicitly disclosed in the '218 patent. *See* Ex. 1003, ¶100. For instance, Andya discloses those compositions are formulated with sodium succinate, trehalose, Tween 20™, benzyl alcohol, histidine, mannitol, and sucrose. Ex. 1004 at 6. A POSITA would understand these are non-toxic carriers to recipients at the dosages and concentrations employed and, accordingly, are "pharmaceutically acceptable carriers" within the meaning of the '218 patent. Exs. 1001 at 19:33–53 ("'Pharmaceutically acceptable' carriers, excipients, or

[17] The USPTO found this limitation anticipated by Andya in the related applications, and Genentech did not dispute this. *See* Exs. 1008 at 123–24, 147–50, 161–62, 175–80, 223–27; 1009 at 91, 154–56; 1010 at 372–73, 380–81.

stabilizers…include…preservatives []such as…benzyl alcohol…amino acids such as…histidine…sugars such as sucrose, mannitol, trehalose [and] non-ionic surfactants such as TWEEN™".); 1003, ¶101. This limitation is at minimum obvious in light of these disclosures.

(b) Claim 5

Claim 5 recites the "therapeutic composition of any one of Claims 1 to 4, wherein the anti-HER2 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." As set forth in Section XII.A.1(a) above, Andya anticipates Claim 1.

Further, as discussed in Section XII.A.1(a)v, Andya teaches a composition comprising humMAb4D5-8. The '218 patent says it is an inherent property of humMAb4D5-8 that SEQ ID NO: 1 is the light chain and SEQ ID NO: 2 is the heavy chain. *See* Ex. 1001 at 4:30–32; 13:65–14:5; 20:39–43 ("Full length human IgG rhuMAb HER2 (humAb4D5-8 in [Ex. 1030] 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…."). A later Genentech publication confirms the inherency of this property. *See* Exs. 1034 at 9 (Fig. 1) (disclosing rhuMAb HER2 heavy and light chain sequences that are identical to SEQ ID NO: 1 and SEQ ID NO: 2); 1003, ¶104. The humMAb4D5-8 composition in Andya, therefore, inherently possesses the "SEQ ID NO: 1" and "SEQ ID NO: 2" limitations of Claim 5. *See* Ex. 1003, ¶104.

The inventors of the ’218 patent did not invent these inherent features.

Again, the purported identification and characterization of a prior art composition does not make reciting those properties novel. *In re Crish*, 393 F.3d 1253, 1258 (Fed. Cir. 2004). For example, in *In re Crish*, the Federal Circuit affirmed a determination that claims directed to a portion of a gene nucleotide’ sequence were anticipated by prior art references disclosing the structure, but not the sequence, of the gene in question. *Id.* at 1258–59. Similarly, the sequence of humMAb4D5-8 “is the identity of the structure of the [antibody],” and is inherent to humMAb4D5-8. *Id.*

Accordingly, Claim 5 is anticipated by Andya. *See also* Ex. 1008 at 123–24, 161–62, 223–27 (USPTO finding identical language in related ’905 application inherent in Andya). This limitation is at minimum obvious in light of these disclosures.

(c) Claims 6 and 7

Claim 6 recites the “therapeutic composition of any one of Claims 1 to 4, which is in the form of a lyophilized formulation or an aqueous solution.” Claim 7 recites the “therapeutic composition of Claim 5, which is in the form of a lyophilized formulation or an aqueous solution.” Claims 1 and 5 are anticipated by Andya. Sections XII.A.1(a)–XII.A.1(b). Further, Andya teaches the lyophilized humMAb4D5-8 compositions are reconstituted with water to form aqueous

solutions. *See* Exs. 1004 at Abstract, 6, 21, 26; 1003, ¶107 (explaining aqueous means a solution containing water). In Figures 5–8, therefore, Andya's composition is an aqueous solution. Ex. 1003, ¶107.

Accordingly, Andya anticipates Claims 6 and 7. *See also* Ex. 1008 at 123–24, 161–62, 223–27 (USPTO finding identical limitation anticipated by Andya in related '905 application). This limitation is at minimum obvious in light of these disclosures.

(d) Andya Enables the Challenged Claims

Andya is a prior art printed publication asserted in this proceeding to establish anticipation. *See* Section V. Prior art printed publications are presumed enabling when asserted in support of anticipation. *See In re Antor Media Corp.*, 689 F.3d 1281, 1287 (Fed. Cir. 2012); *Takeda Pharm. Co. v. TWI Pharm., Inc.*, No. C-11-01609, 2013 WL 12164680, at *16 (N.D. Cal. May 20, 2013); *Lambda Optical Solns., LLC v. Alcatel-Lucent USA Inc.*, No. 10-487, 2015 WL 12806435, *4 (D. Del. July 24, 2015). Therefore, Andya is presumed enabling in this proceeding.

Andya enables the Challenged Claims because a POSITA could have combined Andya's disclosure with their own knowledge to make compositions meeting the Challenged Claims. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); Ex. 1003, ¶109. Andya discloses how to obtain, clone, and purify monoclonal antibodies such as humMAb4D5-8. *See* Ex. 1003, ¶109; Ex. 1004 at 12–15. Further,

Andya says "conventional" purification methods "for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography" can be used with humMAb4D5-8. Ex. 1004 at 13. A POSITA would have known how to characterize and purify humMAb4D5-8 using these "conventional" methods. *See* Ex. 1003, ¶109; *see generally* Ex. 1031.

The ability of POSITAs to make humMAb4D5-8 compositions meeting the Challenged Claims based on Andya's disclosure has been repeatedly confirmed by Genentech itself. For example, in obtaining the '218 patent, Genentech relied upon Andya to meet its 35 U.S.C. § 112 requirement to sufficiently describe how a POSITA could make and use the subject matter of the Challenged Claims. Ex. 1001 at 19:54–57 ("***[t]he humMAb4D5-8 antibody of particular interest herein may be prepared as a lyophilized formulation, e.g. as described in [Andya]***; expressly incorporated herein by reference.") (emphases added). According to Genentech's own representations that Andya provides § 112 support for the claims of the '218 patent, it is enabling prior art. If Andya is not enabling, then the Challenged Claims are invalid for lack of enablement.

Moreover, Andya contains the same disclosure as U.S. Patent No. 6,267,958 ("'958 patent") (Ex. 1011). U.S. patents are presumed to be enabling for their entire disclosure. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354–55 (Fed. Cir. 2003). Further, Genentech repeatedly argued the '958 patent's

disclosure was enabling during prosecution of that patent. *See* Ex. 1012 at 119–121, 172–74, 235–37. In Genentech's own words, "the application [which led to the '958 patent] provides working examples for two different antibodies (anti-IgE antibody and anti-HER2 antibody) which were successfully formulated ***according to the teachings of the instant application***." *Id.* at 120, 172–73. Thus, Genentech has admitted the disclosure of the '958 patent enables a POSITA to make humMAb4D5-8. Indeed, Genentech relied on this admission to get the '958 patent. Genentech's statements regarding the '958 patent should apply equally to the same disclosure in Andya.

Further, based on their own knowledge and the disclosures in Andya, a POSITA would have been able to essentially replicate Andya's Figures 5–8. Ex. 1003, ¶111. Example 1 teaches how to lyophilize and then reconstitute compositions of humMAb4D5-8 that meet the Challenged Claims. *See* Exs. 1004 at 20–29; 1003, ¶111. A POSITA would have known how to lyophilize and reconstitute humMAb4D5-8 compositions based on these disclosures and their own knowledge. *See* Ex. 1003, ¶111; *see generally* Ex. 1031. Furthermore, a POSITA would have known how to calculate and plot the amount of native protein relative to the total peak area shown in Figures 5–8. Ex. 1003, ¶111.

This was further confirmed by preparing, purifying and characterizing humMAb4D5-8 compositions in accordance with how a POSITA would have

understood the disclosures of Andya as of May 6, 1998. *See* Exs. 1042, ¶¶10–24 (citing Exs. 1043–47); 1003, ¶112. The prepared humMAb4D5-8 compositions were characterized and analyzed via cation-exchange chromatography on a Bakerbond® Wide-Pore™ CSX column to separate the charged variants as described in Andya. Exs., 1042 ¶19; 1003, ¶112; 1004 at 28. The results showed that the prepared humMAb4D5-8 compositions met the Challenged Claims, and therefore confirms that a POSITA could have made humMAb4D5-8 compositions meeting the Challenged Claims based on Andya's disclosures. Ex. 1003, ¶112.

2. Ground 2: Claims 1 and 5–7 Are Invalid under 35 U.S.C. § 103(a) as Obvious over Waterside

(a) Claim 1

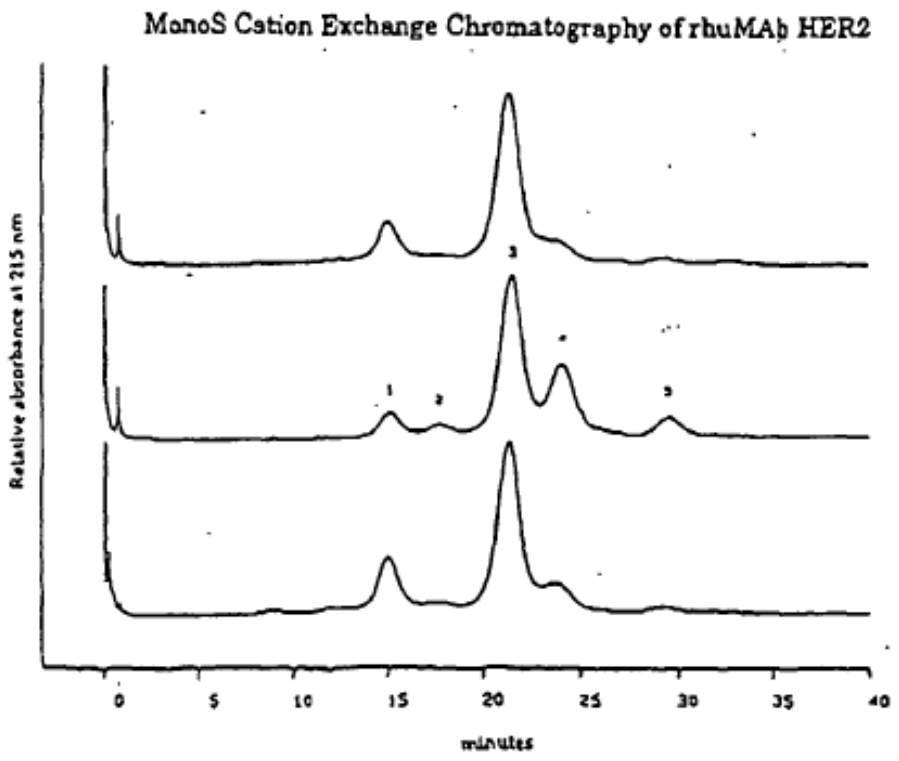
i. Preamble: "A therapeutic composition"

The preamble is not limiting. Section X.A. Nonetheless, Waterside teaches "[a] therapeutic composition" because, as detailed in Section XII.A.2(a)ii, Waterside discloses compositions of rhuMAb HER2, an anti-HER2 antibody, with the claimed degree of purity. *See* Exs. 1006 at 3; 1003, ¶114. Additionally, Waterside teaches that the rhuMAb HER2 is "in Phase III clinical trials (breast cancer)," "halts growth of implanted HER2+ tumors," and "increases chemotherapeutic susceptibility." Ex. 1006 at 3. Waterside also states the conference was about "Process Development And Production Issues for Monoclonal Antibodies" and Genentech, Inc., a known manufacturer of therapeutic compositions, presented the relevant slides. *Id.* at 1, 3.

The preamble is at minimum obvious in light of these disclosures if found to be limiting.

ii. Element [a]: "comprising a mixture of anti-HER2 antibody and one or more acidic variants thereof,"

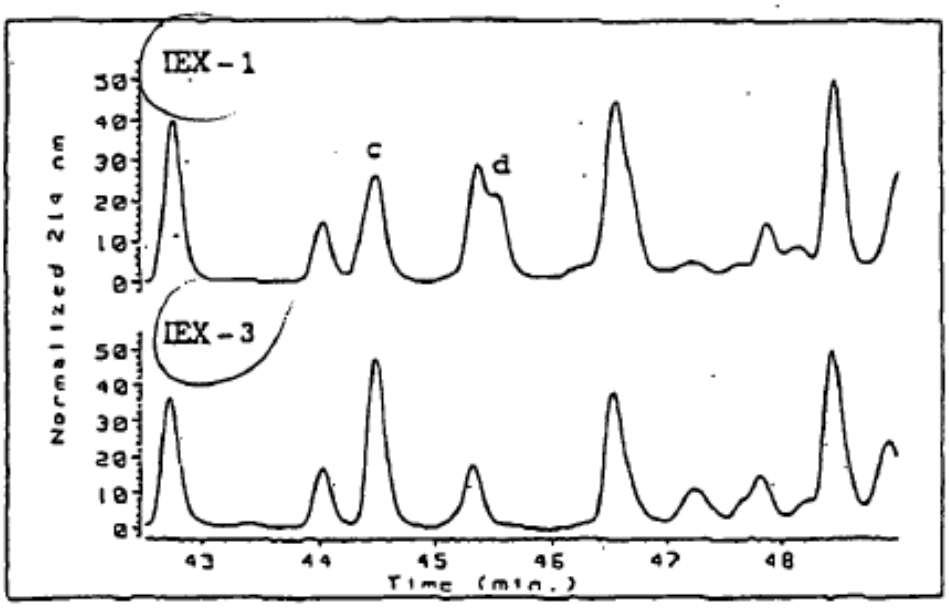
Waterside teaches an anti-HER2 composition. As discussed herein, rhuMAb HER2, the subject of Waterside, is an anti-HER2 antibody. Section VII.A. Waterside discloses chromatograms of "rhuMAb HER2" obtained during "MonoS Cation Exchange Chromatography":



Ex. 1006 at 4. As Dr. Scandella opines, a POSITA would have known these chromatograms represent mixtures of native rhuMAb HER2 and variants thereof. Ex. 1003, ¶¶ 65–66, 116. A POSITA would understand the peaks represent charged

species of rhuMAb HER2 that have eluted from the column. *Id.* Because Waterside teaches using cation-exchange chromatography (*i.e.*, ion-exchange chromatography that uses negative charged resin in the column), negatively charged acidic variants of the protein repel the resin and elute first, followed by the native protein. *Id*. Positively charged basic variants elute last. *Id*., ¶ 47. Accordingly, a POSITA would have understood from Waterside that peaks 1 and 2 represent acidic variants of rhuMAb HER2, peak 3 represents native rhuMAb HER2, and peaks 4 and 5 represent basic variants of rhuMAb HER2.

Confirming the disclosed rhuMAb HER2 compositions include acidic variants, Waterside further teaches peak 1 is deamidated at Asn30 of the light chain. Waterside provides additional information about peak 1 ("IEX-1") and peak 3 ("IEX-3"):



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

See Exs. 1003, ¶117; 1006 at 6; *see also* Section VII.C.2.

As Dr. Scandella explains, the above chromatogram discloses peaks 1 and 3 from page 4 contain "peak c" in varying amounts, and peak 1 contains an additional "peak d." *See* Ex. 1003, ¶¶73, 118. This chromatogram further discloses the amino acid sequence of peaks c and d. *See id*. A POSITA would understand the sequence of peak c includes "N"[18] ("Asn30"), which represents native rhuMAb HER2 with intact Asn30. *See id.*, Ex. 1006 at 6. In contrast, the sequence of peak d shows a change wherein "N" ("Asn30") has been converted to "D"[19] ("Asp30") in "LC" (the

[18] Asparagine is abbreviated as Asn or N. Ex. 1003, ¶118 n.2.

[19] Aspartate is abbreviated as Asp or D. Ex. 1003, ¶118 n.3.

light chain). Ex. 1003, ¶118. A POSITA would therefore have understood peak d to represent a variant of native rhuMAb HER2 (peak c) that has been deamidated at Asn30 in the light chain and converted to aspartate, *i.e.*, an acidic variant. *See id.*; Ex. 1006 at 6; *see also* Section VII.C.2.

Thus, Waterside teaches "a mixture of anti-HER2 antibody and one or more acidic variants thereof." This limitation is at minimum obvious in light of Waterside's disclosures.

iii. Element [b]: "wherein the amount of the acidic variant(s) is less than about 25%,"

As discussed in Section XII.A.2(a)ii above, this limitation is expressly and inherently disclosed in Waterside. The acidic variants in Waterside's rhuMAb HER2 compositions are contained within peaks 1 and 2 of the chromatograms shown on page 4. *See* Exs. 1006 at 4, 6; 1003, ¶119. Element [b] is expressly disclosed because based on inspection alone, a POSITA would have recognized the area under the curve for peak 1 combined with peak 2 in the chromatograms is less than 25% of the total area under the curve for peaks 1 through 5. *See* Ex. 1003, ¶¶56, 119; Section VII.C.2.

Moreover, even if this limitation is not expressly disclosed, it is inherent because it can be proven mathematically that the acidic variants are necessarily present in amounts less than 25%. *See* Section VII.C.2. Using software to calculate the area under the curve for peaks 1 through 5 in the chromatograms, Dr. Scandella

confirmed peaks 1 and 2 represent less than 25% of the total area. Ex. 1003, ¶¶68–71, 119–20; Section VII.C.2. Accordingly, Waterside teaches an anti-HER2 composition "wherein the amount of the acidic variant(s) is less than about 25%."

This limitation is at minimum obvious in light of these disclosures. The '218 patent itself states about 25% is the amount obtained by "initial Protein A chromatography," a known method. Ex. 1001 at 22:60–63. There is nothing critical about the claimed concentration, and compositions falling above the claimed range can easily be brought below merely by collecting and discarding excess acidic variants resolved by chromatography. Ex. 1003, ¶121. A POSITA would have been motivated to do so by the general knowledge that acidic variants and other impurities should be identified and reduced to ensure the antibody has an acceptable level of purity and potency and regulations governing biological products. *Id.*, ¶¶45, 121; 42 U.S.C § 262 (1997).

iv. Claim 1, element [c]: "and wherein the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated,"

As discussed in Section XII.A.2(a)ii above, the acidic variants in the disclosed composition are contained within peaks 1 and 2 of the page 4 chromatograms. Ex. 1006 at 4. Waterside teaches the acidic variants represented by peak 1 are deamidated at Asn30 and converted into an aspartate (Asp30). *Id.* at 6. Furthermore,

peak 2 is inherently also deamidated Asn30. *See* Section VII.C.2; *Schering Corp.*, 339 F.3d at 1377. This is confirmed by other Genentech publications, which show chromatograms of rhuMAb HER2 compositions resolved by cation-exchange chromatography and disclose both peaks 1 and 2 contain deamidated Asn30. *See* Exs. 1005 at 6, 7 (Fig. 2); 1034 at 10 (Fig. 2), 12–13, 15 (Table 6).

Therefore, Waterside teaches the "the acidic variants" (*i.e.*, peaks 1 and 2) "are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated." This limitation is at minimum obvious in light of Waterside's disclosures.

v. Element [d]: "and wherein the anti-HER2 antibody is humMAb4D5-8,"

The rhuMAb HER2 in Waterside was inherently humMAb4D5-8, and a POSITA would have understood this. HumMAb4D5-8 was the only rhuMAb HER2 antibody at the time that met Waterside's descriptions of the antibody: a "humanized (CDR-grafted) version of a murine antibody," with "450-residue IgG1, heavy chains, and 214-residue k light chains," "[e]xpressed in Chinese hamster ovary cells," with "[o]ne glycosylation site in the CH2 domain [*sic*] (Asn-300)," and in Phase III clinical trials for the treatment of breast cancer; and its receptor is a "185 kDa membrane-spanning receptor," "$p185^{HER2}$," and correlated to breast cancer. Exs. 1006 at 3–4; 1003, ¶¶124–25. This limitation would have been at minimum obvious to a POSITA in light of the foregoing, which a POSITA would have known.

See Section VII.A; Ex. 1003, ¶¶34, 125; *see also* Ex. 1035 at 6–8.

vi. Element [e]: "and wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate,"

Element [e] is both explicitly disclosed by Waterside and an inherent property of the humMAb4D5-8 antibody Waterside discloses. It would also have been obvious to a POSITA. As set forth in Section XII.A.2(a)iv, Waterside teaches Asn30 in one light chain of rhuMAb HER2 (which, as discussed above, would have been understood by a POSITA as humMAb4D5-8) is deamidated and converted to Asp30. Ex. 1006 at 6. Moreover, as set forth in Section XII.A.1(a)vi, this limitation is also inherent to humMAb4D5-8. *See Alcon Research, Ltd.*, 687 F.3d at 1369.

vii. Element [f]: "and a pharmaceutically acceptable carrier."

Waterside teaches that the rhuMAb HER2 is "in Phase III clinical trials (breast cancer)," "halts growth of implanted HER2+ tumors," and "increases chemotherapeutic susceptibility." Ex. 1006 at 3. That its antibody mixture could be combined with a pharmaceutically acceptable carrier would be immediately apparent to a POSITA from these disclosures. It at minimum would have been obvious to a POSITA to formulate the rhuMAb HER2 mixture disclosed therein with a pharmaceutically acceptable carrier. Ex. 1003, ¶128. Numerous such carriers (including the specific examples disclosed in the '218 patent) and the methods for

employing them were well known as of May 6, 1998. *Id*. Further, a POSITA would have known using humMAb4D5-8 "augurs well" for the ongoing treatment of human cancers overexpressing the HER2 receptor. Ex. 1030 at 14. Accordingly, a POSITA would have been motivated to formulate the compositions disclosed in Waterside with a pharmaceutically acceptable carrier in order to render them suitable for human therapeutic use. *Id.*; Ex. 1003, ¶129. Pharmaceutically acceptable carriers help make the antibody stable and suitable for delivery and storage. Ex. 1003, ¶¶28–29. Indeed, Waterside itself would have provided further motivation to do so through its disclosure that rhuMAb HER2 may be used to treat breast cancer, was in Phase III clinical trials for such use, and had been produced at a 12,000 L scale indicating production for therapeutic use. Exs. 1006 at 3; 1003, ¶129. That the '218 specification provides no examples of how to make and use the claimed composition with the claimed pharmaceutically acceptable carrier and indicates Genentech knew a POSITA would have known how to make and use at least some claimed embodiments.

(b) Claim 5

Claim 5 recites the "therapeutic composition of any one of Claims 1 to 4, wherein the anti-HER2 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." Claim 1 is obvious over Waterside and the knowledge of a POSITA. Section XII.A.2(a).

Further, and as discussed above in Section XII.A.2(a)v, a POSITA would have understood rhuMAb HER2 in Waterside to be humMAb4D5-8. The additional limitations of Claim 5 are inherent to humMAb4D5-8. *See* Section XII.A.1(b). Where it would have been obvious to a POSITA that rhuMAb HER2 disclosed in Waterside was humMAb4D5-8, the resulting combination would inherently have the characteristics of humMAb4D5-8, including the sequence of humMAb4D5-8. *See Alcon Research, Ltd.*, 687 F.3d at 1369. Accordingly, Claim 5 is also obvious in light of Waterside.

(c) Claims 6 and 7

Claim 6 recites the "therapeutic composition of any one of Claims 1 to 4, which is in the form of a lyophilized formulation or an aqueous solution." Claim 7 recites the "therapeutic composition of Claim 5, which is in the form of a lyophilized formulation or an aqueous solution." As set forth in Sections XII.A.2(a)–XII.A.2(b) above, Claims 1 and 5 are obvious over Waterside and the knowledge of a POSITA. Further, and as discussed above in Section XII.A.1(a)vii, it would have been obvious to have formulated the rhuMAb HER2 compositions disclosed therein with pharmaceutically acceptable carriers.

It would have also been obvious to a POSITA to have mixed those rhuMAb HER2 and pharmaceutically acceptable carrier compositions in water to yield an aqueous solution because that is the preferred state for an injectable drug in the

clinic. Ex. 1003, ¶133. Some proteins, however, are not sufficiently stable in aqueous solutions. Ex. 1003, ¶134. In such cases, it would have been obvious to a POSITA to have lyophilized the rhuMAb HER2 and pharmaceutically acceptable carrier compositions. *Id.* Lyophilization was known to preserve biological structures, effectively extending the shelf life. *Id.* A POSITA could have done so using routine methods known in the art. *Id.*; *see* Section XII.A.2(c). Accordingly, Claims 6 and 7 are also obvious in light of Waterside.

3. Ground 3: Claims 1 and 5–7 Are Invalid under 35 U.S.C. § 103(a) as Obvious over Harris

(a) Claim 1

i. Preamble: "A therapeutic composition"

The preamble is not limiting. Section X.A. Nonetheless, Harris teaches a therapeutic composition because it discloses a composition of rhuMAb HER2, an anti-HER2 antibody, with the claimed degree of purity. *See* Section XII.A.3(a); Ex. 1003, ¶137. This limitation also would have been obvious to a POSITA in light of a POSITA's knowledge that anti-HER2 antibody was the subject of clinical trials and effective against breast cancer. *See* Section VII.A.

ii. Element [a]: "a mixture of anti-HER2 antibody and one or more acidic variants thereof,"

Harris teaches an anti-HER2 composition. Harris describes the use of anti-HER2 antibody "rhuMAb HER2," "a recombinant humanized antibody produced in transfected CHO cells." Ex. 1005 at 5. Harris explains "three lots of rhuMAB

HER2" were run through "[c]ation-exchange chromatography." *Id.* at 6–7. The results are shown in three chromatograms in Figure 2:

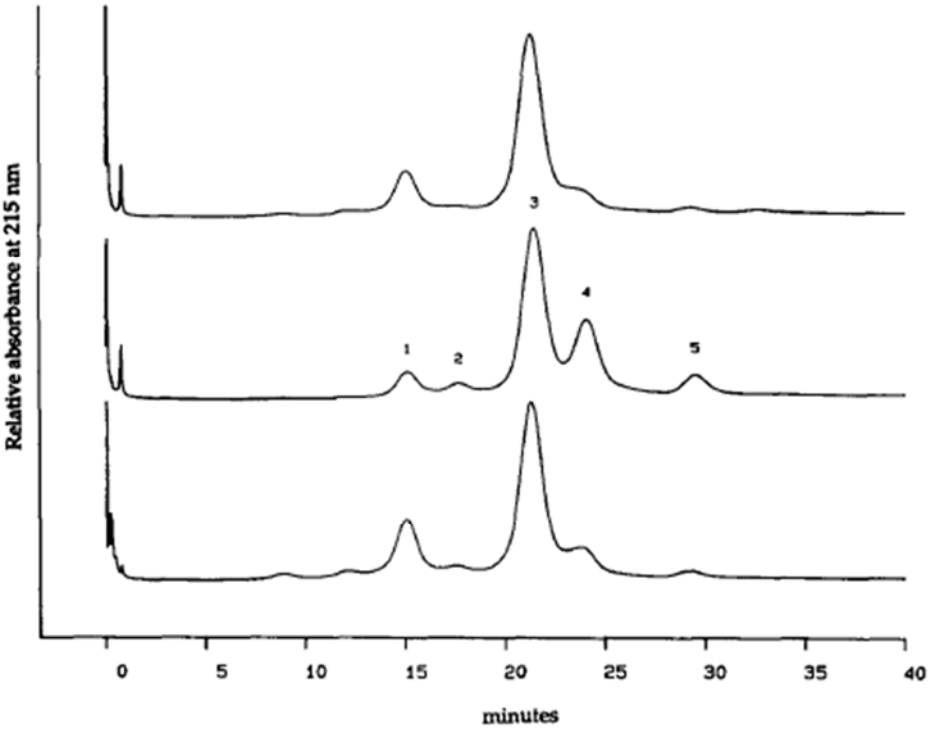


Fig. 2. Cation-exchange chromatography of three lots of rhuMAb HER2. Chromatographic conditions are given in Section 2.2.

Id.

As discussed in Section VII.C.1, Harris identifies five charged species of the composition in the middle chromatogram that were eluted from the column, which are represented by the five numbered peaks in the middle chromatogram. *Id.* Peaks 1 and 2 are described as "[t]he more acidic peaks" and "are deamidated at Asn^{30} in one light chain…." *Id.* Deamidated Asn30 is an acidic variant of rhuMAb HER2. Section VII.C.1; Ex. 1003, ¶¶42, 140. A POSITA would have understood, therefore, that peaks 1 and 2 represent acidic variants. *See* Exs. 1005 at 6; 1003, ¶140. A

POSITA would also have understood the "main peak" (peak 3) represents native rhuMAb HER2. *See* Exs. 1005 at 6; 1003, ¶140. Finally, a POSITA would have known peaks 4 and 5 represent basic variants. *See* Exs. 1005 at 6; 1003, ¶140. For these reasons, Harris teaches a mixture of rhuMAb HER2, an anti-HER2 antibody (peak 3), and acidic variants thereof (peaks 1 and 2). This limitation is at minimum obvious in light of these disclosures.

iii. Element [b]: "wherein the amount of the acidic variant(s) is less than about 25%,"

As discussed above in Section VII.C.1, this limitation is expressly and inherently disclosed in Harris. Harris teaches the acidic variants in the disclosed compositions are contained within peaks 1 and 2 of Figure 2. Harris expressly teaches the acidic variants are present in amounts less than 25%. A POSITA would have recognized upon inspection that the area under the curve for peak 1 combined with peak 2 in the chromatograms is less than 25% of the total area under the curve for peaks 1 through 5. *See* Ex. 1003, ¶141. Moreover, element [b] is inherent in Harris because it can be proven mathematically that the acidic variants are necessarily present in amounts less than 25%. *See* VII.C.1. Using software to calculate the area under the curves for peaks 1 through 5, Dr. Scandella confirmed peaks 1 and 2 represent less than 25% of the total area. Ex. 1003, ¶¶57–60, 142; Section VII.C.1. Accordingly, Harris teaches an anti-HER2 composition "wherein the amount of the acidic variant(s) is less than about 25%."

This limitation is at minimum obvious in light of these disclosures and for the reasons in Section XII.A.2(a)iii.

iv. Element [c]: "and wherein the acidic variant(s) are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated,"

As established in Section XII.A.3(a)ii, Harris teaches peaks 1 and 2 of Figure 2 are deamidated variants. Ex. 1005 at 6. Harris further discloses rhuMAb HER2 degrades by deamidation at one or more asparagine residues. *Id.* at 4–5. As discussed above, the experiment conducted in Harris reveals rhuMAb HER2 is "deamidated at Asn^{30} in one light chain…." *Id.* at 6.

No other acidic variants were resolved by cation-exchange chromatography. *See* Ex. 1003, ¶144. A POSITA would expect acidic variants present in non-negligible amounts to be resolved via cation-exchange chromatography. *Id.* Accordingly, Harris teaches that the "acidic variants" of the rhuMAb HER2 composition "are predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated." *See id.* This limitation is at minimum obvious in light of these disclosures.

v. Element [d]: "and wherein the anti-HER2 antibody is humMAb4D5-8,"

To the extent Harris does not expressly disclose this limitation, it would have been obvious to a POSITA that the rhuMAb HER2 in Harris was to humMAb4D5-

8. *See* Ex. 1003, ¶145. Harris teaches using rhuMAB HER2 made by a single cell line and production of "three lots of rhuMAb HER2." Ex. 1005 at 5. A POSITA would understand this to mean rhuMAb HER2 was already in production. *See* Ex. 1003, ¶145. As discussed above, a POSITA would have known overexpression of the HER2 receptor was correlated with aggressive breast cancer and that targeting this receptor could have clinical benefit. *See* Section VII.A; Ex. 1003, ¶146. A POSITA would also have known using humMAb4D5-8 "augurs well" for the ongoing treatment of human cancers overexpressing the HER2 receptor and that humMAb4D5-8 was the only variant of rhuMAb HER2 in clinical trials in 1995. *See* Ex. 1003, ¶146.

vi. Element [e]: "and wherein the deamidated variants have Asn30 in CDR1 of either or both V_L regions of humMAb4D5-8 converted to aspartate,"

As discussed above, this limitation is inherent to humMAb4D5-8. *See* Section XII.A.1(a)vi. Further, Harris teaches that "Asn^{30}" in protein region CDR1 in one light chain of rhuMAb HER2 is deamidated. Ex. 1005 at 6. Since it would have been obvious to a POSITA that the rhuMAb HER2 disclosed in Harris was humMAb4D5-8, the rhuMAb HER2 would inherently have the characteristics of humMAb4D5-8, including this limitation. *See Alcon Research, Ltd.*, 687 F.3d at 1369.

vii. Element [f]: "and a pharmaceutically acceptable carrier."

To the extent this limitation is not expressly disclosed in Harris, it would have been obvious to a POSITA that the rhuMAb HER2 compositions disclosed therein could be formulated with pharmaceutically acceptable carriers. Ex. 1003, ¶148. Again, numerous such carriers (including the specific examples disclosed in the '218 patent) and the methods for employing them were well known and predictable as of May 6, 1998. *Id.*; Section XII.A.2(a)vii.

A POSITA would have had good reason to apply such carriers to the compositions disclosed in Harris in order to render them suitable for human therapeutic use. Ex. 1003, ¶149. As discussed above, a POSITA would have understood rhuMAb HER2 was already in production. *Id.*

(b) Claim 5

Claim 5 recites a "therapeutic composition of any one of Claims 1 to 4, wherein the anti-HER2 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." As set forth in Section XII.A.3(a) above, Claim 1 is obvious over Harris.

Further, and as discussed above in Section XII.A.3(a)v, it would have been at least obvious to a POSITA that the antibody of interest in Harris was humMAb4D5-8. The additional limitations of Claim 5 are inherent to humMAb4D5-8, and where it would have been obvious to a POSITA that rhuMAb HER2 disclosed in Harris

was humMAb4D5-8, the resulting combination would inherently have the sequence of humMAb4D5-8. *See* Section XII.A.1(b); *Alcon Research, Ltd.*, 687 F.3d at 1369.

Accordingly, Claim 5 is also obvious in light of Harris.

(c) Claims 6 and 7

It would have also been obvious to a POSITA to have mixed those rhuMAb HER2 and pharmaceutically acceptable carrier compositions with water to form an aqueous solution because that is the preferred state for injection. Ex. 1003, ¶153. Some proteins, however, are not sufficiently stable in aqueous solutions. In such cases, it would have been obvious to a POSITA to have lyophilized the rhuMAb HER2 and pharmaceutically acceptable carrier compositions. *Id.* Lyophilization was known to preserve biological structures, effectively extending the shelf life of certain proteins. *Id.* ¶¶130–31, 153. A POSITA could have done so using routine methods known in the art. *Id.*; Section XII.A.2(c). Accordingly, Claims 6 and 7 are also obvious in light of Harris.

B. Lack of Secondary Considerations

Petitioner is not aware of any secondary considerations that would support a finding of non-obviousness. Even if such secondary considerations exist, they cannot overcome the strong *prima facie* case of obviousness discussed above. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010). Petitioner reserves the right to respond to any assertions of secondary considerations that Genentech alleges

during this proceeding.

XIII. CONCLUSION

Petitioner respectfully requests IPR of the Challenged Claims.

* * *

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Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This Petition complies with the type-volume limitations as mandated in 37 C.F.R § 42.24, totaling 13,971 words. Counsel has relied upon the word count feature provided by Microsoft Word.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 9,249,218, along will all exhibits and other supporting documents, were served on August 29, 2017, via FedEx Overnight delivery directed to the assignee for the patent at the following address:

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