IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

U.S. Patent No. 6,339,142

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

Assignee: Genentech, Inc.

Title: Protein Purification Panel: To Be Assigned

Mail Stop *Inter Partes* Review
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PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 6,339,142
UNDER 35 U.S.C. § 311 AND 37 C.F.R. § 42.100

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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 1–3 (the "Challenged Claims") of U.S. Patent No. 6,339,142 ("'142 patent," Ex. 1001). USPTO assignment records state the '142 patent is assigned to Genentech, Inc. ("Genentech"). *See* Ex. 1020 at 1.

The '142 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 '142 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 5:14–18).

The claims require "less than about 25%" of these variants, but that too does not render them patentable. Acidic variant levels within this range are expressly taught multiple times by the prior art cited in this Petition. And the '142 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 6:1–4. This alone renders the range unpatentable. *See* MPEP 2131.05. That is especially true given that the anti-HER2 antibody 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 '142 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 '142 patent, Genentech filed for and obtained another patent on its allegedly inventive purification method. In pursuing the '142 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 '142 patent and U.S. Patent No. 9,249,218 (the "'218 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 ’142 and ’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 ’142 patent purport to claim priority to U.S. Provisional Application No. 60/084,459 (“’459 provisional application”), filed May 6, 1998. *See* Ex. 1001; Ex. 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 '142 patent is available for IPR and that Petitioner is not barred or estopped from requesting an IPR challenging the patent claims on the grounds identified in this petition.

IV. FEES

The undersigned authorizes the PTO 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 '142 patent purports to claim priority back 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 on the following grounds:

Ground	Proposed Statutory Rejections
1	Claims 1–3 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	Claim 1 is invalid under 35 U.S.C. § 102(b) as anticipated by **Waterside**[3] (published April 1996).
3	Claims 2 and 3 are invalid under 35 U.S.C. § 103(a) as obvious over **Waterside** and the knowledge of a person of ordinary skill in the art ("POSITA").
4	Claim 1 is invalid under 35 U.S.C. § 102(b) as anticipated by **Harris**[4]

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

[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 held at the Omni Waterside Hotel in Harborside-Norfolk, Virginia on Apr. 22–25, 1996) ("Waterside") (Ex. 1006).

	(published June 23, 1995).
5	Claims 2 and 3 are invalid under 35 U.S.C. § 103(a) as obvious over **Harris** and the knowledge of a POSITA.

The cited prior art is as follows:

- **Andya** is a PCT application and a printed publication that was accessible to the relevant public more than one year prior to the earliest possible priority date, *i.e.*, May 6, 1998, because Andya was published on February 13, 1997. 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, presented by The Williamsburg BioProcessing Foundation ("WilBio"). The publication includes a series of slides for a presentation by Reed Harris from Genentech's Analytical Chemistry Department on the topic of "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, more than

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[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).

one year prior to May 6, 1998. Exs. 1042, ¶3; 1006 at 2. The Waterside Monoclonal Conference was a popular conference attended by engineers and scientists interested in and working on monoclonal antibodies, such as the anti-HER2 antibody that is the subject of the '142 patent. Exs. 1042, ¶2; 1003, ¶58. WilBio printed and distributed copies of all presentations that were to be given at the conference, including Waterside, to attendees, speakers, and sponsors. Ex. 1042, ¶3. Over 200 people received a copy of Waterside at the 1996 Waterside Monoclonal Conference. *Id.* In addition, a copy of Waterside was provided by Genentech to the USPTO in an Information Disclosure Statement during prosecution of the '218 patent. Ex. 1036 at 81. In doing so, Genentech 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." *Id.* In the UK litigation discussed below (Section VIII), Genentech likewise represented that Waterside was "made available to the public before the priority date of" European Patent Number EP 1 308 455 (the "EP '455 patent"), which allegedly claims priority to the same provisional application as the '142 patent. 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. Thus, Waterside is prior art under 35 U.S.C. § 102(b).

- **Harris** is an article published in the well-known scientific journal, Journal of Chromatography A. *See* Ex. 1003, ¶47. Harris was published June 23, 1995. Ex. 1005 at 1. Additionally, Harris was accessible at the University of Illinois at Chicago ("U.I.C.") library as early as July 7, 1995. *Id.* Harris therefore is a printed publication that was accessible to the public more than one year prior to May 6, 1998. *See id.* Thus, Harris is prior art under 35 U.S.C. § 102(b).

Section XII contains a detailed explanation of the statutory grounds for the unpatentability of each of the Challenged Claims that identifies examples of where each element can be 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) and Dr. Richard Buick (1043), and other supporting exhibits, including authenticating declarations (Exs. 1025; 1037; 1038). Dr. Scandella has over 40 years of experience in protein analysis, purification, and manufacturing. Ex. 1003, ¶¶3–12. Dr. Buick has over a decade of experience in preparing and analyzing recombinant antibodies, including humanized monoclonal antibodies. Ex. 1043, ¶¶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. *Id.*, ¶16. The 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.*, ¶17.

VII. BACKGROUND

A. HumMAb4D5-8

The ’142 patent purports to describe “[a] method for purifying a polypeptide by ion exchange chromatography.” Ex. 1001 at Abstract. The Challenged Claims, however, recite a “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%.” *Id.* at Claim 1.

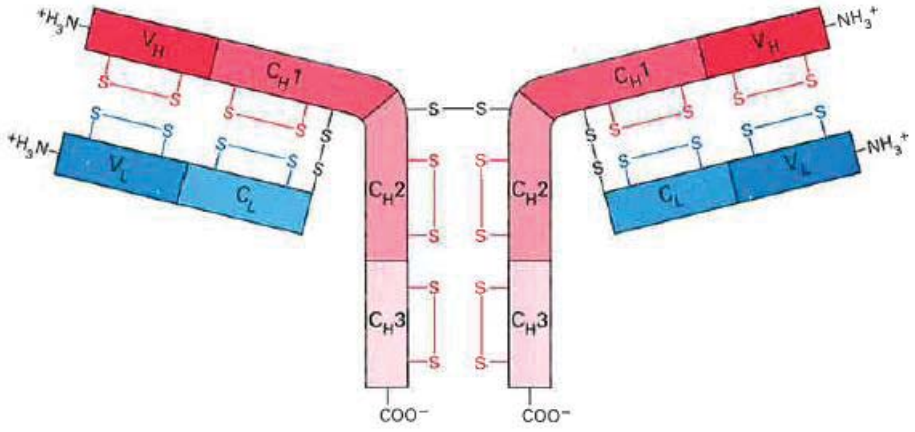
The “anti-HER2 antibody” “humMAb4D5-8” is also known as rhuMAb HER2. *Id.* at 20:48–52, 28:47–48 (Claim 3); Ex. 1003, ¶29 (explaining a POSITA would know humMAb4D5-8 was also called rhuMAb HER2 as of the ’142 patent’s earliest possible priority date). In the art, “hu” or “hum” is used to denote something that has been “humanized,” while “MAb” means a monoclonal antibody. *Id.* 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, ¶31; 1016 at 8.

Antibodies are proteins derived from the immune system that selectively target receptors (humMAb4D5-8 targets the HER2 receptor). Ex. 1003, ¶32. Like all proteins, antibodies comprise chains of amino acid "residues." *See* Ex. 1033, Vol. 3 at 396–97. The typical structure of an antibody—a Y-shape made up of two identical heavy ("H") chains 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 region (C_L) and one variable region (V_L). *Id.* at 402.

[5] $p185^{HER2}$ is also known as the HER2 receptor. Ex. 1003, ¶31.



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, also called the "antigen." *Id*.; Ex. 1003, ¶34.

By 1989, mouse (or 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 (MAb 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 MAb 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 variants created, Carter identified one of these, huMAb4D5-8, as the preferred variant and published that using humMAb4D5-8 "augurs well for the ongoing treatment of human cancers

overexpressing $p185^{HER2}$…." Exs. 1030 at 12, 14; 1001 at 7:67–8:3 (citing Ex. 1030).

B. Protein Purity and Degradation

It was well-known as of May 6, 1998 that proteins such as antibodies undergo changes to their structure after they are synthesized, resulting in a mixture of native and modified protein. Such changes include post-translational modification and protein degradation. *See* Exs. 1003, ¶37; 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, ¶38. Deamidation at asparagine may proceed through a cyclic imide intermediate, succinimide, which then hydrolyzes to form either aspartate (Asp) or iso-aspartate (isoAsp) residue. Ex. 1017 at 6. Deamidation at asparagine is one of the most common routes of protein degradation. Exs. 1003, ¶38; 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, ¶39. Such a variant, resulting from either aspartate or iso-aspartate, is commonly called an "acidic variant." *Id.*; Ex. 1001 at 5:45–49.

Isomerization of aspartate is another mechanism of protein degradation. *See* Exs. 1003, ¶40; 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, ¶40. The change from aspartate (acidic residue) to iso-aspartate (acidic residue) is a neutral change relative to the native protein. *Id.* Thus, the resulting protein variant (isoAsp) is not an acidic variant. *Id.*; Ex. 1034 at 5 (Abstract), 11. Although deamidation and isomerization may proceed through a similar intra-molecular cyclic imide intermediate, they degrade from different starting amino acid residues (asparagine versus aspartate in native protein) and result in different surface charges—*i.e.*, deamidation results in acidic variants and isomerization results in neutral variants compared to the native protein. Ex. 1003 ¶40.

It was known by May 6, 1998 that acidic variants, like other forms of protein degradation, could have a negative influence on a protein's activity and efficacy. *Id.*, ¶41; Ex. 1017 at 7 ("[F]or pharmaceutical preparations, the major concern [of deamidation] is the change in protein function."). It was also known that acidic variants, such as deamidated variants, and other impurities should be identified and reduced to ensure the antibody has an acceptable level of purity and potency. Ex. 1003, ¶42. Indeed, FDA regulations then (and now) required showing biological products are "safe, pure, and potent" before they can be approved. 42 U.S.C § 262

(1997).

Several methods for achieving this goal were available to POSITAs. Ex. 1003, ¶43; *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, ¶43; 1031 at 73–102. As discussed below, 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, ¶¶44–45; 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 often 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 20:48–55 (using "humMAb4D5-8" and "rhuMAb HER2"); 1014 at 1 (using "trastuzumab" and Herceptin®); 1035 at 5 ("Characterization of biological activity of the several resulting humanized versions led to development of only one recombinant humanized anti-p185HER2, rhuMAb HER2 (Herceptin®; trastuzumab) intended for use as a therapy for woman with metastatic breast cancer."); IPR2017-00804, Patent Owner Preliminary Response (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. *See* 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® itself but instead attempted to claim known manufacturing processes and—in the case of the '142 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 '142 patent—were already made public and known in the art well before May 6, 1998.

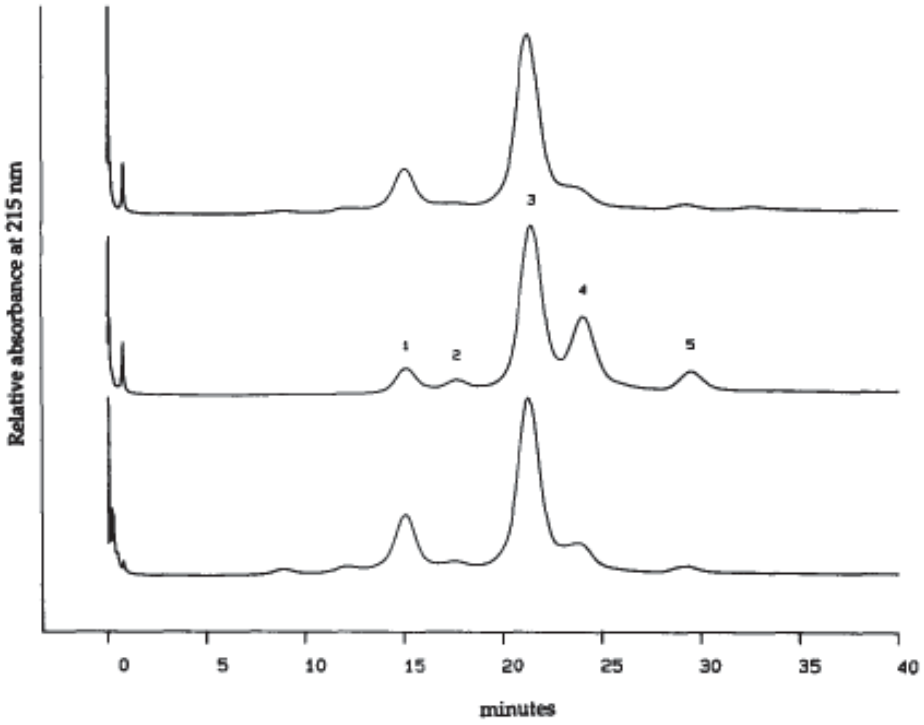
1. Harris

Reed J. Harris published an article on purifying "proteins isolated from mammalian cell culture" in the Journal of Chromatography A 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 (*i.e.*, separating) "charge[d] variants" from native rhuMAb HER2 in "three lots of rhuMAB HER2" using cation-exchange chromatography techniques. *Id.* at 5–7; Ex. 1003, ¶49. A POSITA would have understood that the rhuMAb HER2 in Harris was humMAb4D5-8.[6] Ex. 1003, ¶49.

The results of using cation-exchange chromatography to resolve the three lots of rhuMAb HER2 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). The rhuMAb HER2 compositions had five charged species, including two acidic variants consisting of deamidated variants at Asn30 in one light chain. Each of the peaks was identified by a combination of peptide mapping experiments together 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, ¶51. 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.*, ¶52.

Harris expressly and inherently that taught that the acidic variants were present in amounts less than about 25%. Ex. 1005 at 6. This is expressly taught by Harris 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, ¶53. As Dr. Scandella sets forth in his declaration, the area under peaks 1 and 2 (and therefore, the amount of acidic variants in the compositions) disclosed in Figure 2 was less than approximately 25% of the total area under the curve for peaks 1 through 5. *See 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

that can then be integrated using software such as MATLAB™ and Excel to calculate the percent area under the curve for each peak.[7] Ex. 1003, ¶54.

Dr. Scandella performed these calculations for the rhuMAb HER2 compositions disclosed in Figure 2 and determined that they necessarily 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. ¶¶54–57; *see Schering Corp.*, 339 F.3d at 1377.

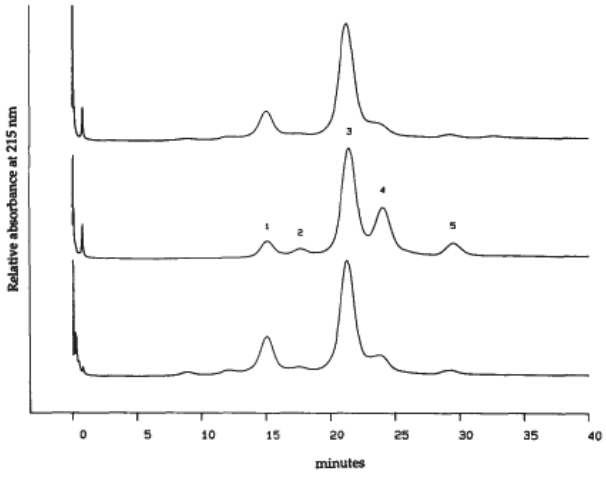
2. Waterside

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 that overexpression of the HER2 receptor was correlated with breast cancer. Ex. 1006 at 3.

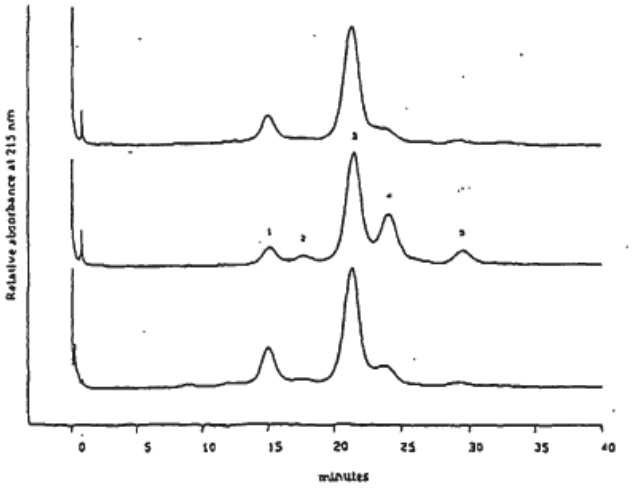
[7] Date Thief, MATLAB™, and Excel were available by May 6, 1998 and have since been periodically updated.

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 antibody referenced by Genentech in Waterside was humMAb4D5-8. Ex. 1003, ¶60. As the below side-by-side 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 (the native form of the protein) and basic variants elute after the main peak. Ex. 1003, ¶63. Accordingly, peaks 1 and 2 identified 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, ¶63.

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 by Waterside because a POSITA reading the chromatograms and associated descriptions would have known the approximate amount of each of the charged species by inspection of the relative area under each of the peaks. Ex. 1003, ¶64. 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 through 5. *Id.* This would have been apparent to a POSITA reading Waterside. *Id.*

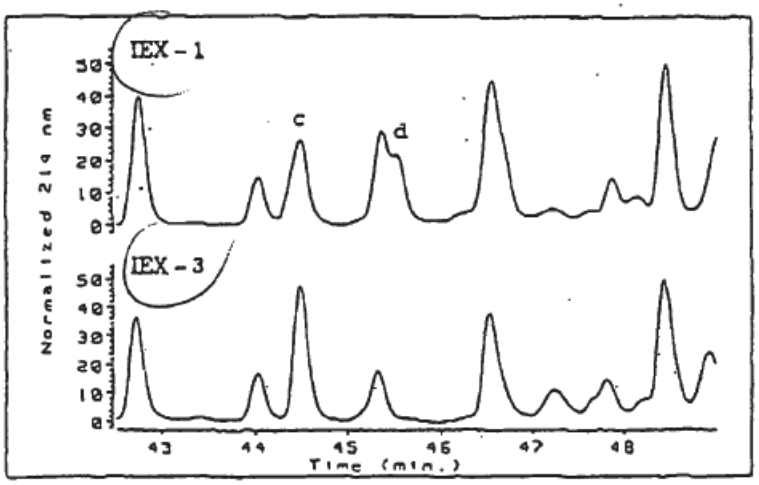
This characteristic is also necessarily present, or inherent, in Waterside because, like Harris, it can be proven mathematically using the information given. *See Schering Corp.*, 339 F.3d at 1377. Dr. Scandella performed these calculations using Data Thief, Excel, and MATLAB™ and determined that the 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%

See Ex. 1003, ¶¶65–68.

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, ¶69.

Genentech further disclosed additional chromatographic analysis confirming peak 1 was deamidated at Asn30, *i.e.*, an acidic variant of rhuMAb HER2:



Exs. 1006 at 6; 1003, ¶70. 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"). Ex. 1003, ¶70; *see* Ex. 1006 at 6. This disclosure confirmed that when Asn30 in rhuMAb HER2 is deamidated, it converts to aspartate. Exs. 1003, ¶70; 1006 at 6. Genentech further disclosed peak 1 from page 4 ("IEX-1") contained "peak d," *i.e.*, deamidated Asn30, whereas peak 3 ("IEX-3") did not. Exs. 1003, ¶70; 1006 at 6. Deamidated variants are acidic in nature. *See* Section VII.B; Ex. 1003, ¶70. Accordingly, peak 1 was an acidic variant of rhuMAb HER2, wherein Asn30 in the light chain had deamidated to aspartate. Exs. 1003, ¶70; 1006 at 4, 6.

Furthermore, peak 2 is inherently deamidated at Asn30. *See Schering Corp.*, 339 F.3d. at 1377. Harris, which disclosed nearly identical (if not identical) chromatograms, taught that 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); Ex. 1003, ¶70; 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. In Andya, Genentech again disclosed humMAb4D5-8 degradation occurred by deamidation

at asparagine residues or isomerization of aspartate residues (*i.e.*, iso-aspartate residues formed by succinimide formation). *Id.* at 6, 21 ("In 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)"), 28; Ex. 1003, ¶72. As discussed above, deamidation at Asn30 results in acidic variants and isomerization of 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%:

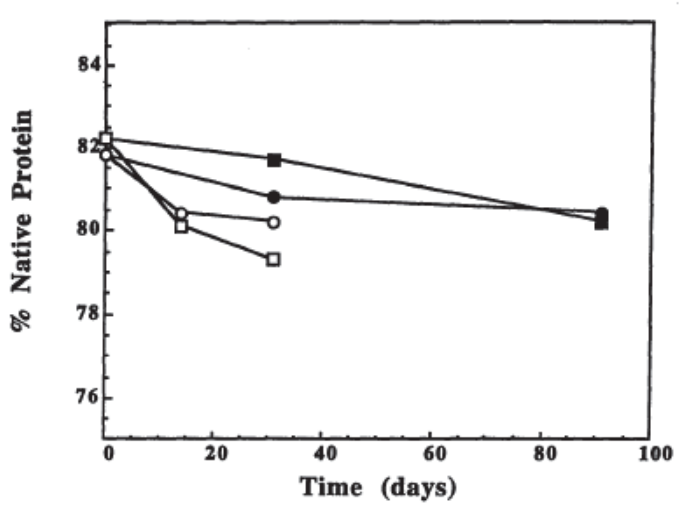


FIG. 5

Id. at 39 (Fig. 5). The remaining 18–19% was degraded protein. Ex. 1003, ¶74 (explaining a POSITA would have understood the percentage of degraded protein in Figures 5–8 is the percentage of native protein at time zero subtracted from 100%). This 18–19% in turn included the sum total of all degraded protein resulting from deamidation at Asn30 (acidic variants), and all degraded protein resulting from succinimide formation at residue 102 (non-acidic variants). *Id.*; Ex. 1004 at 39 (Fig. 5).

Accordingly, a POSITA would understand Figure 5 discloses humMAb4D5-8 compositions with at most 18–19% acidic variants, where those acidic variants are mainly (if not entirely) deamidated at Asn30. *See* Ex. 1004 at 28 ("the major degradation route for rhuMAb HER2 in aqueous solution is deamidation or succinimide formation"); Ex. 1003, ¶74. Applying the same analysis to Figures 6–8, a POSITA would understand those figures disclose humMAb4D5-8

compositions with 78–82% native protein and, at most, 18–22% acidic variants mainly (if not entirely) deamidated at Asn30. Exs. 1003, ¶¶75–79; 1004 at 39–40 (Figs. 6–8).

As set forth below in Section XII, the '142 patent claims are anticipated, or at least obvious, based on Genentech's prior public disclosures in 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 United Kingdom High Court of Justice, Patents Court also found claims of EP '455 invalid as lacking novelty over 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 Patents Court also found all claims of EP '455 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 set aside on appeal on April 16, 2015. 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 VL regions of humMAb4D5-8 converted to aspartate…not directly and unambiguously disclosed” in Andya.). The claims of the ’142 patent do not require these features.[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 ’142 PATENT AND PROSECUTION HISTORY

A. ’142 Patent

The ’142 patent has three claims. As explained above, Claim 1 is the only independent claim and claims a “composition.” *See* Section VII.A. Claim 2 depends from independent Claim 1 and includes one additional element, “a pharmaceutically acceptable carrier.” Claim 3 also depends from independent

[8] The remaining ground for reinstating the EP ’455 patent relates to a position Petitioner does not advance here.

Claim 1 and includes one additional element, "the anti-HER2 antibody is humMAb4D5-8."

These claims do not align with the alleged "invention" described in the specification. The '142 patent describes the "invention" as a particular purification "***method***" using "ion exchange chromatography."[9] Ex. 1001 at Abstract, 1:10–15, 2:12–3:23, 20:47–21:16 (emphasis added). Although the '142 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 5:14–18, 5:46–49.

The '142 patent also notes that 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

[9] The allegedly "novel" purification method described in the '142 patent 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).

composition." Ex. 1001 at 23:6–9 (emphasis added). The patent does not describe "Protein A" as the inventors' invention. Nor could it, as such technique was already known. *See* Ex. 1031 at 169 (explaining protein A chromatography was used to purify monoclonal antibodies as early as 1972). To the contrary, the specification describes this 25% acidic variants composition as in need of purification by its allegedly inventive method:

> Deamidated and other acidic variants of rhuMAb HER2 were produced when the antibody was made by recombinant DNA technology…***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 5:66–6:6, 23:1–16. 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.* Claim 1.

B. Prosecution History

The '142 patent issued from Application No. 09/679,397, filed on October 3, 2000, which is a division of Application No. 09/304,465 (the "'465 application"),

filed on May 3, 1999, now U.S. Patent No. 6,489,447. *See* Ex. 1002 at 2. The '142 patent purports to claim priority to the '459 provisional application, filed on May 6, 1998. *See id.*

1. '397 Application

The Examiner allowed the as filed claims of the '397 application. *See* Ex. 1002 at 95–99 (Office Action dated July 9, 2001). Notably, neither Andya nor Harris were considered by the Examiner when the '142 patent issued. Ex. 1001 at References Cited.

2. The USPTO Repeatedly Rejected Related Applications Based On Andya, Including All Limitations of the Challenged Claims

During prosecution of Application Nos. 10/253,366 (the "'366 application"), 10/949,683 (the "'683 application"), Application No. 12/418,905 (the "'905 application), 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* Ex. 1010 at 372; Ex. 1009 at 91–92; Ex. 1008 at 123–24, 160, 224–25. Each of these related applications also stems from the '459 provisional application.

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 that Andya disclosed the "preparation of rhuMAb 4D5-8 in Example 1" and disclosed "analysis of deamidated (*i.e.* acidic)

variants by CSx chromatography." *Id.* at 372–73 (citing Ex. 1004 at 28, Fig. 5–8). The Examiner further found that Figures 5–8 in Andya disclosed "81–82% native protein at the start of each stabilization experiment[,] [which] means there is 18–19% non-native variants; this range is clearly 'less than about 25%.'" *Id.* at 373. Genentech was only able to over this rejection by amending the claims to require an intermediate wash step during ion exchange chromatography. *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 the preparation of rhuMAb 4D5-8 with less than about 25% acidic variants. *Id.* at 91. Further, the Examiner found that "[w]hile Andya et al 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 only overcame the Andya rejection by narrowing the percent of acidic variants in the composition to less about than 13%. *See id.* at 154–55, 164. The Challenged Claims contain no such limitation.

During prosecution of the '905 application, the Examiner rejected claims

based on Andya directed to a composition of humMAb4D5-8 with less than 25% acidic variants, wherein the acidic variants are predominantly deamidated variants and where the deamidated variants are deamidated at a specified residue—Asn30 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, 223–25; 228–29. In fact, the rejected claims of the '905 application contained every limitation of the issued claims of the '142 patent plus additional limitations not recited in the claims of the '142 patent. According to the Examiner, Figures 5–8 of Andya "show 81–82% native protein at the start of each stabilization experiment[,] [which] means there are 18–19% non-native variants; this range is clearly 'less than about 25%'…." *Id.* at 123. Genentech tried repeatedly, and unsuccessfully, to overcome the Examiner's rejections. Ultimately, Genentech abandoned its claims. *Id.* at 242.

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." *See 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 "A Composition" Is Not Limiting

The preamble of each claim, which recites "[a] 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, ¶27.[10] Accordingly, the preamble is not limiting and is irrelevant to distinguish the claims. *See IMS Tech.*, 206 F.3d at 1434.

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

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

include the carriers, excipients, and stabilizers identified in the specification. *See* Ex. 1001 at 19:41–61. This construction is supported by the patent specification, which states that "'[p]harmaceutically acceptable' carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed." *Id.*; Ex. 1003, ¶28.

Any attempt to argue, as Genentech has previously done, that "pharmaceutically acceptable carrier" 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 described in the specification into the claims of the '142 patent is improper, particularly under the BRI claim construction standard that applies to this Petition. *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.").

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 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. *See e.g.*, 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 1–3 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 composition comprising"

The preamble is not limiting. Section X.A. Nonetheless, Andya discloses a composition because it discloses an anti-HER2 antibody. Section XII.A.1(a)ii; Ex. 1003, ¶82.

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

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

[11] During prosecution of related applications to the '142 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.

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%. *Id.* at 6. 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 in nature. Ex. 1003, ¶85. Accordingly, Figures 5–8 disclose a mixture of both native protein and acidic variants thereof, *i.e.*, a "mixture of anti-HER2 antibody and one or more acidic variants thereof."[12] This

[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.

limitation is at a 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, ¶86. 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, ¶86.

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

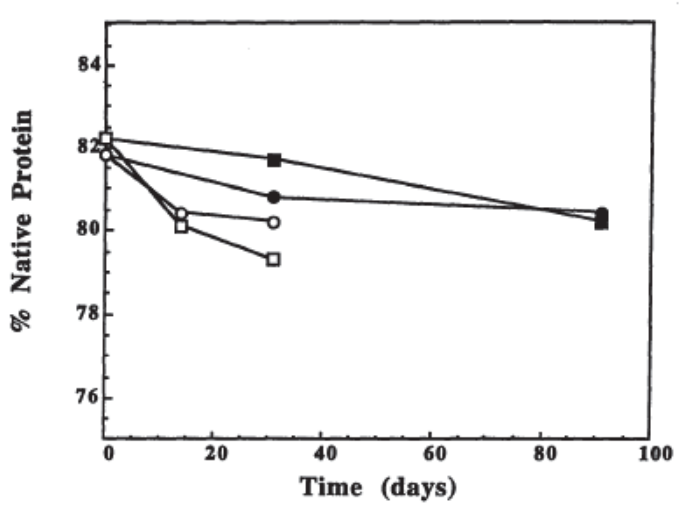


FIG. 5

Exs. 1004 at 39 (Fig. 5); 1003, ¶87. Andya teaches the 18–19% degraded protein depicted in Figure 5 is primarily the result of: (1) deamidation of Asn30 in the light chain; and (2) isomerization of Asp102 in the heavy chain (*i.e.*, formation of 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, ¶87. Accordingly, Andya teaches acidic variants (deamidated variants), comprise no more than 18–19% of the composition disclosed by Figure 5. 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, ¶¶75–79, 88; 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 a minimum obvious in light of these disclosures.

(b) Claim 2

Claim 2 recites the "composition of Claim 1 further comprising a pharmaceutically acceptable carrier." Claim 1 is anticipated by Andya. Section XII.A.1(a). Further, Andya discloses one "object" of the invention is "to provide a stable reconstituted protein formulation which is suitable for subcutaneous administration." 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 '142 patent. Ex. 1003, ¶90. 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 '142 patent. Exs.

[13] 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.

1001 at 19:41–61 ("'Pharmaceutically acceptable' carriers, excipients, or 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, ¶91.[14] This limitation is at minimum obvious in light of these disclosures.

(c) Claim 3

Claim 3 recites the "composition of Claim 1 wherein the anti-HER2 antibody is humMAb4D5-8." As set forth in Section XII.A.1(a) above, Claim 1 is anticipated by Andya. Moreover, and as discussed above in Section VII.C.3, Andya teaches the antibody described by Figures 5–8 in humMAb4D5-8. Ex. 1004 at 19:1–2 ("This example describes the development of a lyophilized formulation comprising full length humanized antibody huMAbD5-8….").[15] This

[14] 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.

[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,

(continued…)

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.

(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); T*akeda 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, ¶94. Andya discloses how to obtain, clone, and purify monoclonal antibodies such as humMAb4D5-8. *See id.*; Ex. 1004 at 12–15.

147–50, 161–62, 175–80, 223–27; 1009 at 91, 154–56; 1010 at 372–73, 380–81.

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, ¶94; *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 '142 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 19:62–65 ("***[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 '142 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 to Andya *et al*. ("'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, ¶96. 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, ¶96. A POSITA would have known how to lyophilize and reconstitute humMAb4D5-8 compositions based on these disclosures and their own knowledge. *See* Ex. 1003, ¶96; *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, ¶96.

Testing completed at Dr. Buick's direction and under his supervision, further confirms that Andya enables the Challenged Claims. HumMAb4D5-8

compositions described in Andya were prepared, purified, and characterized consistently with how a POSITA would have understood Andya as of May 6, 1998. *See* Exs. 1043, ¶¶10–19 (citing Exs. 1044–48); 1003, ¶97. 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. 1043, ¶19; 1003, ¶97; 1004 at 28. The results showed that the 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, ¶97.

2. Ground 2: Claim 1 is Invalid Under 35 U.S.C. § 102(b) as Anticipated by Waterside

(a) Claim 1

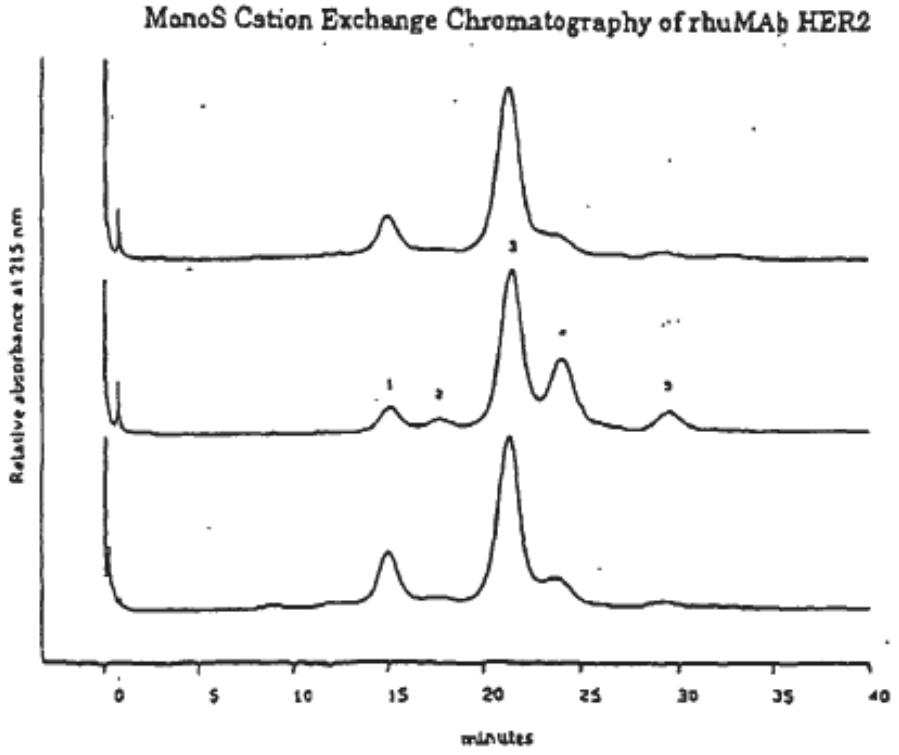
i. Preamble: "A composition comprising"

The preamble is not limiting. Section X.A. Waterside, nonetheless, discloses a composition because it discloses an anti-HER2 antibody. *See* Section XII.A.2(a)ii; Ex. 1003, ¶99.

ii. Element [a]: "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. Sections VII.A; VII.C.2. Waterside discloses chromatograms of "rhuMAb HER2" obtained during

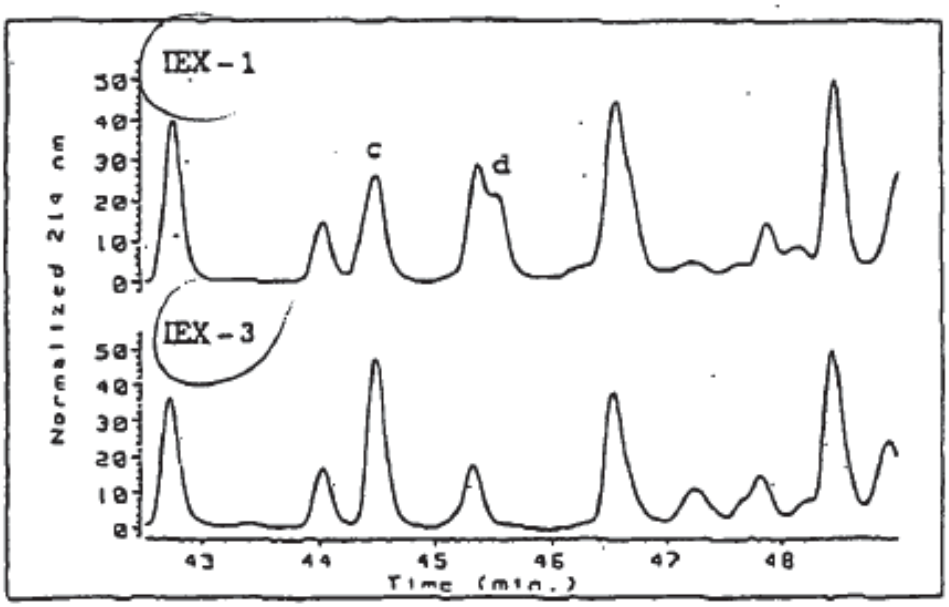
"MonoS Cation Exchange Chromatography":



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, ¶¶ 62–63, 101. 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*. 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, ¶¶70, 102–03; 1006 at 6. *See also* Section VII.C.2.

As Dr. Scandella explains, the above chromatogram discloses peaks 1 ("IEX-1") and 3 ("IEX-3") from page 4 contain "peak c" in varying amounts, and peak 1 contains an additional "peak d." *See* Ex. 1003, ¶¶70, 103. 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"[16] ("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"[17] ("Asp30") in "LC" (the light chain). Ex. 1003, ¶103. 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 a 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 VII.C.2 above, this limitation is expressly and inherently disclosed in Waterside. Waterside discloses the acidic variants in the rhuMAb HER2 compositions are contained within peaks 1 and 2 of the chromatograms shown on page 4. *See* Exs. 1006 at 4, 6; 1003, ¶104. Element [b]

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[16] Asparagine is abbreviated as Asn or N. Ex. 1003, ¶103 n2.

[17] Aspartate is abbreviated as Asp or D. Ex. 1003, ¶103 n3.

is expressly disclosed because based on visual 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, ¶¶64, 104; 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 are less than 25% of the total area. Ex. 1003, ¶¶64–68, 105; 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 '142 patent itself states about 25% is the amount obtained by "initial Protein A chromatography," a known method. Ex. 1001 at 23:5—8. 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, ¶106. 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.*; 42 U.S.C § 262 (1997).

(b) Waterside Enables the Challenged Claims

Waterside is a prior art printed publication asserted in this proceeding to establish anticipation, and therefore is presumed enabling. *See* Sections V, XII.A.1(d) (citing *In re Antor Media Corp.*, 689 F.3d at 1287; *Takeda Pharm.*, 2013 WL 12164680, at *16; *Lambda Optical Solns.*, 2015 WL 12806435, *4).

The disclosures in Waterside enable the Challenged Claims because a POSITA could have combined Waterside's disclosure with their own knowledge to make the claimed invention. Ex. 1003, ¶107. More specifically, a POSITA could have recreated the material shown in the page 4 chromatograms. *Id.* As explained by Dr. Scandella, given a sample of humMAb4D5-8, a POSITA could have used known chromatography methods to generate the same or substantially the same chromatograms. *See id.*

This was further confirmed by preparing, purifying, and characterizing the rhuMAb HER2 (*i.e.*, humMAb4D5-8) compositions described in Waterside in accordance with how a POSITA would have understood the disclosures of Waterside at the relevant time. *See* Exs. 1043, ¶¶27–29 (citing Exs. 1044–1048); 1003, ¶108. The prepared humMAb4D5-8 compositions were characterized and analyzed via cation-exchange chromatography on a Mono S™ column to separate the charged variants as described in Waterside. Exs. 1043, ¶¶27–29; 1003, ¶108;

Ex. 1006 at 4. The results showed that the compositions met the Challenged Claims, and this further confirms that a POSITA could have made rhuMAb HER2 compositions meeting the Challenged Claims based on Waterside's disclosures. Ex. 1003, ¶108.

3. Ground 3: Claims 2 and 3 are Invalid Under 35 U.S.C. § 103(a) as Obvious Over Waterside

(a) Claim 2

Claim 2 recites the "composition of Claim 1 further comprising a pharmaceutically acceptable carrier." As set forth in Section XII.A.1(a) above, Claim 1 is anticipated by Waterside. 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 a minimum would have been obvious to a POSITA to formulate the rhuMAb HER2 mixture disclosed therein with pharmaceutically acceptable carriers. Ex. 1003, ¶110. Numerous such carriers (including the specific examples disclosed in the '142 patent) and the methods for employing them were well known and predictable 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, ¶111. 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 as of April 1996, and had been produced at a 12,000 L scale indicating production for therapeutic use. Exs. 1006 at 3; 1003, ¶111; *see also* Section VII.C.2. That the '142 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. Ex. 1003, ¶111.

(b) Claim 3

Claim 3 recites the "composition of Claim 1 wherein the anti-HER2 antibody is humMAb4D5-8." Claim 1 is anticipated by Waterside. Section XII.A.1(a). 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: "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 as a "185 kDa membrane-spanning receptor," "$p185^{HER2}$" correlated to breast cancer. Exs. 1006 at 3–4; 1003, ¶112. 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, ¶¶31, 36, 112–13; *see also* Ex. 1035 at 6–8.

4. Ground 4: Claim 1 is Invalid Under 35 U.S.C. § 102(b) as Anticipated by Harris

(a) Claim 1

i. Preamble: "A composition comprising"

The preamble is not limiting. Section X.A. Harris, nonetheless, discloses a composition because it discloses an anti-HER2 antibody. *See* Section XII.A.2(a)ii.

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:

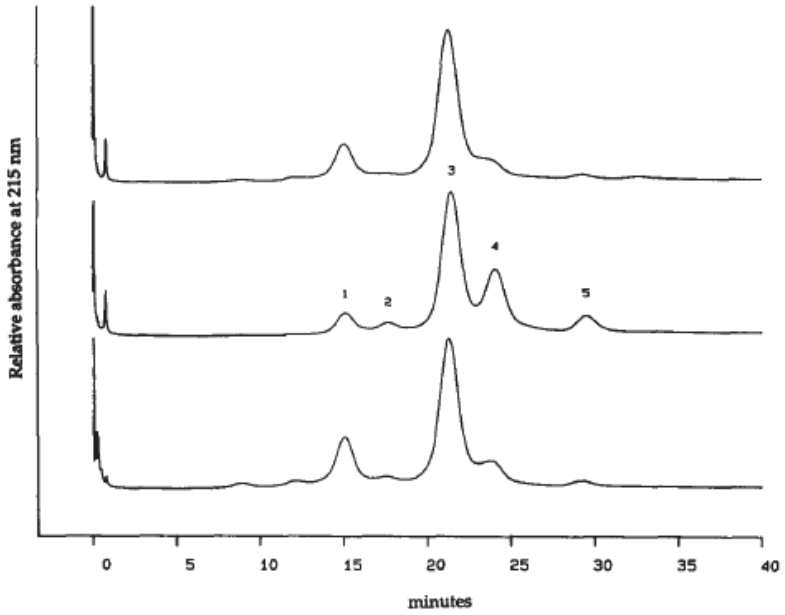

Fig. 2. Cation-exchange chromatography of three lots of rhuMAb HER2. Chromatographic conditions are given in Section 2.2.

Id.

As discussed above 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.B; Ex. 1003, ¶118. A POSITA would have understood, therefore, that peaks 1 and 2 represent acidic variants. *See* Exs. 1005 at 6; 1003, ¶118. A POSITA would also have understood the "main peak" (peak 3) represents native rhuMAb HER2. *See* Exs. 1005 at 6; 1003, ¶118. Finally, a POSITA would have known peaks 4 and 5 represent basic variants. *See* Exs. 1005 at 6; 1003, ¶118. For these reasons, Harris teaches a mixture of rhuMAb HER2, an

anti-HER2 antibody (peak 3), and acidic variants thereof (peaks 1 and 2). *See also* Section VII.C.1. This limitation is at a 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 composition 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, ¶¶53, 119. 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* Section 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, ¶¶54–57, 120; 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. The '142 patent itself states about 25% is the amount obtained by "initial Protein A

chromatography," a known method. Ex. 1001 at 23:5–8. 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.*; 42 U.S.C § 262 (1997).

(b) Harris Enables the Challenged Claims

Like Andya and Waterside, Harris is a prior art printed publication asserted in this proceeding to establish anticipation, and therefore is presumed enabling. *See* Sections V, XII.A.1(d) (citing *In re Antor Media Corp.*, 689 F.3d at 1287; *Takeda Pharm.*, 2013 WL 12164680, at *16; *Lambda Optical Solns.*, 2015 WL 12806435, *4).

The disclosures in Harris enable the Challenged Claims because a POSITA could have combined Harris's disclosure with their own knowledge to make the claimed invention. Ex. 1003, ¶122. More specifically, a POSITA could have recreated the material shown in the Figure 2 chromatograms. *Id.* Given a sample of humMAb4D5-8, a POSITA could have followed the experimental conditions disclosed in Harris to generate the same or substantially the same chromatogram.

See id.

Like for Andya and Waterside, the rhuMAb HER2 (*i.e.*, humMAb4D5-8) compositions described in Harris were prepared, purified, and characterized in accordance with how a POSITA would have understood the disclosures of Harris as of May 6, 1998. *See* Ex. 1043, ¶¶27–29 (citing Exs. 1044–48); *see also* 1003, ¶123. The prepared humMAb4D5-8 compositions were characterized and analyzed via cation-exchange chromatography on a Mono S™ column as described in Harris. Exs. 1043, ¶¶27–29; 1003, ¶123; Ex. 1005 at 5. The results showed that the compositions met the Challenged Claims, and therefore further confirms that Harris is enabling. Ex. 1003, ¶123.

5. Ground 5: Claims 2 and 3 Are Invalid Under 35 U.S.C. § 103(a) as Obvious in View of Harris

(a) Claim 2

Claim 2 recites the "composition of Claim 1 further comprising a pharmaceutically acceptable carrier." As set forth in Section XII.A.4 above, Claim 1 is anticipated by Harris. To the extent the additional subject matter of Claim 2 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, ¶128. Again, numerous such carriers (including the specific examples disclosed in the '142 patent) and the

methods for employing them were well known and predictable as of May 6, 1998. *Id*.; Section XII.A.3(a).

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, ¶126. As discussed above, a POSITA would have understood rhuMAb HER2 was already in production. *Id*; *see also* Section VII.C.1.

(b) Claim 3

Claim 3 recites the "composition of claim 1 wherein the anti-HER2 antibody is humMAb4D5-8." As set forth in Section XII.A.4(a) above, Claim 1 is anticipated by Harris. To the extent Harris does not expressly disclose the additional subject matter of Claim 3, it would have been obvious to a POSITA that the rhuMAb HER2 of Harris was humMAb4D5-8. *See* Ex. 1003, ¶127. 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 that rhuMAb HER2 was already in production. *See* Ex. 1003, ¶127. 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, ¶128. 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, ¶¶36, 123.

B. Lack of Secondary Considerations

Petitioner is not aware of any secondary considerations that would support a finding of non-obviousness. Further, 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.

* * *

Date: August 29, 2017

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 12,168 words. Counsel has relied upon the word count feature provided by Microsoft Word.

/Amanda Hollis/
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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. 6,339,142, 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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