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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-02020
Patent 9,249,218

PATENT OWNER'S RESPONSE

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I. INTRODUCTION

U.S. Patent No. 9,249,218 ("the '218 patent") claims a groundbreaking drug composition that treats HER2-positive breast cancer—a particularly virulent form of the disease. By minimizing the amount of certain kinds of products formed by the degradation of anti-HER2 antibodies (so-called "acidic variants"), the '218 invention provides for a drug composition with improved purity and effectiveness.

Nothing like the invention claimed in the '218 patent was taught in the prior art. Genentech's scientists—including the chemical engineers who pioneered the creation of anti-HER2 antibodies—developed a novel "reverse wash" purification method that reduced acidic variants while leaving the native protein intact.

Pfizer now attempts to rewrite history by suggesting that the '218 invention was disclosed years earlier, and that a person of ordinary skill in the art ("POSA") could have used prior art methods to reduce acidic variants and obtain a purified drug composition as claimed. But Pfizer's three asserted prior art references—Andya, Waterside, and Harris—are not even directed to the same problem. Rather, they address ways of formulating and characterizing an ***already-existing*** anti-HER2 antibody composition. But that crucial first step—creating the purified drug composition itself—was not taught until the '218 invention.

In its institution decision, the Board found a reasonable likelihood that the challenged claims were anticipated by Andya and obvious over Harris. The full

record now refutes those initial conclusions, as well as the additional, originally-denied grounds—obviousness over Andya and obviousness over Waterside—that the Board instituted only in light of *SAS Institute Inc. v. Iancu*, 138 S. Ct. 1348 (2018).

First, each prior art reference fails to disclose a composition containing "one or more acidic variants … wherein the amount of acidic variant(s) is less than about 25%" as required by all challenged claims. Though Pfizer attempts to recast these failings as instances of "inherent" disclosure, Pfizer does not—and cannot—meet the legal standard for establishing inherency. In each case, the undisputed facts—including concessions made by Pfizer's own declarants in their depositions—demonstrate that the prior art's teachings do not "necessarily" and "inevitably" result in the claimed invention, as required for inherent disclosure.

Second, Pfizer's fallback argument—that the claim limitations missing from the prior art would have been obvious—is equally deficient. Pfizer identifies no evidence that a POSA would have been motivated to modify these references to create the '218 invention, let alone any evidence that such efforts would have had a reasonable expectation of success. To the contrary, Pfizer's obviousness "arguments" are generally a single, conclusory sentence appended to a separate anticipation argument, and thus are insufficient as a matter of law.

Finally, Pfizer's challenges fail for the additional reason that none of the prior art references is enabling. Indeed, Pfizer's own expert attempted to make the claimed composition based on the prior art teachings, yet he could not do so. Instead, he and the three separate protein engineering firms that he enlisted in his efforts all were forced to rely on outside teachings and technology developed after the '218 priority date—including Genentech's commercial embodiment of its FDA-approved anti-HER2 drug composition, Herceptin®. Pfizer's inability to obtain the claimed composition using the actual teachings of the prior art confirms that the prior art is not enabling.

The Board should confirm the patentability of the challenged claims.

II. TECHNOLOGY BACKGROUND

A. HER2-Positive Breast Cancer

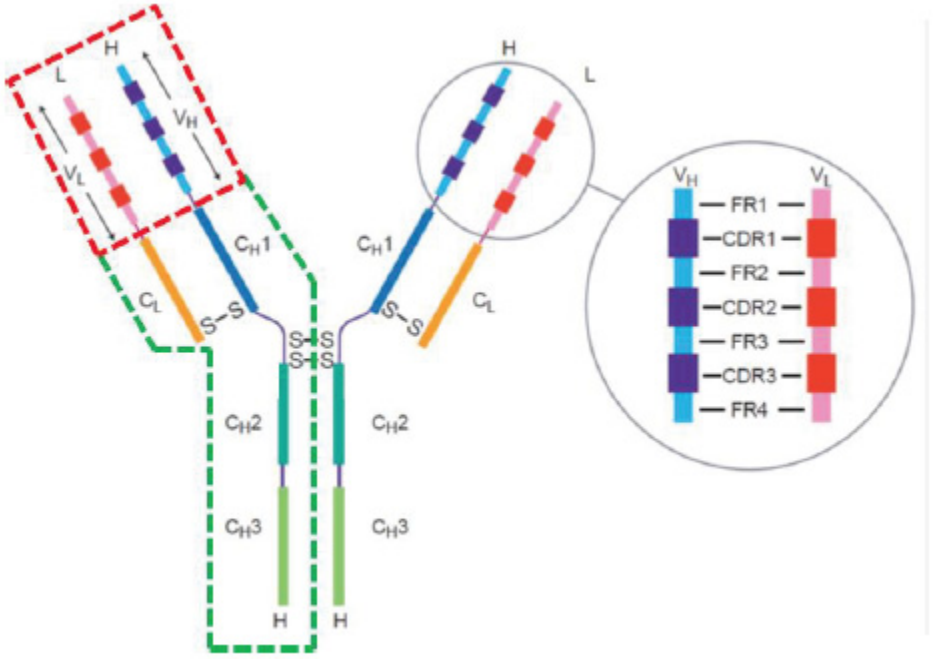
Cancer is a disease involving an abnormal growth of cells (*i.e.*, a tumor) that divides uncontrollably and invades the surrounding tissue. One particularly aggressive form of cancer is known as HER2-positive breast cancer, which is characterized by the overexpression of human epidermal growth factor receptor 2 (*i.e.*, "HER2") proteins due to excessive HER2 gene amplification. (Ex-1013, 9; Ex-2037, ¶59.)

In the early 1990s, a diagnosis of HER2-positive breast cancer was effectively a death sentence: patients had an average life expectancy of only 18

months. (Ex-2001, 138.) The quality of life for those patients was markedly poor—the disease rapidly metastasized (*i.e.*, spread to other parts of the body). (Ex-2002, 887.) The only available treatments were invasive and disfiguring surgery and chemotherapeutic drugs with harsh side effects, and those treatments added little to the patient's life span. (*See id*.)

B. Anti-HER2 Antibodies

Antibodies are proteins used by the immune system to target and neutralize pathogens by binding to a molecular target ("antigen") within the pathogen. (Ex-1001, 6:34-7:2; Ex-2037, ¶¶23-36; Ex-2036, ¶¶10-12.) "Monoclonal" antibodies are directed against a single antigenic site. (Ex-1001, 7:8-9.) As shown below, antibodies are typically Y-shaped, with two heavy chains ("H") and two light chains ("L"):



(Ex-2003, 10 (annotated).)

The heavy chains and light chains each have "variable domains" (respectively, "V_H" and "V_L"), which are the portions of the antibody that bind to the antigen. (*Id.*, 9.) Each variable domain has three "Complementarity Determining Regions" ("CDRs") that contain unique amino acids (or "residues") to target a particular antigen. (*Id.*, 10.)

Beginning in the late 1980s, Genentech scientists humanized a mouse monoclonal antibody designed to recognize and bind to the HER2 receptor. (Ex-1030, 10.) This antibody is referred to as humMAb4D5-8 or trastuzumab. By binding to HER2 receptors, humMAb4D5-8 inhibits the effects of HER2 overexpression. (*Id.*; Ex-2037, ¶59; Ex-2036, ¶¶13-15.)

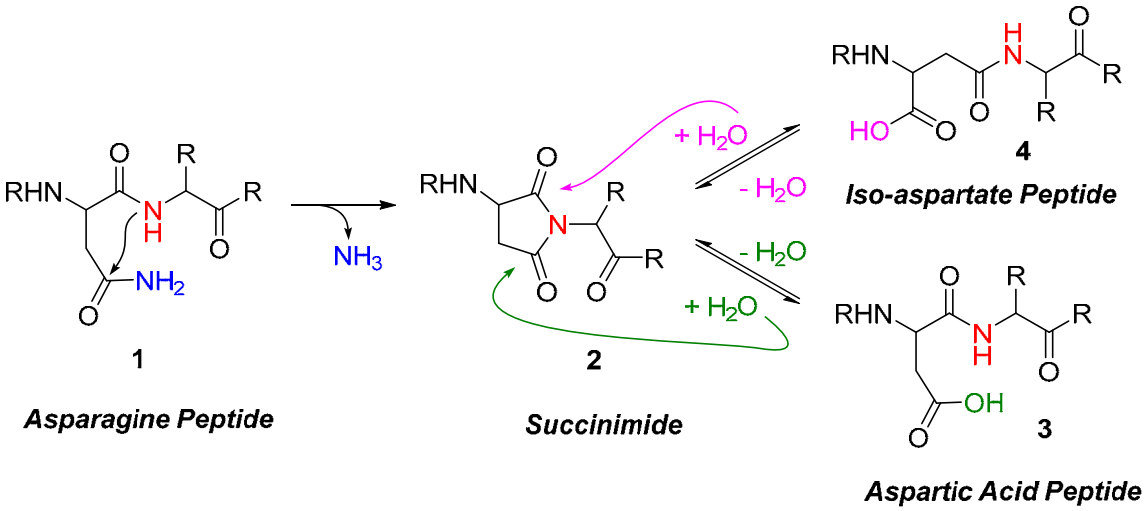
C. Protein Degradation And Acidic Variants

Antibodies intended for pharmaceutical use, such as humMAb4D5-8, are generally produced by inserting a gene sequence coding for the desired protein into a chosen cell line (often a mammalian or bacterial cell line). (Ex-1001, 1:31-34, 20:39-43; Ex-2037, ¶¶28-37; Ex-2036, ¶¶16-19.) The cell line is maintained and grown in a medium that contains sugars, amino acids, and other components that lead the cell line to produce the desired protein. (Ex-1001, 1:34-38; Ex-2037, ¶¶28-37; Ex-2036, ¶¶16-19.)

Like all proteins, antibodies are subject to degradation based on their structure and the surrounding environment. One type of chemical degradation that can occur is a reaction at the amino-acid level that changes the charge of the antibody molecules and results in "variants" of the native, original protein. (Ex-1017, 5-6; Ex-2037, ¶¶31, 36-48; Ex-2036, ¶¶20-22; Ex-2042; Ex-2044, 1108.) Variants that are more acidic than the original protein are referred to as "acidic variants," and variants that are less acidic are referred to as "basic variants," and variants with the same level of acidity are referred to as "neutral variants." (Ex-1001, 5:60-63; Ex-1017, 5-15; Ex-2037, ¶39; *see also* Petition, 13-14.)

"Deamidation" refers to the removal of an amide to form either a free carboxylic acid or a cyclic structure. In the exemplary figure below, asparagine (1) can form a cyclic structure known as a succinimide (2), which can open to form

either aspartic acid (3) or iso-aspartate (4). Thus, deamidation at an asparagine residue (1) can result in aspartic acid (3), iso-aspartate (4), and/or succinimide (2). By analogy, deamidation at glutamine (as opposed to asparagine) can proceed to form glutamic acid, iso-glutamate, and/or glutarimide.



(Ex-2037, ¶¶40-41; *see also* Ex-1017, 6). In the case of asparagine deamidation, the resulting aspartic acid and iso-aspartate peptides are acidic variants, whereas the succinimide is a neutral variant because the overall charge relative to the native protein is unchanged. (Ex-2037, ¶42.) Similarly, deamidation of glutamine can form acidic variants (glutamic acid or iso-glutamate) or a neutral variant (glutaramide). (*Id.*)

Deamidation, however, is only one of many processes by which proteins degrade. Isomerization of aspartate is another mechanism of protein degradation. In this reaction, aspartate is converted to iso-aspartate via a succinimide. (Ex-

1017, 6-7; (Ex-2037, ¶43.) In this process, iso-aspartate is a neutral variant due to the unchanged overall charge, whereas the succinimide is a basic variant because the acid group in the aspartate is lost. (Ex-1017, 6-7; Ex-1004, 21, 28; Ex-2037, ¶43.)

The form and manner of chemical degradation for a given protein composition is highly dependent on the structure and environment surrounding the protein. (Ex-2037, ¶¶44-58; Ex-2036, ¶¶23-39.) As a result, expression and manufacturing conditions, such as the choice of cells, cell culture components, and cell culture and purification conditions (*e.g.*, temperature, pH level), can have a significant impact on chemical degradation. (Ex-2037, ¶¶44-58; Ex-2036, ¶¶23-39.) Therefore, two compositions containing the same antibody will not necessarily contain the same type or amount of variants. (Ex-2037, ¶¶44-58; Ex-2036, ¶¶23-39; Ex-2004, 700-704; Ex-2005, 121-124.)

The pharmacological properties of variants are not predictable, and can impact factors such as stability, efficacy, and safety. (Ex-1017, 6-15; Ex-2037, ¶¶48.) However, because antibody variants are structurally similar to the original antibody protein, it is difficult to separate out antibody variants from a composition containing the original antibody protein. (Ex-1034, 5-6; Ex-1001, 1:38-41, 2:45-49; Ex-2037, ¶¶48.)

III. THE '218 PATENT

The '218 invention is the culmination of work by Genentech scientists to create a purified, stable, and effective anti-HER2 antibody. Genentech pioneered this field decades ago and was awarded numerous patents for its achievements. (*E.g.*, Ex-1019; Ex-1043.) And in the course of developing a commercial product—ultimately approved by the FDA and sold under the trade name Herceptin®—Genentech scientists Greg Blank and Carol Basey successfully developed a novel purification method. This method allowed them to achieve compositions as claimed in the '218 patent. (Ex-2035, ¶¶5-11.)

More specifically, this method—referred to as "reverse wash" purification—reduced the amount of acidic variants and produced an anti-HER2 antibody composition that consistently met quality control standards. (Ex-1001, 2:27-49; Ex-2035, ¶¶5-11; Ex-2037, ¶¶59-63.) As the name implies, "reverse wash" purification involves a step that, contrary to standard purification practices, reverses one or more attributes of buffer (for example, conductivity, pH, or both) during the purification process. (Ex-1001, 2:32-39.) As a result, Dr. Blank and Ms. Basey were able to achieve and identify anti-HER2 antibody compositions containing less than 25% acidic variants, and wherein the acidic variants are predominantly deamidated variants of specific amino acids in the protein sequence (*i.e.*, deamidated at asparagine-30). (*Id.*, 3:49-55; Ex-2035, ¶¶5-11; Ex-2037,

¶¶59-63.) Controlling the variant profile is especially important when developing therapeutic antibodies for production because it achieves a consistent composition with consistently high rate of recovery of the desired antibody across batches, ensuring that the resulting cancer treatment drug is consistently pure and effective. (Ex-1001, 2:45-49; Ex-2037, ¶¶30-35, 48-49,59-63.)

IV. PRIOR ART

A. Andya

Andya (Ex-1004) is an International PCT Application (WO 97/04801) published on February 13, 1997 and assigned to Genentech. It was considered during prosecution of the '218 patent and is incorporated by reference into the specification. (Ex-1001, 19:54-57; Ex-1002, 121.)

Andya is directed to antibody formulations. (Ex-1004, 3.) In Example 1, Andya investigates lyophilized formulations of anti-HER2 antibodies with succinate or histidine buffer and surfactant, with or without various sugars. (*Id.*, 21.) Andya indicates that the anti-HER2 antibody formulations were lyophilized and reconstituted in an aqueous solution, and that the "loss of native protein due to deamidation or succinimide formation was assessed." (*Id.*, 28.) Andya presents the results of this assessment in Figures 5-8, which show that the reconstituted formulations initially contained 78-82% "native (not degraded) protein." (*Id.*, 6, 39-40.) Andya does not disclose the particular contents of the remaining 18-22%

non-native protein or indicate whether it contained any acidic variants (let alone any particular acidic variants)—Andya simply states the amount of native protein as a percentage of the composition as a whole. (*Id.*, 6; *see also id.*, 28, 39-40; Ex-2037, ¶¶64-70.)

Andya also describes "early screening studies" in which a different anti-HER2 antibody composition was tested. (Ex-1004, 21, 25-26; Ex-2037, ¶67.) Andya states that when the screening-study composition degraded, it produced at least one acidic variant (deamidated at asparagine). (*Id.*, 21 (explaining that the screening-study composition "was observed to degrade by deamidation (30Asn of light chain)").)

Andya does not describe how to create the pre-formulation antibody composition used for Example 1, nor does it describe how to create the composition used for the early screening studies. (*See* Ex-1004, 20-29; Ex-2037, ¶¶67-72; Ex-2036, ¶¶43-48, 57.) Andya also does not indicate (contrary to Pfizer's suggestion (Petition, 23-24, 39)) that the two compositions are the same or otherwise degrade in the same manner. (*See* Ex-1004, 20-29; Ex-2037, ¶¶67-72.)

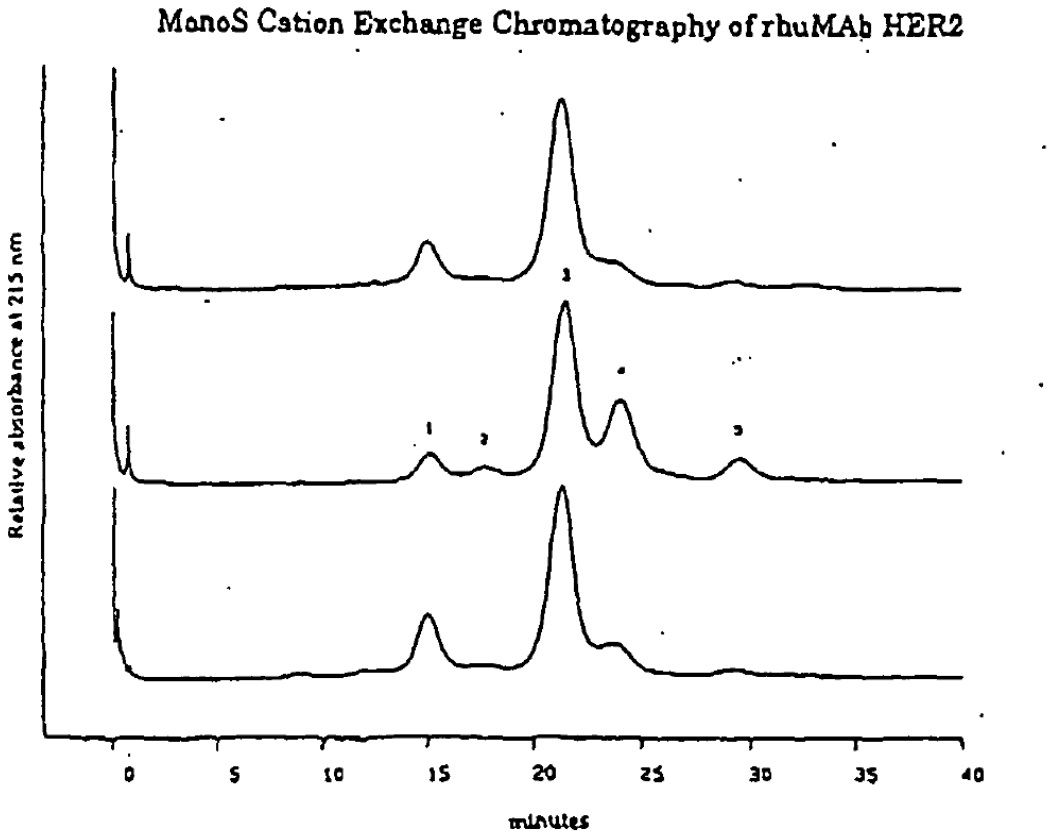
Genentech's internal, unpublished documents demonstrate that Andya's Example 1 starting composition (*i.e.*, pre-formulation) was a humMAb4D5-8 antibody composition made using the "reverse wash" method taught in the '218 patent. (Ex-2034, ¶¶4-9; Ex-2035, ¶¶12-37; Exs-2018-2027.) The reverse wash

method was not publicly known at the time, and Andya itself provides no indication that the Example 1 starting composition had been prepared using that method. (Ex-1004, 12-18; Ex-2037, ¶¶66, 71-74; Ex-2035, ¶¶12-13.)

B. Waterside

Waterside (Ex-1006) is a series of slides by Genentech analytical chemist Reed Harris titled "Chromatographic Techniques for the Characterization of Human Monoclonal Antibodies: rhuMAb HER2." (*Id.*, 3.) It purports to correspond to a presentation delivered by Mr. Harris at the Waterside Monoclonal Conference on April 22, 1996. (*Id*., 2.) It was considered during the prosecution of the '218 patent. (Ex-1002, 122.)

Waterside is directed to the characterization of antibodies referred to as "rhuMAb HER2." (Ex-1006, 3; Ex-2037, ¶¶74-79.) It depicts the use of analytical "Mono-S" cation exchange chromatography to characterize several rhuMAb HER2 compositions. (Ex-1006, 4.) Waterside shows that such compositions may contain both acidic and basic variants, and teaches it was "[d]ecided not to remove the deamidated material [*i.e.*, acidic variants]." (*Id*., 5-7) Waterside does not quantify the amount or relative percentage of each type of protein within the compositions. (*Id.*; Ex-2037, ¶¶79-81.) For example, Waterside presents the following analytical chromatograms:



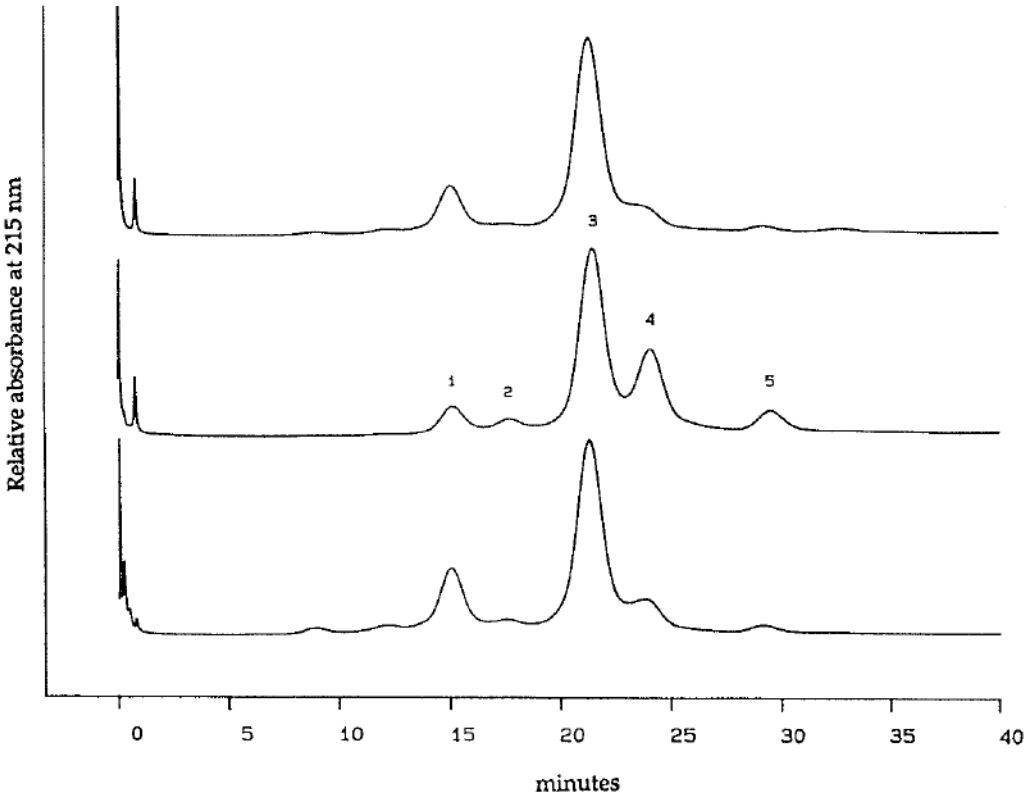
(*Id.*, 4.) The central peak in each trace appears to represent native protein, with the area to the left representing acidic variants and the area to the right representing basic variants. But as seen above, there are no demarcations along the y-axis to indicate a reference baseline (*i.e.*, a "zero point"), and no demarcations along the x-axis to indicate the points at which the line transitions from representing one type of protein to another. (Ex-2037, ¶79.)

Waterside also does not disclose how to make the rhuMAb HER2 compositions being tested. (*See* Ex-1006, 3-7; Ex-2037, ¶77; Ex-2036, ¶¶51-53, 59.)

C. Harris

Harris (Ex-1005) is an article by Genentech analytical chemist Reed Harris titled "Processing of C-terminal Lysine and Arginine Residues of Proteins Isolated from Mammalian Cell Culture," which was published in the Journal of Chromatography A in 1995. Harris was considered during prosecution of the '218 patent. (Ex-1002, 122.)

Harris describes the use of analytical Mono-S cation exchange chromatography to characterize several rhuMAb HER2 compositions. (Ex-1005, 4-5; Ex-2037, ¶¶82-86.) Harris includes chromatograms indicating that the rhuMAb HER2 compositions may contain acidic and basic variants:



(Ex-1005, 7.) Harris does not quantify the amount of native proteins or variants, nor does it provide x-axis and y-axis coordinates to indicate the height and width of the portions of the curve representing different types of proteins. (Ex-2037, ¶85.)

Harris also does not disclose how to make the rhuMAb HER2 compositions being tested. (*See* Ex-1005, 4-9; Ex-2037, ¶83; Ex-2036, ¶¶49-50, 58.)

V. PERSON OF ORDINARY SKILL

The Board decided in its institution decision that a POSA has 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, and further that a POSA has knowledge of and experience regarding protein analysis and protein chemistry, including protein preparation and purification, and formulation of therapeutic proteins for human use. (Paper 16, 8.) For purposes of this proceeding, Genentech will apply the definition adopted by the Board.

VI. CLAIM CONSTRUCTION

A. "Therapeutic Composition"

In its institution decision, the Board adopted Pfizer's argument that the preamble is not limiting and declined to construe the term "therapeutic

composition." (Paper 16, 7.)[1] Respectfully, the Board's interpretation is not consistent with the claims and the specification as understood by a POSA. A POSA would understand the term "therapeutic composition" to be limiting, and in particular to require "a composition containing a therapeutically effective amount of a polypeptide." (Ex-2037, ¶17.)[2]

As Dr. Carbonell explains, this construction reflects the term's plain meaning: to be "therapeutic," a composition must contain a therapeutically effective amount, *i.e.*, a sufficient amount of the relevant antibody to have

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[1] Notably, in Pfizer's follow-on petition challenging the same claims of the '218 patent, Pfizer ***concedes that the preamble is limiting***, and argues that the term should be construed to mean "a composition appropriate for administration in a therapeutic treatment regimen." IPR2018-00331, Petition at 15.

[2] This is the proper construction under both the "broadest reasonable interpretation" ("BRI") standard, which currently applies, as well as the *Phillips* standard applied by district courts. (Ex-2037, ¶16.) The PTO recently issued a Notice of Proposed Rulemaking that proposes replacing the BRI standard with the *Phillips* standard. 83 Fed. Reg. 21,221-21,226 (May 9, 2018). Genentech reserves all rights with respect to any subsequent changes made to the Board's claim construction standard.

medicinal or healing properties. (*Id.*; *see also, e.g.*, Ex-2015 (Taber's Cyclopedic Medical Dictionary), 1934 (defining "therapeutic" as "[h]aving medicinal or healing properties").)

This construction is further compelled by the language of the claims as a whole. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (explaining that a claim preamble must be "read in the context of the entire claim" and "has the import that the claim as a whole suggests for it" (internal quotation marks omitted)). In addition to requiring a "therapeutic composition," all of the challenged claims require a "pharmaceutically acceptable carrier." As Dr. Carbonell explains, this limitation confirms that the claims are directed to a composition that has a therapeutically effective amount of the purified protein—there would be no reason to include a pharmaceutically acceptable carrier unless there were also a therapeutically effective amount of the protein to make up a therapeutic composition. (Ex-2037, ¶17.)

This construction is also fully supported by the specification, which explains that "[t]he polypeptide purified as disclosed herein … is then used for various diagnostic, ***therapeutic*** or other uses …. For example, the polypeptide may be used to treat a disorder in a mammal by administering ***therapeutically effective amount*** of the polypeptide to the mammal." (Ex-1001, 20:25-31; *see also id.*,

6:41-44 ("[A]dministration of the antibody to a mammal suffering from a disease or disorder can result in a ***therapeutic*** benefit in that mammal.").)[3]

A POSA would not, as Pfizer argues (Petition, 32-34), understand the preamble to be non-limiting such that the word "therapeutic" would be read out of the claims entirely. (Ex-2037, ¶17.)[4] The specification explains that one purpose of the invention is to overcome the "formidable challenge" of separating "the desired protein from the mixture of compounds fed to the cells and from the by-products of the cells themselves to a purity sufficient for use as a human ***therapeutic***." (Ex-1001, 1:38-41.) The use of the word "therapeutic" demonstrates that the claims are directed specifically to such an embodiment. (Ex-2037, ¶17.)

The "therapeutic composition" preamble thus "breathes life and meaning into the claims and, hence, is a necessary limitation to them." *In re Paulsen*, 30

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[3] Except as otherwise noted, each emphasis in this brief is added.

[4] Pfizer also argues, in the alternative, that the preamble should be construed to mean "an anti-HER2 antibody with the claimed degree of purity," but Pfizer concedes that this construction is indistinguishable from reading out the term entirely because the claims "already require an anti-HER2 antibody having a specified amount of acidic variants." (Petition, 34.)

F.3d 1475, 1479 (Fed. Cir. 1994) (internal quotation marks omitted); *see also Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 952 (Fed. Cir. 2006) ("[I]f the claim drafter chooses to use ***both*** the preamble and the body to define the subject matter of the claimed invention, the invention so defined, and not some other, is the one the patent protects." (emphasis in original, internal quotation marks omitted)).

Indeed, the Federal Circuit and various district courts have found similar preambles to be limiting. *E.g.*, *Manning v. Paradis*, 298 F.3d 1098, 1103 (Fed. Cir. 2002) ("[T]he preamble ['treating a subject in cardiac arrest'] defines the intended purpose of the invention because unless oxygen were delivered to the heart of the subject in a ***therapeutic amount*** the invention would have no purpose," therefore the preamble "must be construed to require the delivery of an amount of oxygen ***sufficient to have a therapeutic effect***."); *UCB, Inc. v. Accord Healthcare*, 2015 WL 2345492, *4 (D. Del. May 14, 2015) (construing preamble "***therapeutic composition***" as limiting); *Spectrum Pharms., Inc. v. Sandoz Inc.*, 2013 WL 6865692, *15 (D. Nev. Sept. 30, 2013) (construing preamble "pharmaceutical composition for ***therapeutic*** use" as limiting).[5]

[5] Construing the preamble as limiting is not outcome-determinative but provides an additional reason why the challenged claims are patentable over the prior art.

VII. ARGUMENT

A. Andya Does Not Anticipate Or Render Obvious The Challenged Claims.

1. Andya Does Not Disclose "One Or More Acidic Variants."

Andya fails to teach a composition with "one or more acidic variants" as required by all challenged claims. Pfizer asserts that the challenged claims are anticipated by particular antibody compositions described in Andya: the "Example 1" formulations (also referred to as the "reconstituted formulations") that are analyzed in Figures 5-8. (Petition, 38-39.) Yet as Pfizer concedes, Andya does not describe the complete contents of the protein in the Example 1 formulations but merely indicates that formulations contain 78-82% "native (not degraded) protein," with no disclosure of the contents of the remaining 18-22%. (Ex-1004, 6, 39-40 (Figs. 5-8); Petition, 39.) However, Pfizer asserts that the non-native contents of the Example 1 formulations—and specifically, the presence of "one or more acidic variants"—can be inferred from Andya's description of a ***different*** composition: the "screening study" composition. (Petition, 39.) In other words, based on the speculation that the Example 1 formulations degrade in the same manner as the screening-study composition, Pfizer contends that the Example 1 formulations ***inherently*** contains one or more acidic variants. Pfizer's argument is legally and factually erroneous.

Andya's Example 1 describes studying the stability of particular lyophilized and reconstituted formulations, *i.e.*, the Example 1 formulations. (Ex-1004, 3, 20.) In preparation for that analysis, however, the Andya inventors reference "early screening studies." (Ex-1004, 21.) Andya states that, as part of these studies, a liquid state anti-HER2 antibody composition "was observed to degrade by deamidation (30Asn of light chain) and isoaspartate formation via a cyclic imide intermediate, succinimide (102Asp of heavy chain)." (*Id.*) Thus, this screening-study composition included at least one acidic variant, *i.e.*, deamidated at asparagine. (Ex-2037, ¶87.)

Andya makes no such disclosure regarding the Example 1 formulations. (Ex-2037, ¶¶88-93.) Since the purpose of Example 1 is to demonstrate the stability of the formulations, the relevant issue is the ***amount*** of native protein as compared to non-native protein—hence the repeated disclosures regarding the percentage of native protein present. (Ex-1004, 6, 39-40.) But the precise form of the non-native protein (*e.g.*, acidic, basic, neutral) is irrelevant and thus not discussed. (Ex-2037, ¶¶91-93.) Instead, Andya merely states that "the major degradation route for rhuMAb HER2 in aqueous solutions is deamidation or succinimide formation" and therefore in the Example 1 formulations (which are aqueous solutions) the "loss of native protein due to deamidation or succinimide formation was assessed." (Ex-1004, 28.) In other words, Andya notes potential degradation paths (deamidation,

succinimide formation) but does not indicate which particular type of degradation actually occurred in the Example 1 composition—or if the type of degradation was even observed. (Ex-2037, ¶¶91-93.) And, as Pfizer's declarant Dr. Scandella concedes, one of those potential degradation paths—succinimide formation—results in only basic variants. (Ex-2038, 93:11-15; Ex-2037, ¶93; Ex-1017, 6-7.) Thus, Andya does not indicate whether the Example 1 composition contains any acidic variants.

Nor is it possible to infer the non-native contents of the Example 1 composition from the screening study. There is no dispute that Andya fails to disclose the contents of the screening-study composition—let alone indicate that the screening-study composition and Example 1 composition are the same. Dr. Scandella agreed, testifying that "I don't see that Andya discloses the composition of the liquid state in their early screening studies," and "I'm not sure what they used in the early screening studies." (Ex-2038, 94:8-13; 96:21-97:8); *see also* Ex-2037, ¶¶88-89.) In fact, Andya ***contrasts*** the screening-study composition with the separate compositions studied in Example 1. (Ex-2037, ¶¶88-89.) Andya explains that in light of the screening studies, the Example 1 "lyophilized formulations" were studied under ***different*** conditions, including varying buffers, pH, surfactant, and the presence or absence of various sugars. (Ex-1004, 21 ("The lyophilized formulations were therefore studied with: (a) 5 or 10 mM succinate buffer, pH 5.0

or (b) 5 or 10 mM histidine buffer, pH 6.0. … Both buffers contained the surfactant, polysorbate 20 … These buffers were used with and without various sugars."); Ex-2037, ¶¶88-89.)

As Dr. Carbonell explains, it is well-established that lyophilizing and reconstituting an antibody may change the manner in which the protein degrades. (Ex-2037, ¶90; *see also, e.g.*, Ex-2013, 427, 430-432.) And it is equally well-established that the degradation of an antibody in an aqueous solution is dependent on the excipients and conditions of the solution. (Ex-2037, ¶90; Ex-1034, 6, 8-9, 15.) Indeed, Pfizer's declarant Dr. Scandella concedes that degradation—including deamidation of huMAb4D5-8—depends on the conditions to which the antibody is exposed, including buffer composition, buffer concentration, pH, temperature, storage conditions, and whether the protein is or has been lyophilized, as well as the formulation, including whether stabilizers are added. (Ex-2038, 62:9-65:2, 67:5-68:11.)

These concessions are fatal to Pfizer's theory of inherent anticipation because—as Dr. Scandella further concedes—Andya does not disclose that the Example 1 formulations and the screening study composition share all these relevant attributes. (*Id.*, 94:8-13; Ex-2037, ¶89.) Therefore, there is no basis to conclude that the Example 1 formulations would degrade in the same manner as the screening-study composition and that therefore one or more acidic variants are

necessarily present. (Ex-2037, ¶¶89-93.)[6] Pfizer's inherent anticipation theory thus fails as a matter of law. *Trintec Indus. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002) ("Inherent anticipation requires that the missing descriptive

[6] In its institution decision, the Board stated that it inferred deamidation occurred in the Example 1 formulations because the Example 1 experiments were conducted at the same pH levels (5.0 and 6.0) as some of the early screening studies where deamidation occurred. (Paper 16, 20.) However, the mere fact that the different compositions were in solutions with the same pH level is insufficient to demonstrate that they ***necessarily*** degraded in the same manner in view of the various other components that were present and variables that were being tested in the Andya formulations. (Ex-2037, ¶¶90-93.)

material is 'necessarily present,' not merely probably or possibly present, in the prior art.").[7]

2. Andya Does Not Disclose A Composition Containing The Particular "Deamidated Variants" Required By The Challenged Claims.

Andya fails to teach a composition with the particular acidic variants required by each challenged claim, *i.e.*, acidic variants that are "predominantly deamidated variants wherein one or more asparagine residues of the anti-HER2 antibody have been deamidated" and "wherein the deamidated variants have Asn30 … converted to aspartate." As discussed above, Andya does not disclose whether the Example 1 formulations contains ***any*** acidic variants. But even if one were to conclude (incorrectly) that Andya discloses that the Example 1 formulations contain at least one acidic variant, the formulations do not necessarily

[7] The EPO Board of Appeal considered the identical issue and held that "the skilled person has no reason to conclude that the same degradation necessarily takes place in the reconstituted formulations [as in the screening-study composition]." (Ex-1023, 17-18.) During prosecution of the related Application No. 12/418,905 ("the '905 application"), the Examiner similarly found that Andya "discloses nothing" about the degraded proteins in the Example 1 formulations and therefore in Example 1 "there might be no acidic variants at all." (Ex-1008, 226.)

contain the particular required variants—Asn30 deamidated to Asp30—and thus do not inherently anticipate the challenged claims as Pfizer contends. (Petition, 44.)

Andya's anti-HER2 antibody (humMAb4D5-8) contains numerous residues where acidic variants may form, including twenty-five asparagine residues and thirty-one glutamine residues. (Ex-1001, 23:35-25:20; Ex-2037, ¶¶94-96.) Moreover, deamidation at any asparagine or glutamine residue can proceed via a cyclic structure, respectively, succinimide or glutarimide—neither of which is an acidic variant. (Ex-1017, 6; Ex-2037, ¶97) Thus, as Dr. Scandella concedes, deamidation is only one of many potential degradation pathways, deamidation may occur at residues other than Asn30 (*e.g.*, other asparagine and glutamine residues), and deamidation may not generate an acidic variant. (Ex-2038, 47:10-21, 54:17-55:7, 58:10-19.)

Nor can one infer that the Example 1 formulations would degrade in the same manner as the screening-study composition. (Ex-2037, ¶¶98-100.) As discussed above, numerous undisclosed factors could cause the different compositions to degrade differently. (*Id.*, ¶¶38-48, 99.) Furthermore, as Dr. Carbonell explains, even if one were to conclude (incorrectly) that deamidation in the Example 1 formulations would occur at Asn30, such deamidation would not necessarily result in Asp30 as required by the claims. (Ex-2037, ¶¶98-100; Ex-

1017, 6.) Therefore, Pfizer's inherent anticipation theory once again fails as a matter of law. *Trintec Indus.*, 295 F.3d at 1295.

3. Andya Is Not Enabling.

Pfizer's petition also fails to demonstrate that Andya is enabling, and thus for that additional reason the Board should find that the challenged claims are patentable over Andya. *Verizon Servs. Corp. v. Cox Fibernet Va., Inc.*, 602 F.3d 1325, 1337 (Fed. Cir. 2010) ("[A] patent claim cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." (internal quotation marks omitted)); *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) ("[I]n order to render an invention unpatentable for obviousness, the prior art must enable a person of ordinary skill to make and use the invention.").

a. Pfizer relies on an incorrect presumption that Andya is enabling.

As an initial matter, Genentech disputes Pfizer's assertion that a prior art publication should be entitled to a presumption of enablement. (Petition, 48.) Genentech recognizes that the Board has stated that prior art publications should receive a presumption of enablement in IPRs. *See Samsung Elecs. Co., Ltd. v. Queen's Univ. at Kingston*, IPR2015-00584, Paper 53, *22-23 & n.4 (P.T.A.B.

July 27, 2016).[8] Genentech respectfully submits, however, that the Board's prior decisions are not consistent with the allocation of the burden of proof Congress mandated in the AIA.

Section 316(e) requires that the petitioner bear the burden of proof regarding all propositions of unpatentability, which necessarily includes the question of whether a prior art publication is enabling, and therefore there should be no presumption of enablement. *See* 35 U.S.C. § 316(e); *Aqua Prods., Inc. v. Matal*, 872 F.3d 1290, 1306 (Fed. Cir. 2017) (en banc) ("[I]n an [IPR], the burden of persuasion is on the petitioner to prove unpatentability by a preponderance of the evidence, and that burden ***never*** shifts to the patentee." (internal citation and quotation marks omitted)); *cf. Takeda Pharm. Co. v. Handa Pharm., LLC*, No. C-11-00840, 2013 WL 9853725, at *64-65 (N.D. Cal. Oct. 17, 2013) (finding that in district court proceedings the challenger bears the burden of proving that a non-patent prior art reference is enabling); *Jacobs Vehicle Equip. Co. v. Pac. Diesel*

[8] Genentech is not aware of any decision designated "precedential" or "informative" in which the Board has held that prior art publications should receive a presumption of enablement.

Brake Co., 829 F. Supp. 2d 11, 33 (D. Conn. 2011), *aff'd*, 494 F. App'x 96 (Fed. Cir. 2013) (same).[9]

In its institution decision, the Board suggested that the Federal Circuit recognized a presumption of enablement for prior art printed publications in *In re Antor Media Corp.*, 689 F.3d 1282 (Fed. Cir. 2012). (Paper 16, 21.) But that case addressed a different question, namely what burden should be placed on a patent examiner in a non-adversarial *ex parte* patent prosecution proceeding in order to comply with 35 U.S.C. § 132. *See id.* at 1289 ("[W]e therefore hold that, during patent prosecution, an examiner is entitled to reject claims as anticipated by a prior art publication or patent without conducting an inquiry into whether or not that prior art reference is enabling."). *In re Antor Media* has no applicability on the allocation of the burden of proof in IPR proceedings, which involve a petitioner

[9] Pfizer suggests that since Andya shares a specification with a patent, it also should be entitled to the presumption of enablement that applies to prior art patents. (Petition, 48.) Section 316(e), however, requires that the IPR petitioner bear the burden of proving ***all*** propositions of unpatentability, and draws no distinctions between patent and non-patent prior art references. *See* 35 U.S.C. § 316(e).

who is not subject to the resource constraints of an examiner and are separately governed by the standard mandated by Congress in Section 316(e).

b. Andya fails to enable a POSA to obtain the claimed composition without undue experimentation.

"Enablement of prior art requires that the reference teach a skilled artisan—at the time of filing—to make or carry out what it discloses in relation to the claimed invention without undue experimentation." *In re Morsa*, 803 F.3d 1374, 1377 (Fed. Cir. 2015). Andya fails to teach a POSA to make the composition set forth in the challenged claims, let alone how to do so without undue experimentation. (Ex-2037, ¶¶101-119.)

Andya discloses a method for ***formulating*** an existing rhuMAb HER2 composition. (Ex-1004, 3-5.) But Andya does not disclose the contents of or specific method of preparing the ***starting composition*** used in the Andya experiments. (*See id.*; Ex-2037, ¶¶104-105, 113-115.) Thus, even if Andya had disclosed that the final output of its formulation experiments was a composition that necessarily falls within the scope of the challenged claims (it does not), Andya still would not be enabling. Without that critical disclosure of the specific starting composition and how to prepare it, Andya cannot enable a POSA to create a

composition as claimed. (Ex-2037, ¶¶104-119.)[10] *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 501 F.3d 1263, 1268 (Fed. Cir. 2007) (finding prior art reference not enabling, despite disclosing the claimed composition, because "it does not tell [a POSA] how to obtain it").

Tellingly, neither Pfizer nor its declarants Dr. Scandella and Dr. Buick addressed the Federal Circuit's *Wands* factors, *i.e.*, the legal standard for assessing whether a disclosure is enabling. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). But as Dr. Carbonell explains in his accompanying declaration, the *Wands* factors confirm that Andya is not enabling. (Ex-2037, ¶¶101-119.)

(1) The breadth of the claims and (2) the nature of the invention: The challenged claims are directed to a composition comprising a mixture of an anti-HER2 antibody and one or more acidic variants thereof, wherein the amount of acidic variants is less than about 25%, and further wherein the acidic variants are predominantly Asn30 deamidated to Asp30. (Ex-2037, ¶¶107-108.) Additionally, under the correct construction of "therapeutic composition," the claims further

[10] This is akin to disclosing a method for baking bread that can be used with multiple types of dough, *e.g.*, if one performs the method with rye dough, the method produces rye bread. But disclosing the baking method without disclosing a recipe for rye dough does not enable one to make rye bread.

require that the composition contain a therapeutically effective amount of the anti-HER2 antibody. (*Id.*, ¶17.) *See* Section VI(A).

(3) The state of the prior art: As of May 1998, the art taught that anti-HER2 antibody compositions contained at least about 25% acidic variants. (Ex-2037, ¶¶109-110.) For example, the '218 patent teaches that prior art techniques produced compositions with at least about 25% acidic variants. (Ex-1001, 22:57-63.) Similarly, Waterside teaches that its rhuMAb HER2 composition has 25% deamidated Asn30. (Ex-1006, 7.) Other references, such as Andya and Harris, do not quantify the amount of acidic variants in their anti-HER2 antibody compositions. (Ex-2037, ¶¶109-110.) While general methods of protein preparation and purification were known, nothing in the prior art disclosed the "reverse wash" method, nor any other specific method, for reducing the amount of acidic variants in such compositions. (*Id.*, ¶¶110, 116-117.)

(4) The level of ordinary skill in the art: The Board adopted Pfizer's proposal regarding the level of ordinary skill in the art, *i.e.*, 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, and knowledge of and experience regarding protein analysis and protein chemistry, including protein preparation and purification, and formulation of therapeutic

proteins for human use. (Paper 16, 8; *see also* Ex-2037, ¶111.) In May 1998, a POSA at this level of skill would not have had the knowledge or experience to be able obtain the claimed composition without undue experimentation. (Ex-2037, ¶¶111, 116.)

(5) The level of predictability in the art: Protein purification is a highly unpredictable art, as Dr. Scandella concedes. (Ex-2037, ¶112; Ex-2038, 71:20-72:17 ("[I]n the 1990s, the purification of recombinant proteins was not trivial, for purification for manufacturing scale."; "Q. Personally, did you deal with unpredictable issues in protein purification in the 1990s? A. Yes, I did.") This is especially true with respect to the type and amount of acidic variants in an antibody composition, as protein degradation (including deamidation) is highly variable and depends on the manufacturing and storage conditions (*e.g.*, choice of cells, cell culture components, harvest time, and conditions during cell culture, purification, formulation, and storage including temperature, pH level, and other buffer components). (Ex-2037, ¶112; 2036, ¶¶66-78; Ex-2038, 29:18-30:9, 33:3-4, 36:15-18, 62:9-65:5, 66:18-68:11; Ex-2039, 63:8-13, 142:13-17.) It has long been established that "[i]n cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 838-39 (C.C.P.A. 1970).

(6) The amount of direction provided and (7) the existence of working examples: Pfizer relies upon the particular formulations tested in Figures 5-8 of Andya. Andya's Example 1 teaches how to formulate these compositions, but Andya is silent regarding specifically how to make the antibody they contain. (Ex-2037, ¶¶113-115.) Indeed, Andya provides no specific procedure for making these—or any—anti-HER2 antibody compositions, nor any working examples of producing anti-HER2 antibody. (Ex-2037, ¶¶113-115.) Dr. Scandella concedes as much. (Ex-2038, 99:14-19,100:6-10.) Rather, as discussed above, Andya describes a method for ***formulating*** an existing humMAb4D5-8 composition but does not disclose the contents of the starting composition, nor any method of obtaining it. (Ex-1004, 21; Ex-2037, ¶¶113-115.) At best, Andya provides broad general disclosure regarding methods of making antibodies. (Ex-1004, 12-16.) However, as Dr. Carbonell explains, an antibody composition is defined by the specific process and conditions under which it was produced, such that disclosure of general types of methods does not teach one how to arrive at any specific antibody composition having any particular variant profile. (Ex-2037, ¶¶112.) *Impax Labs., Inc. v. Aventis Pharm., Inc.*, 545 F.3d 1312, 1315 (Fed. Cir. 2008) (finding that broad general disclosures rather than a specific disclosure of the claimed invention, combined with an absence of any working examples, supported finding that prior art was not enabling); *see also In re Donohue*, 766 F.2d 531, 533

(Fed. Cir. 1985) (to be enabling, prior art must "sufficiently describe the claimed invention to have placed the public in possession of it").

(8) The quantity of experimentation needed: Based on Andya's disclosure, it would require extensive experimentation to obtain the disclosed composition. (Ex-2037, ¶¶116-119.) As Dr. Carbonell explains, a POSA attempting to obtain the specific compositions that Pfizer relies on, and having no specific guidance or working examples within Andya itself (as discussed above), would need to begin with what is disclosed in the art generally regarding how to obtain an anti-HER2 antibody, such as the Carter WO92/22653 reference ("Carter '653 PCT") identified in Andya. (Ex-1004, 21; Ex-2037, ¶¶116-119.) However, as Dr. Carbonell explains, extensive research would be required to develop a method to obtain a composition having the claimed acidic variant profile. (Ex-2037, ¶¶116-119.)

For example, the '218 inventors experimented with numerous cation exchange resins using various column bed heights, elution conditions including sequential steps and gradients of differing pH and/or conductivity, different salts to modulate conductivity, and protein modifiers in order to develop the novel "reverse wash" method that achieved the inventive composition as claimed. (Ex-2035, ¶¶5-11; Ex-2037, ¶¶118.)

Importantly, as explained by Dr. Blank, Genentech's records establish that—although not disclosed in Andya—Andya's Example 1 starting composition (*i.e.*,

pre-formulation) was a humMAb4D5-8 antibody composition made in accordance with the not-yet-public "reverse wash" method taught in the '218 patent. (Ex-2035, ¶¶12-37; Ex-2034, ¶¶4-9; Exs-2018-2027.) Thus, the Example 1 formulations had 78-82% native protein because ***the Andya inventors were starting with a composition that had already been purified in accordance with the non-public reverse wash method***. Andya's Example 1 study simply confirmed that the tested formulations maintained stability. (Ex-2037, ¶¶87-91.) But a POSA starting with the disclosure in Andya would have no knowledge of the reverse wash method—or any other method to obtain the specific starting composition—and thus it would require significant, undue experimentation for a POSA to obtain the specific Andya compositions that Pfizer relies on. (Ex-2037, ¶¶101-119.) *Forest Labs.*, 501 F.3d at 1268 (finding that a failure to disclose how to obtain the disclosed composition rendered prior art non-enabling).

c. Dr. Buick's experiments fail to demonstrate that Andya is enabling.

Pfizer, in an attempt to show that Andya is enabling, improperly relies on certain experiments performed by its declarant Dr. Buick. (Petition, 50-51.) In these experiments, Dr. Buick purported to use Andya to create and purify a rhuMAb HER2 antibody composition that (according to Pfizer) falls within the scope of the challenged claims. (*See id.*; Ex-1042 ¶¶10-24.) But Dr. Buick did not

rely solely on teachings from Andya to create his composition—indeed, he conceded that he barely relied on it at all. (Ex-2039, 42:6-44:21; Ex-2037, ¶¶120-135; Ex-2036, ¶60.) Dr. Buick further conceded that he did not rely on ***any*** established prior art method for creating and purifying an antibody. (Ex-2039, 32:1-8, 52:9-13, 81:13-82:9, 108:19-109:5, 116:4-117:13, 128:22-130:7; Ex-2037, ¶¶121-123.) Instead, with the benefit of hindsight provided by the '218 invention, Dr. Buick created his composition using a complicated daisy-chain of methods and inputs drawn from an array of alleged prior art sources that are not part of Pfizer's asserted grounds, as well as modern-day equipment and technology not available as of the priority date. (Ex-2037, ¶¶120-135; Ex-2036, ¶¶54-78.) Such experiments plainly fail to show that Andya is enabling. (Ex-2037, ¶¶120-135.) Moreover, Dr. Buick conceded that he did not even attempt to lyophilize or formulate his antibody as disclosed by Andya. (Ex-2039, 112:21-113:19). For this additional reason, Dr. Buick's experiments are irrelevant with respect to any alleged recreation of the Andya compositions upon which Pfizer relies.

Furthermore, Dr. Buick was not a person of ordinary skill in the art as of the May 1998 priority date of the '218 patent (not yet having earned a bachelor's degree at that time), such that his work necessarily reflects a hindsight-based perspective from one trained on post-dating technology. (Ex-1042, ¶7 & Ex-A, 17-18; Ex-2039, 57:7-58:3.) And Dr. Buick's experiments required work that far

exceeded the level of skill in the art in May 1998. (Ex-2037, ¶120.) Dr. Buick relied on advanced work from numerous experts at three separate protein bioengineering firms—Fusion Antibodies, Proteome Factory, and Atum—to perform different aspects of his experiments over at least nine months. (Ex-2039, 12:12-17, 16:15-17:16, 18:22-19:14, 20:19-21:8. 24:6-26:14; Ex-2037, ¶¶120-135.)

The table below sets forth the various steps performed by each of the three firms and the source of each protocol (to the extent Pfizer and/or Dr. Buick provided that information):[11]

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[11] Dr. Buick's report failed to provide, and he was unable to answer questions in his deposition providing, information necessary to evaluate the tests and data and the significance and reliability of his experiments, including information about how the tests were performed and the data generated, how the data were used to determine acidic variant values, and the conditions and results of the tests discussed in his report (*e.g.*, Ex-2039, 22:9-18, 54:3-56:8, 67:1-3, 73:19-74:4 83:2-6, 87:6-9, 91:5-93:19, 101:8-102:20, 104:2-11, 106:7-108:1, 114:15-115:6, 126:9-128:21, 132:3-6, 134:14-16, 138:12-22, 153:11-13, 158:13-21, 160:5-161:15). *See* 37 C.F.R. § 42.65. Genentech requested this information shortly after Dr. Buick's deposition but Pfizer failed to produce it.

Process Step	Source[12]
DNA synthesis and cloning	Unknown/Atum's protocol
Transfection	ThermoFisher protocol; Ausubel; Jordan
CHO cells	Andya; Harris; Waterside
Cell culture	Jordan; Ausubel; "routine methods"
Protein A Purification	Carter '653 PCT; GE Healthcare (2011)
Mono-S Chromatography	Harris; Fusion Antibodies' protocol
Bakerbond Chromatography	Andya; Proteome Factory's protocol

First, as seen above, Dr. Buick's protocol is not based on Andya, nor any teaching in the prior art.[13] To the contrary, despite Pfizer's assertion that methods of obtaining antibody compositions were well-known in the prior art, Dr. Buick relied on three separate firms to develop a novel method never before practiced by

[12] (Ex-1042, ¶¶4, 8, 16, 19, 27, Ex B. 30-37; Ex-2039, 32:1-8, 52:9-13, 81:13-82:9, 108:19-109:5, 116:4-117:13, 128:22-130:7.)

[13] Dr. Buick's experiments allegedly pertaining to Andya largely overlap with his experiments allegedly pertaining to Waterside and Harris, and the flaws discussed above demonstrate that Waterside and Harris are not enabling for the same reasons that Andya is not enabling. (Ex-2037, ¶¶167-178, 206-217.)

any person or group. (Ex-2037, ¶¶120-135; Ex-2039, 32:1-8, 52:9-13, 81:13-82:9, 108:19-109:5, 116:4-117:13, 128:22-130:7.) The fact that the claimed composition could not be obtained by any known procedure in the prior art, but instead required months of work by numerous experienced scientists, demonstrates that the experimentation required was not "merely routine." *In re Wands*, 858 F.2d at 737.

For example, Andya Example 1 refers to the anti-HER2 antibody described in the Carter '653 PCT. (Ex-1004, 21.) Dr. Buick thus purported to rely on Carter (Ex-1043) for certain elements of his experiments. (Ex-1042 ¶10.) Yet Dr. Buick only cherry-picked certain of Carter's teachings—whereas Carter teaches antibody production using a human embryonic kidney ("HEK") cell line (Ex-1043, 68-69), Dr. Buick chose to use Chinese hamster ovary ("CHO") cells (Ex-1042, ¶8). As explained by Dr. Carbonell and Dr. Prentice, the use of different cells impacts the cellular metabolism and cell culture environment, post-translational modification and chemical degradation of a protein, and thus the formation of acidic variants. (Ex-2037, ¶121; Ex-2036, ¶¶63-64; Ex-2004, 701-704; Ex-2005, 122.)[14] Further, Dr. Buick chose to perform "transient" transfection rather than "stable"

[14] Dr. Buick admitted at his deposition that he performed separate HEK cell experiments and that he considered them "relevant," yet he failed to include them in his declaration. (Ex-2039, 40:4-9.)

transfection as a POSA would when attempting to practice the prior art. (Ex-2037, ¶121; Ex-2036, ¶¶63-64.)

Dr. Buick similarly cherry-picked from a large number of different sources—rather than relying on Andya, or any other prior art reference in Pfizer's instituted grounds—in order to select the process and inputs for each separate step in his experiments. (Ex-2037, ¶¶120-133; Ex-2036, ¶¶66-78.) At each point in the protocol, Dr. Buick had numerous choices: which expression vector to use, how to optimize the DNA sequence, how to conduct DNA cloning, how to perform transfection, which cells to use, which cell culture media and conditions to select, and how, when, and under what conditions to perform harvesting, separation, and purification. (Ex-2037, ¶¶121-130; Ex-2036, ¶¶66-78.) As explained by Dr. Carbonell and Dr. Prentice, these choices individually and in combination affect the cell culture and purification environments, post-translational modification and chemical degradation of a protein, and thus can have a significant impact on whether and to what extent an antibody composition would contain acidic variants. (Ex-2037, ¶¶120-125; Ex-2036, ¶¶57-78; *see also* Ex-2004, 700-704; Ex-2005, 121-124; Ex-2040, 205; Ex-2041, 1040, 1049-50; Ex-2042; Ex-2043, 20; Ex-2044; Ex-2045, 246, Figs. 1,4; Ex-2046, 4279; Ex-2047; Ex-2048, 1205-1209, Fig. 9;

Ex-2049, 10346, 10351, Fig. 7; Ex-2050, 2152-2155; Ex-2053, 12409; Ex-2054, 1573; Ex-2055, 785; Ex-2056, 2147; Ex-2057, 1432.)[15]

Moreover, Dr. Buick did not merely rely on teachings not found in Andya, he also chose ***not*** to practice the teachings that are set forth in Andya. (Ex-2037, ¶¶123-135; Ex-2036, ¶¶62-64, 75.) For example, Andya discloses that its Example 1 formulations were made using different succinate or histidine buffer, pH, surfactant, and sugar combinations. (Ex-1004, 21; Ex-2037, ¶123.) Yet Dr. Buick concedes that he failed to use succinate buffer, histidine buffer, sugars, or surfactant in any of his experiments. (Ex-2039, 13:2-19.) He likewise concedes that he failed to lyophilize his antibody as taught in Andya's Example 1. (*Id.*, 112:21-113:1.) Each of these factors could affect the antibody composition, including whether and to what it extents it degrades by forming acidic variants. (Ex-2037, ¶¶121-123, 135-136.) Thus, Dr. Buick's experiments are plainly irrelevant with respect to what a POSA ***following the teachings of Andya*** could have obtained.

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[15] For this reason, FDA regulations for biologic drugs require the disclosure of the process by which a drug is made including detailed information about each of the above steps. *E.g.*, 42 U.S.C. § 262(*l*)(2); 21 C.F.R. § 601.2(a).

The fact that Dr. Buick failed to follow Andya—or any established prior art protocol—and instead, with the benefit of hindsight, had to create his own method out of whole cloth, is not surprising and confirms that Andya is not enabling. (Ex-2037, ¶¶120-125; *see also* Ex-2035, ¶¶5-11 ('218 inventor detailing the extensive experimentation to develop the novel method that achieved the claimed composition).)

Second, Dr. Buick and the three separate firms working at his direction all relied on methods and technologies that post-date the May 1998 priority date. This further confirms that the amount of experimentation required to obtain the claimed composition in light of Andya was anything but "routine." *In re Wands*, 858 F.2d at 737.

For example, Fusion Antibodies and Proteome Factory calibrated their protocols using Herceptin®—Genentech's own anti-HER2 drug composition. (Ex-1042 ¶19; Ex-2039, 139:6-140:7.) Herceptin® was not approved and available for sale until September 1998. (Ex-1004, 1; Ex-1014, 2.) Thus, a POSA attempting to follow Andya's teachings would have been required to undertake far more experimentation, as they would not have had Genentech's composition as a reference to guide their work. (Ex-2037, ¶131.)

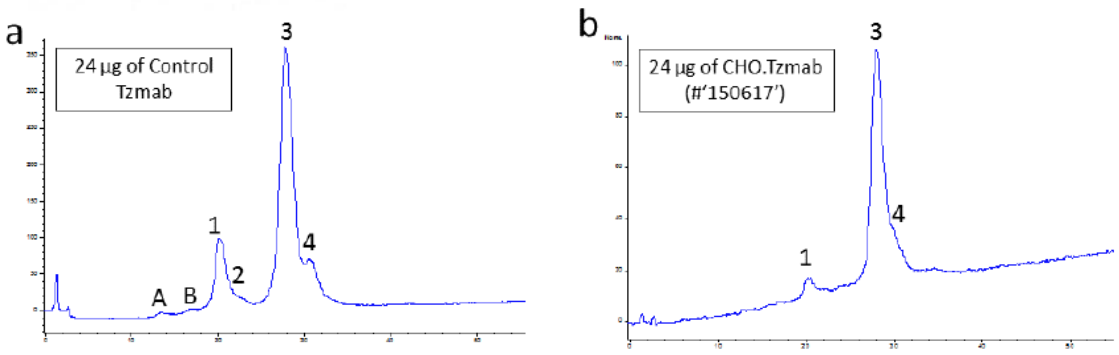
Similarly, Dr. Buick states that he selected a particular type of purification (protein-A Sepharose purification) because it is mentioned in Andya. (Ex-1042

¶16; *see also* Ex-1004, 13.) Yet when performing the purification, Fusion Antibodies used a protein-A Sepharose protocol released ***in 2011*** rather than an earlier version of the protocol that was available at the time of (although not disclosed in) Andya—and that Dr. Buick had available to him and thus could have used for his experiments. (Ex-1042 ¶16.) Dr. Buick testified that the two different protocols are "identical" (Ex-2039, 108:13), but his testimony is contradicted by the express disclosures in the protocols themselves. (Ex-2037, ¶¶124-128.) For example, as explained by Dr. Carbonell, the 2011 protocol differs from the prior art protocol with respect to the filter, wash, buffer, storage and neutralization steps—each of which could impact protein degradation and the formation of acidic variants. (*Id.*, ¶¶124-128; Ex-1046, 3-5; Ex-1045, 4-5; Ex-2058, 30-32.)

Furthermore, Dr. Buick relied on Atum to synthesize and clone anti-HER2 antibody DNA, but he allowed Atum to employ its own protocols to determine the sequence of the DNA. (Ex-2039, 31:5-14 ("[T]he protocols that they used were protocols that they were comfortable using for DNA synthesis and cloning. There was no need for Fusion to – or myself to have any reason to change their protocol.").)

Third, Dr. Buick's own analysis fails to show that his supposed attempt to follow the teachings of Andya produced a composition falling within the scope of the claims—and thus fails to show that Andya is enabling. *Forest Labs.*, 501 F.3d

at 1268 (prior art that does not teach a POSA how to obtain a claimed composition is not enabling). Dr. Buick asserts that he sent a sample from one of the batches he manufactured with his novel method to Proteome Factory for cation-exchange chromatography analysis on a Bakerbond column "in accordance with the methods described in Andya." (Ex-1042, ¶¶8, 19.) According to Dr. Buick, his experiment would have been successful if the chromatographic analysis matched a chromatographic analysis of commercial Herceptin®. (Ex-2039, 139:6-140:3.) Indeed, Proteome Factory calibrated their equipment using commercial Herceptin® (something that could not have been done in the prior art) specifically so that they could attempt to obtain the same chromatographic profile. (*Id.*; *see also* Ex-1042, ¶19.) Yet despite those efforts, Proteome Factory obtained very different profiles for commercial Herceptin® (left below) and Dr. Buick's composition purportedly based on the teachings of Andya (right below):



(Ex-1042, 44 (Figs. 6a, 6b).) As seen above, the chromatograms differ starkly—even setting aside the unlabeled peaks on the left-hand side, the commercial

Herceptin® displays six different peaks while Dr. Buick's composition displays only two (at best three, if one were to include the supposed "peak 4"). Furthermore, Dr. Buick concedes that the yield of his composition was so low that he could not even test the contents of peak 1. (Ex-1043, ¶21.) Nor could Dr. Buick explain how the peaks of his composition were integrated or how the baseline was drawn to calculate the area under the curve. (Ex-2039, 138:7-22.) This is plainly insufficient to meet Pfizer's burden of demonstrating that Andya's teachings enable a POSA to obtain a composition falling within the scope of the claims.

Finally, Dr. Buick's experiments further demonstrate that Andya does not enable a POSA to create a "therapeutic composition" as required by all challenged claims. (Ex-2037, ¶114.) As discussed above, under the proper construction of the term, a "therapeutic composition" is a composition that contains a therapeutically effective amount of the anti-HER2 antibody. *See* Section VI(A). To treat an average female adult with humMAb4D5-8, commercial Herceptin®, would require an initial dosage of over 300 milligrams and a maintenance dosage of over 150 milligrams. (Ex-1014 (FDA-approved dosage of 2-4 mg/kg body weight.) Dr. Buick failed to demonstrate that he was able to obtain such a composition. To the contrary, he failed to report the amount of antibody he produced and could not provide that information at his deposition. (Ex-2039, 55:3-11.) Moreover, both

Dr. Scandella and Dr. Buick admitted that they did not even consider how much antibody composition was needed for a composition to be therapeutically effective. (Ex-2038, 42:18-43:19; Ex-2039, 55:12-18.)

d. Genentech has not conceded that Andya enables the '218 invention.

Pfizer also argues that Genentech previously conceded that Andya enables the claimed compositions. (Petition, 49-50.) That is incorrect and relies on clear mischaracterizations of Genentech's prior statements. In each case, Genentech merely explained that Andya (itself a Genentech patent application) teaches a method for ***formulating*** an already-existing antibody composition.

For example, in the '218 patent, Genentech explained that "[t]he humMAb4D5-8 antibody of particular interest herein may be prepared as a ***lyophilized formulation***, *e.g.* as described in [Andya, which is] expressly incorporated herein by reference." (Ex-1001, 19:54-57.) In other words, Genentech explained that ***after*** creating an antibody composition in accordance with the teachings of the '218 patent, that composition could be formulated via the method taught in Andya. At no point did Genentech suggest that Andya would enable one to create the claimed antibody composition itself. (*See id.*) Dr. Scandella agreed that the '218 patent refers to Andya for how to make a lyophilized formulation. (Ex-2038, 105:9-11).

Similarly, during the prosecution of U.S. Patent No. 6,267,958 ("the '958 patent"), a U.S. counterpart to Andya, Genentech explained that "the application [for 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." (Ex-1012, 172.) Once again, Genentech simply stated that the disclosure is enabling for what it teaches—a method for ***formulating*** an anti-HER2 composition. None of Genentech's statements relate to the question of how to obtain any particular starting composition, let alone the novel composition taught in the '218 patent.

4. Pfizer Has Not Asserted A Cognizable Obviousness Theory.

Pfizer fails to advance a legally cognizable obviousness theory with respect to Andya.[16] Pfizer's entire obviousness argument for each claim element consists

[16] In its institution decision, the Board correctly found that Pfizer "has not presented [its obviousness] arguments sufficiently, as it has not explained an obviousness rationale," and thus denied institution with respect to obviousness over Andya. (Paper 16, 17.) The Board subsequently issued a separate institution decision instituting review of this ground in light of the Supreme Court's decision in *SAS Institute Inc. v. Iancu*, 138 S. Ct. 1348 (2018)—not based on any reevaluation of the merits. (Paper 25, 2.)

of a single, conclusory sentence. For example, following its (incorrect) argument that Andya discloses the "one or more acidic variants" limitation, Pfizer states: "This limitation is at a minimum obvious in light of these disclosures." (Petition, 40.) Pfizer includes similar conclusory sentences regarding the claim elements requiring Asn30 deamidated to Asp30. (*Id*., 43, 45.) Pfizer's bare assertions fall well below the required legal standard.

To provide a cognizable obviousness analysis, a petition must include an "explanation of how the teachings of the references would be arranged or combined or why a person of ordinary skill would have made the combination" and "some ***reason*** why a person of ordinary skill in the art would have thought to combine ***particular*** available elements of knowledge, as evidenced by the prior art, to reach the claimed invention." *Heart Failure Techs., LLC v. Cardiokinetix, Inc.*, IPR2013-00183, Paper 12, *9 (P.T.A.B. July 31, 2013) (citing *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007)) (emphasis in original); *see also Veeam Software Corp.*, Paper 7, *12 (when a petition does not articulate how the prior art discloses or renders obvious every limitation of the claimed subject matter, the "Petitioner's presentation is incomplete and, therefore, insufficient to demonstrate obviousness").

Pfizer's single-sentence, conclusory assertions contain no such reasoning or explanation as to how a POSA would modify Andya to achieve the claimed

invention. Nor does Pfizer even attempt to show that a POSA would have been motivated to make such modifications or have a reasonable expectation of success in doing so. That failure of proof is fatal. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) ("Because … conclusory statements [regarding a motivation to combine prior art] cannot satisfy the petitioner's burden of demonstrating obviousness, the Board did not have sufficient evidence on which to base its legal conclusion of obviousness."); *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 995-97 (Fed. Cir. 2009) (rejecting obviousness argument where challenger had not established a reasonable expectation of success).

Indeed, a POSA would have had no reason to modify the Andya formulations. As Dr. Scandella agreed, Andya itself affirms that the Example 1 formulations showed acceptable degradation. (Ex-2038, 118:8-11; *see also* Ex-1004, 29; Ex-2037, ¶137.) Moreover, for the same reasons described above that Andya does not enable an antibody composition as claimed, a POSA would not have had a reasonable expectation of success in obtaining such a composition based on the disclosure of Andya. (*See* Section VII(A)(3), incorporated herein by reference; Ex-2037, ¶¶136-140.)

Thus, the Board should reject Pfizer's obviousness ground and find that the challenged claims are not rendered obvious by Andya.

B. Waterside Does Not Render Obvious Any Of The Challenged Claims.

1. Pfizer Fails To Establish That Waterside Qualifies As A Prior Art "Printed Publication."

Pfizer fails to establish that Waterside qualifies as a printed publication under 35 U.S.C. § 102. To meet that standard and be eligible for consideration in an IPR, a document must have been "sufficiently accessible to the public interested in the art." *In re Cronyn*, 890 F.2d 1158, 1160 (Fed. Cir. 1989). A petitioner bears the burden of establishing public accessibility. *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1350 (Fed. Cir. 2016). Pfizer has failed to demonstrate that Waterside qualifies as a printed publication for two separate reasons.

First, Pfizer failed to properly authenticate Waterside. "To satisfy the requirement of authenticating or identifying an item of evidence, the proponent must produce evidence sufficient to support a finding that the item is what the proponent claims it is." Fed. R. Evid. 901(a); *see also GoPro, Inc. v. Contour IP Holding LLC*, IPR2015-01080, Paper 55, *11 (P.T.A.B. Oct. 26, 2016) (finding Rule 901 satisfied when declarant with personal knowledge testifies that document is a "true and correct copy of the [document] that was distributed"). Pfizer's declarant Mr. Carson does ***not*** state that the copy of Waterside that Pfizer relies on is a "true and correct" copy of a document distributed at the Waterside conference, nor does he otherwise purport to authenticate it. For example, Mr. Carson simply

states that Waterside "appears to be in the same format WilBio would have used" (Ex-1041 ¶6)—but it is printed in a standard, boilerplate format, not any special format unique to WillBio. Thus, Mr. Carson's declaration fails to satisfy Pfizer's burden of authenticating Waterside. *See, e.g.*, *Celltrion, LLC v. Biogen, Inc.*, IPR2017-01230, Paper 10, *15 (P.T.A.B. Oct. 12, 2017).[17]

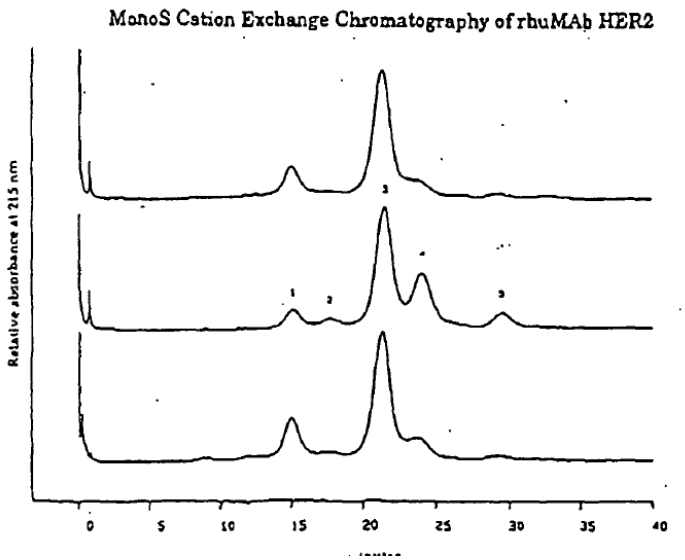
Second, Pfizer failed to show that Waterside was "sufficiently accessible to the public interested in the art." *In re Cronyn*, 890 F.2d at 1160. Pfizer does not identify any way in which the interested public could have learned about the

[17] Pfizer also suggests that Genentech "confirmed" that Waterside was a printed publication because it cited a version of Waterside in an IDS and because it elected not to dispute that Waterside was publicly available before the priority date of the European counterpart patent. (Ex-1027, 1.) Neither is legally sufficient for Pfizer to meet its burden. *LG Elecs., Inc. v. Advanced Micro Devices, Inc.*, IPR2015-00329, Paper 13, *12 (P.T.A.B. July 10, 2015) (holding that the mere fact that a document is cited in an IDS "is insufficient to demonstrate that a document is a printed publication."); *Argentum Pharm. LLC v. Research Corp. Techs., Inc.*, IPR2016-00204, Paper 19, *10-11 (P.T.A.B. May 23, 2016) (holding that a stipulation in separate proceedings cannot be used to satisfy the petitioner's burden of demonstrating that a prior art reference constitutes a "printed publication").

Waterside conference in advance let alone the particular subject matter of the Waterside reference, nor any way in which the interested public could have located the Waterside reference after the fact. *See Coal. for Affordable Drugs VIII, LLC v. Trs. of the Univ. of Penn.*, IPR2015-01835, Paper 56, *19-20 (P.T.A.B. Mar. 6, 2017) (finding that a slide presentation was not a printed publication because press release announcing conference did not mention subject matter of the slides and petitioner failed to present evidence that persons of ordinary skill could otherwise locate the slides following the conference). Pfizer thus failed to meet its burden of demonstrating that Waterside was sufficiently accessible to the interested public.

2. Waterside Fails To Disclose A Composition That Contains "Less Than About 25%" Acidic Variants.

Waterside does not disclose a composition "wherein the amount of acidic variant(s) is less than about 25%," as required by all challenged claims. Pfizer relies on a single Waterside analytical chromatography drawing as allegedly disclosing this element:



(Ex-1006, 4.) According to Pfizer, the above drawing depicts three different compositions that contain less than 25% acidic variants, either expressly (based on Dr. Scandella's alleged visual inspection of the drawing) or inherently (based on Dr. Scandella's alleged calculation of the area under each curve using computer software). (Petition, 55-56.) Neither theory is supportable. Dr. Scandella conceded that his visual inspection was "not a high-precision measurement" and that he could not actually determine the area under the curve in that manner. (Ex-2038, 130:9-18; Ex-2037, ¶144.) Moreover, Dr. Scandella's purported computer calculations are not supported by Waterside and fall far short of demonstrating that a composition with less than 25% acidic variants "must inevitably result" from Waterside's disclosures. *In re Montgomery*, 677 F.3d 1375, 1380 (Fed. Cir. 2012) (explaining that inherency requires that a missing claim element "must inevitably result" from a reference's disclosure).

As explained by Dr. Carbonell, Waterside's drawing (above) cannot be used to determine the amount of acidic variants in the Waterside composition because the figure does not provide quantified reference points. (Ex-2037, ¶¶141-148.) The three different line drawings are stacked one atop another, with no indication of the baseline (*i.e.*, y-axis zero point) for any of them. (*Id.*, ¶144.) There are also no clear dividing lines along the x-axis to indicate where the portions of each curve representing native proteins and variants begin and end. (*Id.*, ¶144.) Nor does Waterside present the underlying data or methodology used to generate the drawing, including any information to assess the margin of error in how it was drawn. (*Id.*, ¶¶142-145.) As the Federal Circuit has held, unless the reference sets forth specific quantitative values or explicitly provides a scale from which the drawing can be measured, "arguments based on measurement of a drawing are of little value." *Nystrom v. TREX Co.*, 424 F.3d 1136, 1149 (Fed. Cir. 2005) (quoting *In re Wright*, 569 F.2d 1124, 1127 (C.C.P.A. 1977); *see also* MPEP § 2125 (similar).

Indeed, this case demonstrates why such drawings should not be considered. Waterside itself states that "25% of the pool has deamidated Asn-30." (Ex-1006, 7. Thus, under Dr. Scandella's assumption that "deamidation results in acidic variants," the pool would necessarily contain at least 25% acidic variants since deamidated Asn-30 is only one of multiple types of acidic variants that may be

present in rhuMAb HER-2 compositions. (Ex-2037, ¶¶141-142). Yet Dr. Scandella ignores this express statement in favor of attempting to measure the figure—without knowing how the chromatogram was constructed or the margin of error in the drawing. Dr. Scandella concedes that software-based analysis "depends on the quality of the data input," that the absence of zero-points required him to use his judgment to estimate where in the drawings to draw the reference baselines, and that a POSA could have selected different baselines that would have produced results that "might differ by a percent or two." (Ex-2038, 131:6-15, 135:12-18, 137:7-8.)[18] Although Dr. Scandella asserts that, in his opinion, these differences are not significant, they confirm that he cannot say what percentage of acidic variants are ***necessarily*** and ***inevitably*** present in the depicted composition. (Ex-2037, ¶¶143, 147-150.) Indeed, Dr. Scandella performed the same analysis on the Waterside and Harris chromatograms—which purportedly disclose the ***same*** chromatogram—yet he obtained ***different*** amounts of acidic variants in each composition. (Ex-1003 ¶¶60, 71.) Without a reliable scale as a benchmark, Dr. Scandella's measurements do not show that any particular amount of acidic

[18] Dr. Scandella concedes that he failed to calculate a margin of error for his software analysis (Ex-2038, 131:16-22). Any margin of error would compound these differences. (Ex-2037, ¶¶147-150.)

variants is necessarily and inevitably present, as required to demonstrate inherency. *Trintec Indus.*, 295 F.3d at 1295.

Moreover, Dr. Scandella performed additional analyses of the Waterside and Harris chromatograms that were omitted from his declaration (and produced after their existence was revealed at his deposition). (Ex-2059, 1-4; Ex-2037, ¶147.) As Dr. Carbonell explains, these analyses show as much as a 5.2% variation in the calculated percentages of acidic variants. (*Id*.). If such an upward adjustment were applied to the acidic variant calculations Dr. Scandella chose to include in his report, then even under Dr. Scandella's flawed approach the majority of Waterside and Harris chromatograms would have more than 25% acidic variants. (*Id*.)

Even setting aside the uncertainty in measuring the Waterside drawing, Dr. Scandella's calculations are fundamentally flawed because he undercounted the amount of acidic variants. (Ex-2037, ¶¶149-150.) When measuring the amount of acidic variants depicted in the chromatograms, Dr. Scandella concedes that he omitted the area prior to the point selected as the 13-minute mark. (Ex-1003, ¶70; Ex-2038, 149:11-18.) However, as Dr. Carbonell explains, the chromatograms show material eluting during that time period, and that material would be acidic variants. (Ex-2037, ¶¶149-150.) Thus, even if it were possible to determine the amount of acidic variants necessarily and inevitably present in Waterside by measuring the drawings in Waterside (it is not), Dr. Scandella's failure to account

for all of the depicted acidic variants nevertheless renders his measurements irrelevant. (*Id.*, ¶¶147-150.)

3. Waterside Is Not Enabling.

a. Waterside fails to enable a POSA to obtain the claimed composition without undue experimentation.

Waterside is not enabling prior art. Unlike with Andya (Petition, 48-51), Pfizer does not even attempt to argue that Waterside is enabling (*see id.*, 51-61), nor does Dr. Scandella (*see* Ex-1003).[19] Instead, Pfizer improperly attempts to include such arguments in the declaration of Dr. Buick without addressing those arguments in its petition—or even citing to those portions of Dr. Buick's declaration. (*E.g.*, Ex-1042 ¶¶6-7, 25-29.) The Board has repeatedly rejected arguments raised only in an accompanying declaration. *E.g.*, *Cisco Sys., Inc. v. C-Cation Techs., LLC*, IPR2014-00454, Paper 12, *10 (P.T.A.B. Aug. 29, 2014) (informative); *Apple Inc. v. ContentGuard Holdings, Inc.*, IPR2015-00453, Paper 9, *8-9 (P.T.A.B. July 13, 2015). Thus, the Board should find the challenged claims patentable for the additional reason that Pfizer failed to present properly any

[19] As discussed in Section VII(A)(3)(a) (incorporated herein by reference), there should be no presumption of prior art enablement in an IPR.

evidence that Waterside is enabling.[20] But even if the Board were to consider the issue on the merits, the Board should nevertheless find that the *Wands* factors confirm that Waterside is not enabling.[21]

For example, Waterside (like Andya) describes the ***analysis*** of an antibody composition, but it provides no disclosure as to how to ***obtain*** the composition in the first place. (Ex-1006, 3-7; Ex-2037, ¶¶159-163; Ex-1006, 3-7.) Indeed, Dr. Scandella testified that "Waterside describes the characterization of the products

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[20] Dr. Buick admits that he considered the teachings of Waterside and Harris collectively in a single analysis—he did not consider whether each reference was independently enabling. (Ex-1042 ¶¶25-29.) Pfizer's petition, however, relies on each reference in a separate ground and does not present an argument that the two references should be considered in combination with each other (nor in combination with Andya). Thus, Dr. Buick's analysis of the references in combination cannot support Pfizer's petition.

[21] *Wands* factors (1)-(5) are directed to the patented invention and the skill-level, unpredictability, and overall state of the art, and thus the analysis with respect to these factors is the same with respect to all asserted prior art references. The discussion of these factors in Section VII(A)(3)(b) is incorporated herein by reference.

but not how they were made." (Ex-2038, 157:9-13). Thus, as Dr. Carbonell explains, the lack of guidance (*Wands* factor 6) and lack of working examples (*Wands* factor 7) in Waterside mean that a POSA could not obtain the claimed composition based on Waterside's teachings but would instead need to look elsewhere—as, in fact, Dr. Buick was required to do (as discussed further below). (Ex-2037, ¶¶158-165.) Yet as Dr. Carbonell explains and as discussed in Section VII(A)(3)(b) (incorporated herein by reference), there were no teachings in the prior art that would allow a POSA to obtain the claimed composition without undue experimentation (*Wands* factor 8).

Further, evidence from the counterpart EP '455 patent opposition demonstrates that even the analytical method identified by Waterside (and described in Harris) is not enabling. In the EP '455 patent opposition, the opponent conceded that Waterside alone was not enabling, but argued that it would be enabling in conjunction with Harris. (Ex-1023, 23-24.) In support of that theory, the opponent submitted a declaration by its protein characterization expert Dr. Wang. (Ex-2010 ¶1.) Dr. Wang attempted to match the chromatogram depicted in Harris (allegedly the same as the chromatogram in Waterside). (*Id.* ¶5.) But critically, Dr. Wang admitted that—despite repeated attempts with different columns and different instruments—he was unable to achieve such a chromatogram based on the teachings in Harris:

> For reasons unknown to us ***we were not able to obtain the cation-exchange profile*** as given in Fig. 2 of [Harris]. We have tried another MonoS column and used a different instrument under the same experimental conditions described in 2.2 of [Harris] but ***were not able to obtain the cation-exchange profile*** in accordance with Fig. 2 of [Harris].

(*Id*. ¶5.)

After those failures, Dr. Wang changed his protocol and instead used the teachings of a ***different, post-dating reference*** by the same author ("Harris 2001") to create a purportedly matching chromatogram. (*Id.* ¶6.) The EPO Board of Appeal, however, readily recognized that Dr. Wang's repeated failures demonstrated that Harris and Waterside were not enabling:

> As shown by [the Wang declaration], the skilled person aiming at solving the problem [of obtaining a composition with less than 25% acidic variants] by following the teaching of [Waterside] and aware of routine conditions of MonoS cation exchange chromatography of rhuMAb HER2 as disclosed in [Harris] would not have succeeded in separating the acidic variants from the native antibody molecule.

(Ex-1023, 23-24.)

Dr. Wang's failures confirm that Waterside (and Harris) do not enable the claimed invention. (Ex-2037, ¶166.) *In re Donohue*, 766 F.2d at 533 ("[F]ailures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling.").[22]

b. Dr. Buick's experiments fail to demonstrate that Waterside is enabling.

Dr. Buick attempts to show that Waterside is enabling through certain experiments (as he did with Andya), yet as before he could not actually obtain a composition using prior art methods and technologies—let alone methods disclosed by Waterside—and thus his experiments actually confirm that Waterside is not enabling. (Ex-2037, ¶¶167-178.)

[22] Despite the fact that Dr. Scandella included Dr. Wang's declaration describing his failed attempt to recreate the Waterside/Harris chromatography in his list of materials considered (Ex-1003, 88), Dr. Scandella testified that in forming his opinions he did not consider ***any*** attempts to recreate the Waterside/Harris chromatography other than those by Dr. Buick and Genentech. (Ex-2038, 125:14-22.)

As an initial matter, Dr. Buick did not purport to create a different composition based on Waterside's teachings. Instead, he relied on the ***same composition*** that he allegedly made according to ***Andya's*** teachings. (Ex-1042 ¶26; Ex-2037, ¶167.) As demonstrated in the table in Section VII(A)(3)(c) above and by his own testimony, Dr. Buick concedes that hardly any steps of his protocol for making an antibody composition are actually taught in Waterside—only the use of CHO cells and taking "cell culture harvests straight through to purification." (Ex-2039, 52:1-53:16.) Thus, for all the reasons discussed in Section VII(A)(3)(c) (incorporated herein by reference), Dr. Buick's experiments fail to demonstrate that Waterside teaches a POSA how to obtain the claimed composition. (Ex-2037, ¶¶167-178.)

Moreover, Dr. Buick admits that he failed to actually follow what is taught in Waterside. For example, Waterside discloses 12,000 liter manufacturing scale production, while Dr. Buick's production was done on a one- to two-liter scale. (Ex-2039, 53:17-54:2; Ex-1003, ¶112; Ex-1006, 4.)[23] Such differences in scale impact both the process and the final product. (Ex-2012, 258-261; Ex-2037,

[23] Harris similarly indicates that its composition was produced on a manufacturing scale. (Ex-1005, 5; *see also* Ex-1003 ¶52.)

¶¶169-171; Ex-2036, ¶¶62-63.) For this additional reason, Dr. Buick's work demonstrates nothing about whether Waterside was enabling.

Additionally, Dr. Buick purported to ***analyze*** his composition using the Mono-S chromatography identified by Waterside. (Ex-1042, ¶27.) But a method for carrying out Mono-S analytical chromatography is not even taught in Waterside—it is taught in ***Harris***. (*Id.*; Ex-2037, ¶¶175-176.) Further, although Dr. Buick purported to use the Harris Mono-S technique to test the composition, the analysis in fact departed from the protocol—for example, by performing cation exchange at 22°C rather than at 40°C as Harris instructs. (Ex-1005, 5; Ex-1042, 34-35; Ex-2037, ¶176.) Changes in temperature can have a significant impact on how an antibody composition degrades, as well as on the accuracy of a chromatogram. (Ex-2014, 3, Fig. 5; Ex-2037, ¶176.) Indeed, Dr. Buick's own analysis showed that "acidic variants of trastuzumab increase over time whenever the antibody is stored at 40 degrees C." (Ex-2039, 63:8-13; 142:13-143:14; Ex-1042, 37, 43 (at 40°C peak 1 increases from 16% to over 25% of the area in one day). And just as with Andya, Fusion Antibodies once again calibrated cation-exchange protocols using commercial Herceptin® itself. (Ex-1042, ¶27.) Thus, for these additional reasons, Dr. Buick's analysis is not informative of whether a POSA actually following the teachings of Waterside (or Harris) would have obtained the claimed composition. (Ex-2037, ¶174.)

4. Waterside Does Not Render Obvious A Composition That Contains "Less Than About 25%" Acidic Variants.

As discussed above, Waterside fails to disclose a composition "wherein the amount of acidic variant(s) is less than about 25%" as required by all challenged claims. Pfizer argues, in the alternative, that even if Waterside does not disclose such a composition, this element would have been obvious. (Petition, 56.) Pfizer's argument is legally improper because Pfizer's ***only*** evidence of a motivation to modify Waterside below a 25% threshold level of acidic variants is the disclosure of the '218 patent itself, which cannot be used as an invalidating reference. (*See id.* (relying on the '218 patent to suggest a 25% threshold level).) *Application of Roberts*, 470 F.2d 1399, 1401-02 (C.C.P.A. 1973) (reversing obviousness determination that was "reachable only by reconstructing the invention from the prior art with the benefit of [patentee's] own disclosure"); *Commvault Sys., Inc. v. Realtime Data LLC*, IPR2017-02007, Paper 11, *16 (P.T.A.B. Mar. 15, 2018) (Petitioner relied on "improper hindsight" "us[ing] Patent Owner's own invention … as a basis for the combination.").

And in fact, Waterside ***teaches away*** from removing acidic variants, stating: "Decided ***not to remove*** the deamidated material." (Ex-1006, 7; Ex-2037, ¶¶179-180, 185.) This is not surprising, as removing acidic variants involves considerable work and results in loss of yield (Ex-1034, 5-6; Ex-2037, ¶180), and

Pfizer identifies no evidence that anyone prior to the '218 patent believed there would be a benefit from reducing the amount of acidic variants to "less than about 25%" (*see* Petition, 56).[24] Waterside's teaching away from the removal of acidic variants is strong evidence of non-obviousness. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements.").

Nor would a POSA have had a reasonable expectation of success in achieving the claimed compositions based on Waterside, as discussed in Section VII(B)(3) (incorporated herein by reference). (Ex-2037, ¶¶181-185.) As Dr. Carbonell explains, there are many variables that can impact acidic variant profile, and without specific guidance as to how to obtain a composition with less than 25% acidic variants, a POSA in May 1998 would not have had a reasonable expectation of being able to do so. (Ex-2037, ¶¶180-184.)

[24] As Dr. Scandella concedes, FDA guidance at the time did not set any absolute limits or targets for variant profile. (Ex-2038, 79:22-80:10; Ex-2037, ¶138; Ex-2052, 5-6.)

C. Harris Does Not Render Obvious The Challenged Claims.

1. Harris Does Not Disclose A Composition That Contains "Less Than About 25%" Acidic Variants.

Harris fails to disclose a composition that contains "less than about 25%" acidic variants as required by all challenged claims. Pfizer contends that the chromatographic drawing in Harris (which Pfizer asserts is "nearly (if not) identical" to the Waterside drawing) can be measured in order to calculate that the depicted composition contains less than 25% acidic variants. (Petition, 22, 63.) But the Harris drawing suffers from the same deficiencies as the Waterside drawing—most notably, Harris does not provide any quantified points along the x-axis corresponding to the different protein components, and it does not provide any quantified points along the y-axis at all (including a reference baseline). (Ex-1005, 5; Ex-2037, ¶¶186-190.) There is thus insufficient detail to rely on any calculations derived from the drawing, and inadequate disclosure to find that Harris expressly or inherently teaches a composition with less than about 25% acidic variants. (Ex-2037, ¶¶186-190.) *See* Section VII(B)(2), which is incorporated here by reference.

2. Harris Is Not Enabling.

As with Waterside, Pfizer fails to present a *prima facie* case that Harris is enabling,[25] and the Board should not consider Pfizer's improper attempt to incorporate an enablement argument via the declaration of Dr. Buick. Pfizer's petition does not even cite to the paragraphs of Dr. Buick's declaration (Ex-1042, ¶¶25-29) in which Dr. Buick purports to demonstrate that Harris is enabling. Nor does Dr. Scandella opine that Harris is enabling. (Ex-1003.)

Moreover, Pfizer and Dr. Buick treat Harris and Waterside as providing the same teachings, and Dr. Buick does not attempt to separately establish their enablement. (Ex-1043, ¶¶25-29.) In any event, like Waterside, there is no dispute that Harris does not teach how to make the antibody composition that was analyzed. As Dr. Scandella testified, "[i]n describing their experimental conditions for the cation-exchange chromatography, Harris refers to two lots of rhuMAb HER2, but it doesn't say how they prepared them." (Ex-2038, 122:14-22; *see also* Ex-2037, ¶¶198-202.). And while Dr. Buick purportedly used Harris's Mono-S method to analyze his composition, the only teaching from Harris that Dr. Buick relied for making his composition was the use of CHO cells. (Ex-2039, 50:8-

[25] As discussed in Section VII(A)(3)(a) (incorporated herein by reference), there should be no presumption of prior art enablement in an IPR.

51:2). The Board should reject Dr. Buick's experiments and find that Harris is not enabling for the reasons set forth in Section VII(B)(3), which is incorporated herein by reference. (Ex-2037, ¶¶192-218.)

3. Harris Does Not Render Obvious A Composition That Contains "Less Than About 25%" Acidic Variants.

As discussed above, Harris fails to disclose a composition that contains "less than about 25%" acidic variants as required by all challenged claims. Pfizer argues, in the alternative, that this element would have been obvious, but Pfizer's argument is legally deficient. Pfizer does not articulate a separate obviousness argument but simply asserts that this limitation would have been obvious in light of Harris for the same reason it would have been obvious in light of Waterside. (Petition, 64.) But as discussed in Section VII(B)(4) (incorporated herein by reference), Pfizer's only evidence of a motivation to modify Waterside (and thus, Harris) to obtain a composition with less than 25% acidic variants comes from the teaching in the '218 patent itself, which is plainly improper. (Petition, 56.)

Notably, Harris itself does not provide a motivation to modify its composition—Harris does not discuss biological activity of rhuMAb acidic variants, does not suggest separating out any charge species, and does not suggest that the analyzed lots should be further purified. (Ex-2037, ¶¶186-191; *see also* Ex-2038, 153:8-11, 154:14-20 (Dr. Scandella conceding Harris does not suggest

removing charge variants).) And for the reasons discussed above in Sections VII(B)(3)-(4) and VII(C)(2) (incorporated herein by reference), a POSA would not otherwise have a motivation to modify Harris nor a reasonable expectation of success in achieving the claimed invention by doing so. (Ex-2037, ¶¶219-223.)

Thus, the Board should find that Pfizer failed to meet its burden of demonstrating that Harris renders obvious a composition that contains "less than about 25%" acidic variants. (Ex-2037, ¶¶186-191.)

D. The Present IPR Proceedings Are Unconstitutional And Fail To Comply With The AIA.

IPRs are unconstitutional as applied retroactively to a patent, like the '218 patent, that claims priority to an application filed and/or a patent issued prior to the AIA. *See Oil States Energy Servs., LLC v. Greene's Energy Grp., LLC*, 138 S. Ct. 1365, 1379 (2018). Additionally, IPR proceedings do not comply with due process under the Constitution, and invalidating a patent in an IPR without just compensation is an unconstitutional taking. *See id.* Furthermore, the Board's May 2, 2018 decision (Paper 25) instituting review of the previously-denied grounds in light of the Supreme Court's decision in *SAS Institute Inc. v. Iancu*, 138 S. Ct. 1348 (2018) did not comply with 35 U.S.C. § 314(b) because it was made more than three months after Genentech's December 14, 2017 preliminary response.

VIII. CONCLUSION

The Board should confirm the patentability of the challenged claims.

Respectfully submitted,

Date: June 29, 2018

/David L. Cavanaugh/
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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Response, contains 13,985 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d).

Respectfully submitted,

Dated: June 29, 2018

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CERTIFICATE OF SERVICE

I hereby certify that, on June 29, 2018, I caused a true and correct copy of the following materials:

- Patent Owner's Response
- Certificate of Compliance
- Patent Owner's Motion to Seal
- Patent Owner's Updated Exhibit List
- Exhibits 2018-2059

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IPR2017-02020
Patent Owner's Exhibit List

Patent Owner's Exhibit Number	Exhibit Name
2001	David Holzman, *Gene Therapy for HER-2-Related Cancer*, MOLECULAR MEDICINE TODAY 138 (1996)
2002	Russ Hoyle, *Genentech Is Poised for an Anti-Cancer Breakthrough*, 16 NATURE BIOTECHNOLOGY 887 (1998)
2003	Jatinderpal Kalsi, et al., *Structure-function Analysis and the Molecular Origins of Anti-DNA Antibodies in Systemic Lupus Erythematosus*, EXPERT REVS. MOLECULAR MED. 1-28 (1999)
2004	Shohei Kishishita, et al., *Effect of Temperature Shift on Levels of Acidic Charge Variants in IgG Monoclonal Antibodies in Chinese Hamster Ovary Cell Culture*, 119 J. BIOSCIENCE & BIOENGINEERING 700-705 (2015)
2005	Nigel Jenkins, *Modifications of Therapeutic Proteins: Challenges and Prospects*, 53 CYTOTECHNOLOGY 121-125 (2007)
2006	Declaration of Carol Basey (submitted in European Patent Office Case No. T 2522/10-3304)
2007	Declaration of Gregory Blank (submitted in European Patent Office Case No. T 2522/10-3304)
2008	Declaration of John Simpson (submitted in European Patent Office Case No. T 2522/10-3304)
2009	Declaration of Laura Storto (submitted in European Patent Office Case No. T 2522/10-3304)
2010	Declaration of Dongyuan Wang (submitted in European Patent Office Case No. T 2522/10-3304)
2011	Declaration of Janet Yang (submitted in European Patent Office Case No. T 2522/10-3304)
2012	Matthias Brunner, *Investigation of the Interactions of Critical Scale-Up Parameters (pH, pO2 and pCO2) on CHO Batch Performance and Critical Quality Attributes*, 40 BIOPROCESS BIOSYST. ENG. 251-263 (2017)
2013	Michael J. Pikal, et al., *The Effects of Formulation Variables on the Stability of Freeze-Dried Human Growth Hormone*, 8 PHARM. RES. 427-436 (1991)

Patent Owner's Exhibit Number	**Exhibit Name**
2014	Srinivasa Rao, et al., *Separation of Monoclonal Antibodies by Weak Cation-Exchange Chromatography Using ProPac and ProSwift Columns* (2010)
2015	TABER'S CYCLOPEDIC MEDICAL DICTIONARY (18th Ed. 1997)
2016	Declaration of Robert J. Gunther, Jr. in Support of Motion for Admission *Pro Hac Vice*
2017	Declaration of Daralyn J. Durie in Support of Motion for Admission *Pro Hac Vice*
2018	Genentech, Inc. Excerpts of Notebook 22722 (Janet Yang)
2019	Genentech, Inc. Excerpts of Notebook 22723 (Janet Yang)
2020	Genentech, Inc. Excerpts of Notebook 24207 (Janet Yang)
2021	Genentech, Inc. Excerpts of Notebook 24208 (Janet Yang)
2022	Genentech, Inc. Excerpts of Notebook 26196 (Janet Yang)
2023	Genentech, Inc. Excerpts of Notebook 29916 (Janet Yang)
2024	Genentech, Inc. Excerpts of Notebook 20705 (Carol Basey) PROTECTIVE ORDER MATERIAL
2025	Genentech, Inc. Clinical Manufacturing Formula Document Lot No. M21-4 PROTECTIVE ORDER MATERIAL
2026	Genentech, Inc. Clinical Manufacturing Formula Document Lot No. M21-5 PROTECTIVE ORDER MATERIAL
2027	Genentech, Inc. Clinical Manufacturing Formula Document for Buffer Recipe PROTECTIVE ORDER MATERIAL
2028	*Curriculum Vitae* of Dr. Gregory S. Blank, Ph.D.
2029	Genentech, Inc. Clinical Manufacturing Formula Document Lot No. M21-4 PUBLIC
2030	Genentech, Inc. Clinical Manufacturing Formula Document Lot No. M21-5 PUBLIC
2031	Genentech, Inc. Clinical Manufacturing Formula Document for Buffer Recipe PUBLIC

Patent Owner's Exhibit Number	**Exhibit Name**
2032	Modified Default Standing Protective Order and Patent Owner's Certification of Agreement to Terms
2033	Modified Default Standing Protective Order – Redline
2034	Declaration of Stephanie Mendelsohn
2035	Declaration of Gregory S. Blank, Ph.D.
2036	Declaration of Holly Prentice, Ph.D.
2037	Declaration of Ruben G. Carbonell, Ph.D.
2038	Deposition Transcript of Carl Scandella, Ph.D., May 31, 2018
2039	Deposition Transcript of Richard Buick, Ph.D., June 7, 2018
2040	Horvath et al., *Characterization of a Monoclonal Antibody Cell Culture Production Process Using a Quality by Design Approach*, 45 MOLECULAR BIOTECHNOLOGY 203 (2010)
2041	Hossler et al., *Cell Culture Media Supplementation of Bioflavonoids for the Targeted Reduction of Acidic Species Charge Variants on Recombinant Therapeutic Proteins*, 31(4) BIOTECHNOLOGY PROGRESS 1039 (2015)
2042	Khawli et al., *Charge Variants in IgG1*, 2(6) mABs 613 (2010)
2043	Konakovsky et al., *Metabolic Control in Mammalian Fed-Batch Cell Cultures for Reduced Lactic Acid Accumulation and Improved Process Robustness*, 3, 5 BIOENGINEERING (2016)
2044	Liu et al., *Impact of Cell Culture on Recombinant Monoclonal Antibody Product Heterogeneity*, 32(5) BIOTECHNOLOGY PROGRESS 1103 (2016)
2045	Naciri & Kuystermans, *Monitoring pH and Dissolved Oxygen in Mammalian Cell Culture Using Optical Sensors*, 57 CYTOTECHNOLOGY 245 (2008)
2046	Nagashima et al., *Application of a Quality by Design Approach to the Cell Culture Process of Monoclonal Antibody Production, Resulting in the Establishment of a Design Space*, 102 J. PHARM. SCIS. 4274 (2013)
2047	Rice et al., *Measurement of Transient cDNA Expression in Mammalian Cells Using Flow Cytometric Cell Analysis and Sorting*, 12 CYTOMETRY 221 (1991)

Patent Owner's Exhibit Number	**Exhibit Name**
2048	Tang et al., *Insights into the Generation of Monoclonal Antibody Acidic Charge Variants During Chinese Hamster Ovary Cell Cultures*, 102 APPLIED MICROBIOLOGY & BIOTECHNOLOGY 1203 (2018)
2049	Xie et al., *Elucidating the Effects of pH Shift on IgG1 Monoclonal Antibody Acidic Charge Variant Levels in Chinese Hamster Ovary Cell Cultures*, 100 APPLIED MICROBIOLOGY & BIOTECHNOLOGY 10343 (2016)
2050	Zhang et al., *Culture Temperature Modulates Monoclonal Antibody Charge Variation Distribution in Chinese Hamster Ovary Cell Cultures*, 37 BIOTECHNOLOGY LETTERS 2151 (2015)
2051	Genentech, Inc. Excerpts of Notebook 20705 (Carol Basey) PUBLIC
2052	FDA Q6B GUIDANCE 1999
2053	Robinson & Robinson, *Deamidation of human proteins,* 98 PROC. NAT'L ACAD. SCI. 12409 (2001)
2054	Sinha et al., *Effect of Protein Structure on Deamidation Rate in the Fc Fragment of an IgG1 Monoclonal Antibody*, 18 PROTEIN SCI. 1573 (2009)
2055	Geiger & Clarke, *Deamidation, Isomerization, and Racemization at Asparaginyl and Aspartyl Residues in Peptides*, 262 J. BIOLOGICAL CHEM. 785 (1987)
2056	Stratton et al., *Controlling Deamidation Rates in a Model Peptide: Effects of Temperature, Peptide Concentration, and Additive*s, 90(12) J. PHARM. SCIS. 2141 (2001)
2057	Huang et al., *In Vivo Deamidation Characterization of Monoclonal Antibody by LC/MS/MS*, 77 ANALYTICAL CHEM. 1432 (2005)
2058	Lain, *Protein A: The Life of a Disruptive Technology*, BIOPROCESS SPECIAL REPORT 29 (Sept. 2013)
2059	Spreadsheets Produced by Pfizer on June 25, 2018